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WHO Drug Information

Contents

Quality Assurance News

453 WHO External Quality Assurance Assessment Scheme Phase 9
466 WHO Biowaiver Study Project for COVID-19 Outbreak: Dexamethasone Solubility Results for Biopharmaceutical Classification System

Consultation Documents

472 Dissolution Test for Solid Oral Dosage Forms. Draft proposal for revision in The International Pharmacopoeia
485 WHO Biowaiver Project – Preparation for cycle IV (2021): Prioritization exercise of active pharmaceutical ingredients on the WHO Model List of Essential Medicines for solubility determination and Biopharmaceutics Classification System-based classification
492 Zanamivir (Zanamivirum) – Draft proposal for inclusion in The International Pharmacopoeia
502 Zanamivir powder for inhalation, pre-metered (Zanamiviri pulvis pro inhalatione) – Draft proposal for inclusion in The International Pharmacopoeia
509 Powders for inhalation (pulvis ad inhalationem) - Draft proposal for inclusion in The International Pharmacopoeia
516 Good Manufacturing Practices: Water for Pharmaceutical Use
540 Revision of Chapter 2.1: General Identification Tests - Draft proposal for inclusion in The International Pharmacopoeia
548 Policy: Evaluating and Publicly designating Regulatory Authorities as WHO Listed Authorities
559 Good Regulatory Practices for Regulatory Oversight of Medical Products
597 3.6 Test for histamine-like substances (vasodepressor substances) - Draft proposal for inclusion in The International Pharmacopoeia
600 Albendazole chewable tablets (albendazoli compressi manducabili) - Draft proposal for inclusion in The International Pharmacopoeia
606 Good Reliance Practices in regulatory decision-making for medical products: high-level principles and considerations

International Nonproprietary Names (INN)

641 Proposed INN List No. 124 – COVID-19 (Special Edition)
687 Recommended INN List No. 84
Abbreviations and websites

CHMP Committee for Medicinal Products for Human Use (EMA)
EMA European Medicines Agency (www.ema.europa.eu)
EU European Union
FDA U.S. Food and Drug Administration (www.fda.gov)
Health Canada Federal department responsible for health product regulation in Canada (www.hc-sc.gc.ca)
HPRA Health Products Regulatory Authority, Ireland (www.hpra.ie)
HSA Health Sciences Authority, Singapore (www.hsa.gov.sg)
ICDRA International Conference of Drug Regulatory Authorities
ICH International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (www.ich.org)
IGDRP International Generic Drug Regulators Programme (https://www.igdrp.com)
MHLW Ministry of Health, Labour and Welfare, Japan
MHRA Medicines and Healthcare Products Regulatory Agency, United Kingdom (www.mhra.gov.uk)
Medsafe New Zealand Medicines and Medical Devices Safety Authority (www.medsafe.govt.nz)
Ph. Int The International Pharmacopoeia (http://apps.who.int/phint/)
PRAC Pharmacovigilance Risk Assessment Committee (EMA)
PMDA Pharmaceuticals and Medical Devices Agency, Japan (www.pmda.go.jp/english/index.htm)
Swissmedic Swiss Agency for Therapeutic Products (www.swissmedic.ch)
TGA Therapeutic Goods Administration, Australia (www.tga.gov.au)
U.S. United States of America
WHO World Health Organization (www.who.int)
WHO MHP WHO Access to Medicines and Health Products Division (www.who.int/medicines/en/)
WHO RPQ WHO Regulation and Prequalification Department
WHO PQT WHO Prequalification Unit (https://www.who.int/topics/prequalification/en/)
WHO HPS WHO Health Product Policy and Standards Department

Note: The online version of this issue (freely available at www.who.int/medicines/publications/druginformation) has direct clickable hyperlinks to the documents and websites referenced
WHO

External Quality Assurance Assessment Scheme

Phase 9

INTRODUCTION

The participation of Pharmaceutical Quality Control Laboratories (PQCLs) in appropriate proficiency testing schemes is an internationally recognised requirement as this enables the PQCL to demonstrate, monitor and improve the quality of the analytical services provided. Proficiency testing covers the overall performance of a laboratory, evaluating the process from the reception and storage of samples, the experimental work in the laboratory, the interpretation and the transcription of the data and the conclusions to the reporting sheets. Failure at any of these stages also reflects on the competence of the respective laboratory.

In support of PQCLs, the World Health Organization (WHO) offers proficiency testing through its External Quality Assurance Assessment Scheme (EQAAS) which offers a platform for PQCLs to measure their performance through a confidential system of blind testing. Since 2000, the EQAAS is organized by WHO with the assistance of the European Directorate for the Quality of Medicines and HealthCare (EDQM).

This proficiency testing scheme also serves to demonstrate the reliability of laboratory analytical results by objective means; thereby fostering the establishment of mutual confidence/recognition within collaborating networks, promoting work sharing based on reliance, especially in countries with limited or no quality control testing capabilities.

The EQAAS is facilitated in accordance with the International Organization for Standardization and International Electrotechnical Commission (ISO/IEC) standards for proficiency testing (i.e. ISO/IEC 17043:2010). This Scheme has entered its tenth phase period in 2020. Laboratories across WHO’s six regions have participated in the past comparative external assessment studies and more than 1 100 studies involving 33 different tests were carried out.

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DESCRIPTION OF EQAAS PHASE 9

During EQAAS Phase 9, laboratories were provided with the opportunity to evaluate their performance with regards to three procedures using mebendazole chewable tablets as a common test sample (as depicted in Figure 1).

![EQAAS Phase 9 diagram]

**Figure 1:** Schematic presentation of analytical procedure bouquet incorporated into EQAAS Phase 9.

- **Procedure 1:** the aim of this procedure was to assess the performance of the laboratory with regards to the determination of the assay by liquid chromatography. Laboratories were requested to determine (in triplicate) the percentage content of mebendazole in mebendazole chewable tablets using the liquid chromatography method from the monograph on mebendazole chewable tablets of *The International Pharmacopoeia*.

- **Procedure 2:** the aim of this procedure was to assess the performance of the laboratories with regards to the identification by Infrared Absorption Spectrophotometry. Laboratories were requested to confirm the polymorphic form of mebendazole present in mebendazole chewable tablets through infrared absorption spectrophotometry; and

- **Procedure 3:** the aim of this procedure was to assess the performance of laboratories with regard to the performance of a dissolution test. Laboratories were requested to carry out the dissolution test and to determine the percentage of mebendazole released at 60 minutes from mebendazole chewable tablets, according to the monograph of *The International Pharmacopoeia* published by WHO.
STATISTICAL METHODS

For procedures 1 and 3, the following approaches applied: Different approaches may be adopted to assign the content of the analyte in the samples. The methods commonly applied in the WHO EQAAS operated in accordance with the Proficiency Testing Scheme developed by the EDQM are the use of a theoretical value or the addition of a known quantity of the analyte to the sample (“true” value) confirmed in the feasibility study or the use of a consensus value based on the results from the participants. To determine the consensus value, robust statistics are generally applied (e.g. the median value, mean interquartile range, Huber’s robust mean) to avoid the influence of “outliers” on the overall mean.

The target standard deviation is set based on experience, or on the reported or expected precision of techniques, and according to fitness for purpose.

Assigned value

The assigned values used in this study are the consensus values obtained when calculating the Huber’s robust mean. Table 1 provides a summary of the consensus values and the values obtained during the feasibility studies.

**Table 1**: Summary of consensus values and feasibility study values for procedures 1 and 3

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Consensus Value</th>
<th>Feasibility Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Procedure 1</strong>: Mebendazole Assay</td>
<td>99.25%</td>
<td>99.2%</td>
</tr>
<tr>
<td><strong>Procedure 3</strong>: Mebendazole Dissolution</td>
<td>69.0%</td>
<td>72.8%</td>
</tr>
</tbody>
</table>
Target standard deviation

The target values for the standard deviation (TSD) for procedures 1 and 3 are summarized in Table 2.

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Target value for TSD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procedure 1: Mebendazole Assay</td>
<td>0.8%</td>
</tr>
<tr>
<td>Procedure 3: Mebendazole Dissolution</td>
<td>3.5%</td>
</tr>
</tbody>
</table>

The target value for the TSD for the assay values took into account the variability between the mean results, calculated at the EDQM on the basis of the individual values reported by the participants.

The uncertainty of the assigned value was found to be negligible compared with the defined TSD and can be ignored in the interpretation of the performance scores.

Scoring

The z-score gives a bias estimate of the result. Absolute z-scores less than 2 are acceptable. A zone of doubtful performance exists for absolute z-scores between 2 and 3. Those do not necessarily have to be unacceptable since there is some uncertainty how close the consensus value is to the true value. An absolute z-score of 3 or more can be interpreted as an unacceptable performance.

Corrective actions should also be triggered when z-scores are frequently in the doubtful zone. For the purposes of this exercise, the calculation of a z-score has then been made for each laboratory according to:

\[
z - \text{score} = \frac{\bar{x} - \hat{x}}{TSD}
\]

Where \( \bar{x} \) is the unrounded mean value calculated by EDQM based on the reported results of the individual laboratory, 
\( \hat{x} \) is the assigned value, 
TSD is the target value for the standard deviation.
As a first step, a check for high standard deviations (Cochran’s test) and for outlying means (Grubbs’ test) was carried out. An outlier is a value that is so unlikely in the light of the overall distribution of results, that it would have an unreasonable impact on the calculation of certain statistics (e.g. the overall mean and the overall standard deviation). These tests do not necessarily detect values that are obviously unacceptable to a trained eye. Standard deviations or relative standard deviations printed on a black background are only to indicate that these values are high compared to the (R)SDs found in other laboratories, but they do not necessarily imply that they are unacceptable.

The purpose of (R)SDs is to provide participants with comparative material so that they can interpret their own data in the light of the performances of other laboratories and draw their own conclusions. It is also important to be aware that the SD for precision is not the same as the SD for accuracy (TSD) on which the z-scores are based.

Since only correct identification of the mebendazole polymorph was requested from the participants (yes / no), for procedure 2, no consensus value or z-score was determined, thus no statistical evaluation of data sensu stricto was carried out.

**DISCUSSION OF THE RESULTS REPORTED FOR EQAAS PHASE 9**

A total of 43 participants participated in Phase 9 of the EQAAS. The tests were well designed and the results obtained were subjected to sound statistical evaluation, as described above.

The z-scores of the participants in procedure 1 are depicted in Figure 2. The black dots indicate the respective z-scores. Thirty-six (36) of the laboratories, which equates to eighty-four per cent of the laboratories, reported satisfactory results (|z-score| < 2). Four (4) laboratories reported doubtful results (2 < |z-score| > 3). Three (3) laboratories reported unsatisfactory results (|z-score| ≥ 3). Eight (8) laboratories showed a high variability between the individual results they reported and are therefore found to be outliers for the standard deviation according to Cochran’s test. One laboratory expressed the results in mg instead of as a percentage of the declared content, which resulted in the high z-score. If reported in percentage as requested in the protocol, they would have obtained a result of 100.41%.
Figure 2: The z-scores of the participants in procedure 1.

The characteristic IR bands used for the identification of mebendazole polymorphs A, B and C are listed in Table 3.

TABLE 3: The characteristic IR stretching frequencies used for the identification of mebendazole polymorphs A, B and C

<table>
<thead>
<tr>
<th>Form</th>
<th>-NH</th>
<th>&gt;C=O</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>3370 cm⁻¹</td>
<td>1730 cm⁻¹</td>
</tr>
<tr>
<td>B</td>
<td>3340 cm⁻¹</td>
<td>1700 cm⁻¹</td>
</tr>
<tr>
<td>C</td>
<td>3410 cm⁻¹</td>
<td>1720 cm⁻¹</td>
</tr>
</tbody>
</table>

Figure 3 depicts the changes in the characteristic stretching frequencies at 3370 cm⁻¹ and 3410 cm⁻¹ of polymorph A and polymorph C respectively in the DRIFT-IR spectra of a commercially available product containing mebendazole. The conversion from polymorph C into the thermodynamically stable polymorph A is clearly detected by the decrease in the intensities of the 3404 cm⁻¹ band and increase in the intensities of the 3369 cm⁻¹ band.
**Figure 3:** Characteristic stretching frequencies (cm\(^{-1}\)) and the areas thereof in the DRIFT-IR spectra of a commercially available product 3 at 0 (top), 3 (middle) and 6 (bottom) months respectively indicating the decreasing polymorph C and increasing polymorph A content\(^3\).
Figure 4 depicts the IR spectra of mebendazole ICRS and the mebendazole extracted from the chewable tablets used during EQAAS Phase 9.
Figure 4: IR spectra of (a) mebendazole ICRS and (b) the mebendazole extracted from the chewable tablets used during EQAAS Phase 9.

The presence of the strong absorption bands at 3404 and 1720 cm$^{-1}$ in the IR spectrum of mebendazole ICRS (Figure 4 (a)) are characteristic of polymorphic form C. From Figure 4 (b), it is clear that the polymorph predominantly present in the chewable tablets was polymorph A due to the presence of the strong absorption bands at 3370 & 1732 cm$^{-1}$. The outcomes of the results reported by the participants in procedure 2 are depicted in Figure 5.

![Bar chart](chart.png)

Figure 5: Summary of responses received for the identification of the predominant mebendazole polymorphic form present in the mebendazole chewable tablets in procedure 2.

Twenty-nine (29) of the laboratories correctly identified that polymorphic form A was the predominant form present in the chewable tablets. Five (5) laboratories reported unsatisfactory results as they indicated that the predominant polymorphic form present was C. Nine (9) laboratories did not report results for this procedure. Six (6) of them explained that the IR equipment was lacking or out of working order.

The z-scores of the participants in procedure 3 are depicted in Figure 6. The black dots indicate the respective z-scores. Thirty-eight (38) of the forty-three (43) participants submitted results for procedure 3.
Thirty-one (31) of the laboratories, which equates to seventy-two (72) per cent of the laboratories, reported satisfactory results (|z-score| < 2). Seven (7) laboratories reported unsatisfactory results (|z-score| ≥ 3). Four (4) laboratories showed a high variability between the individual results they reported and are therefore found to be outliers for the standard deviation according to Cochran’s test. Five (5) laboratories did not report any results for this procedure.

**Figure 6:** The z-scores of the participants in procedure 3.
POST-EQAAS PHASE 9 ASSISTANCE PROGRAM

Laboratories that produced acceptable results were encouraged to use the EQAAS as a stimulus for continuous improvement, whilst those laboratories that reported unacceptable results were requested to investigate their procedures. These laboratories are subject to a root cause investigation, the results of which they are invited to share and use as the basis for corrective and preventive action plans and targeted training, as and where necessary.

To assist such laboratories, WHO invited them to participate in a Post-EQAAS Phase 9 Assistance Program (PEP-9-AP). Participation in this PEP-9-AP was voluntary and free of cost – Figure 7.

Figure 7: Post-EQAAS Phase 9 Assistance Program (PEP-9-AP) flyer.

Laboratories from four (4) different countries responded to the invitation, and three (3) expressed interest in the PEP-9-AP. The PEP-9-AP consisted of four (4) parts, as depicted in the following flow diagram (Figure 8).
Figure 8: Flow diagram illustrating the rollout of the PEP-9-AP.
During Part I, the participating laboratories were requested to provide copies of their preliminary investigation report, raw data and processed results generated during the testing phase. A risk-based assessment tool was developed to facilitate identification of all potential assignable causes that might have led to the reporting of failing/unacceptable results. All information provided by the laboratories were then reviewed and subjected to the risk-based assessment tool. Comprehensive reports with feedback were compiled and issued to the respective laboratories. These reports detailed potential assignable causes for the delivery of failing/unacceptable results.

In Part II, the participating laboratories had to investigate and verify the assignable causes. Verified assignable causes were then subjected to a Root Cause Analysis (RCA) in an attempt to establish the Root Cause(s) (RC) of the failures. Thereafter the laboratories were assisted (during Part III) to develop and implement a corrective action plan with detailed Corrective Actions (CA) to address and prevent the potential reoccurrence of similar failures in future.

During Part IV, the laboratories were requested to review and monitor the effectiveness of the implemented CAs.

To conclude, the PEP-9-AP aimed to assist laboratories in the effective management of non-conforming results through the collection of information, analysing of information, identification and investigation of the quality problems, and assisting in taking the appropriate and effective corrective and/or preventive action in an attempt to prevent their recurrence, and ultimately building capacity within these PQCLs.

References


WHO Biowaiver Study Project for COVID-19 Outbreak: 
Dexamethasone Solubility Results for Biopharmaceutical 
Classification System

Dexamethasone is a corticosteroid considered today as one of the few medicines able to reduce mortality in patients infected with COVID-19 who are critically or severely ill (mortality reduction of 8.7% and 6.7% respectively at 28 days)\(^1,2\). It is hypothesized that its benefits are probably due to reduced inflammation which is a key component of the disease in some hospitalized patients.

According to the World Health Organization (WHO) Director-General, Dr Tedros Adhanom Ghebreyesus: “The next challenge is to increase production and rapidly and equitably distribute dexamethasone worldwide, focusing on where it is needed most”\(^3\). The WHO Norms and Standards for Pharmaceuticals (NSP) Team therefore conducted a high priority assessment of dexamethasone within the ongoing WHO Biowaiver Study Project to generate scientifically valid solubility data in support of regulatory decisions to improve access to this medicine in the current global public health emergency.

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Over the past four years, the WHO Biowaiver Study Project, designed in 2017 and launched in 2018 with a pilot phase, has supported the initial revision and subsequent maintenance of the WHO Biopharmaceutical Classification System (BCS), which is also known as WHO Biowaiver List. Leveraging on the 1995 BCS, the WHO and several regulatory agencies from all over the world recognized the possibility of an optimized and shorter pharmaceutical development pathway by waiving the in vivo bioequivalence studies for medicines that qualify based on a set of defined criteria. This regulatory provision can be applied when developing multisource (generic) products, as well as for pre- and post-approval changes requiring bioequivalence studies.

Eligible medicines are immediate-release, solid oral dosage forms containing active pharmaceutical ingredients (APIs) Class I (highly soluble and highly permeable) or Class III (highly soluble and low permeable) according to the BSC scientific framework. The intended impact of such a WHO classification is high with regards to access to the medicines, particularly for emergency situations.

The WHO Biowaiver List has been recognized by WHO and its Regional and Country Offices as a Global Public Health Good to achieve Universal Health Coverage, to contribute to the sustainable development goals and to increase access to essential medicines.

In June 2020, on the occasion of the annual meeting on regulatory guidance for multisource products hosted by the NSP Team with the Prequalification of Medicines Team - Assessment group, the NSP Team presented a set of APIs for prioritization and study within the WHO Biowaiver Study Project (study cycle IV, 2021). The proposed set included medicines that were undergoing clinical trials to address the COVID-19 emergency. During the meeting, the experts stressed the need for an urgent solubility assessment of dexamethasone for BCS purposes. In addition, it was recommended that the results of such experiments should be shared with the broader scientific community to facilitate regulatory decisions affecting production and, ultimately, the availability of dexamethasone to patients.

---


Methods

Dexamethasone solubility was studied in parallel by three independent institutions selected from the network of laboratories that are supporting the WHO Biowaiver Project: i) the University Miguel Hernández University of Elche in Alicante, Spain; ii) the University of Health Sciences and Pharmacy in St. Louis, United States of America; and iii) the National Institutes for Food and Drug Control in Beijing, China.

Equilibrium solubility studies were performed according to the provisions specified in the WHO “Protocol to conduct equilibrium solubility experiments for the purpose of Biopharmaceutical Classification System-based classification of active pharmaceutical ingredients for biowaiver”\(^6\). This protocol was specifically developed and optimized for the WHO Biowaiver Project and employs a harmonized methodology that has been demonstrated to control experimental variabilities across global laboratories as illustrated in: “Global testing of a consensus solubility assessment to enhance robustness of the WHO biopharmaceutical classification system” [Valeria Gigante, Giovanni M. Pauletti, Sabine Kopp, Minghze Xu, Isabel Gonzalez-Alvarez, Virginia Merino, Michelle P. McIntosh, Anita Wessels, Beom-Jin Lee, Kênnia Rocha Rezende, Gerhard K.E. Scriba, Gaurav P. S. Jadaun, Marival Bermejo, ADMET and DMPK (2020), doi: http://dx.doi.org/10.5599/jese.850. Advanced online article: https://pub.iapchem.org/ojs/index.php/admet/issue/view/58].

Dexamethasone solubility was studied at the therapeutic dose of 6 mg, which is the same dosage used in the COVID-19 Recovery Trial\(^7\) and currently recommended in adults and adolescents over 12 years of age (weighing more than 40 kg)\(^2,8\) for the treatment of patients with severe and critical COVID-19.

Dexamethasone can be administered orally or intravenously leading to similar systemic drug exposure (i.e. high oral bioavailability).

Results

In this study, the solubility profiles of the following solid state forms of dexamethasone were evaluated: dexamethasone, dexamethasone micronized, dexamethasone phosphate and dexamethasone sodium phosphate. The experimental results for all these forms were consistent across the laboratories (Table 1).

---


Table 1. WHO equilibrium solubility classification of dexamethasone

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Therapeutic area</th>
<th>Indication</th>
<th>Highest therapeutic dose (mg)b</th>
<th>API PQ EOI/Q</th>
<th>WHO classification c</th>
</tr>
</thead>
<tbody>
<tr>
<td>dexamethasone</td>
<td>(1) Gastrointestinal medicines (2) Immunomodulators and antineoplastics (3) Medicines for pain and palliative care (4) Corticosteroids for COVID-19*</td>
<td>(1) Antiemetic medicines (2) Acute lymphoblastic leukaemia (2) Multiple myeloma (3) Medicines for other common symptoms in palliative care (4) Treatment of patients with severe or critical COVID-19*</td>
<td>(1) (3) 0.5 to 10 mg a day depending on the disease being treated (2) 40 mg (4) 6 mg a day *</td>
<td>Yes</td>
<td>I/III</td>
</tr>
</tbody>
</table>

a 21st WHO Model List of Essential Medicines (2019) 
b According to Summary of Product Characteristics from WHO-PQ or National/Regional Regulatory Authority. 
c According to the WHO guidelines, Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability (1), APIs belonging to Classes I and III are eligible for biowaiver. Once experimental permeability data are available, the exact class attribution will be possible (i.e. either Class I or Class III). The present solubility characterization is already sufficient to provide an indication as to whether or not an API is eligible for biowaiver.


As detailed in the WHO guideline entitled “Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability” (WHO Technical Report Series, No. 1003, Annex 7, 2017), an API is considered “highly soluble” when the highest single therapeutic dose of the API as recommended by the approved label or summary of product characteristics of the originator product is soluble in 250 mL or less of aqueous media over the entire pH-range of 1.2 – 6.8. The dose/solubility volume (DSV) is the volume of liquid necessary to completely dissolve the API.
The results from these experimental solubility assessments revealed that the DSV for dexamethasone is consistently less than 250 mL over the entire physiological pH range: pH 1.2 - pH 6.8. Thus, it is concluded that dexamethasone is a highly soluble API, consistent with the definition of a BSC Class I/III compound. Consequently, dexamethasone at doses relevant for therapeutic intervention in COVID-19 patients seems eligible for a regulatory waiver from in vivo bioequivalence studies (Table 2).

Comparative in vitro dissolution data, supported by the necessary considerations underpinning dexamethasone pharmaceutical development, are still expected to be generated and submitted to the regulatory authorities by the manufacturers.

Table 2. Experimentally determined pH-dependent API solubility using a globally harmonized protocol

<table>
<thead>
<tr>
<th>Medicine</th>
<th>pH</th>
<th>Highest ter. dose (mg)</th>
<th>MW of the solid used</th>
<th>Cs mean mg/mL a</th>
<th>DSV</th>
<th>Solubility Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexamethasone and dexamethasone micronized</td>
<td>1.2</td>
<td>6</td>
<td>392.46</td>
<td>0.595</td>
<td>10.08</td>
<td>Highly Soluble (BSC I/III)</td>
</tr>
<tr>
<td></td>
<td>4.5</td>
<td>6</td>
<td></td>
<td>0.704</td>
<td>8.52</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6.8</td>
<td>6</td>
<td></td>
<td>0.567</td>
<td>10.58</td>
<td></td>
</tr>
<tr>
<td>Dexamethasone phosphate b</td>
<td>1.2</td>
<td>7.2</td>
<td>472.4</td>
<td>3.009</td>
<td>2.39</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4.5</td>
<td>7.2</td>
<td></td>
<td>4.027</td>
<td>1.79</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6.8</td>
<td>7.2</td>
<td></td>
<td>3.97</td>
<td>1.81</td>
<td></td>
</tr>
<tr>
<td>Dexamethasone sodium phosphate c</td>
<td>1.2</td>
<td>7.8</td>
<td>516.4</td>
<td>0.078</td>
<td>100.00</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4.5</td>
<td>7.8</td>
<td></td>
<td>0.109</td>
<td>71.56</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6.8</td>
<td>7.8</td>
<td></td>
<td>0.062</td>
<td>125.81</td>
<td></td>
</tr>
</tbody>
</table>

a Experimental data showing the mean values from the three individual experiments
b Used at the dose of 7.2 mg of dexamethasone phosphate corresponding to 6 mg of dexamethasone
c Used at the dose of 7.8 mg of dexamethasone sodium phosphate corresponding to 6 mg of dexamethasone
Conclusions

Dexamethasone is a corticosteroid (Figure 1) that has been therapeutically used since the 1960s to reduce inflammation in a range of conditions, including inflammatory disorders and certain cancers. It was first included in the WHO Model List of Essential Medicines in 1977 and listed in multiple formulations for different indications. Dexamethasone is also included in the 95% of the national essential medicines lists redacted by Member States.

Today, dexamethasone is an off-patent medicine, generally affordable and available in most countries. However, some shortages have been reported in recent years. To address the COVID-19 emergency, it is recommended to facilitate the development and production of this medicine by the pharmaceutical industry through dissemination of the outcome of these equilibrium solubility studies and the provisional BCS-based classification for regulatory purposes.

At the same time, it is important to take the globally available API quantities and manufacturing capacity into consideration to be able to estimate the impact of repurposing dexamethasone from existing indications to the recent therapeutic opportunity for use in the treatment of patients with severe and critical COVID-19. Those considerations will be critical to ensure that patients have access to the safe, effective, quality and affordable medicines they need.

Figure 1. dexamethasone structure.
DISSOLUTION TEST FOR SOLID ORAL DOSAGE FORMS

Draft proposal for revision in *The International Pharmacopoeia*

**DRAFT FOR COMMENTS**

Please send any comments you may have on this draft working document to **Dr Herbert Schmidt**, Technical Officer, Norms and Standards for Pharmaceuticals, Technical Standards and Specifications (schmidt@who.int) by **31 August 2020**.

Working documents are sent out electronically and they will also be placed on the WHO Medicines website (http://www.who.int/medicines/areas/quality_safety/quality_assurance/guidelines/en/) for comments under the “Current projects” link.

If you wish to receive our draft guidelines, please send your e-mail address to jonessi@who.int and your name will be added to our electronic mailing list.

*Note from the Secretariat.* Chapter 5.5 Dissolution test for solid oral dosage form is based on the internationally-harmonized texts developed by the Pharmacopoeial Discussion Group (PDG). It is proposed to add to the chapter a section for the analysis of Suspensions and powders for suspension, which did not undergo harmonization and is not part of the PDG text. Comments are sought on the new section.

*Changes from the current text are indicated in the text by insert or delete.*
Revision of chapter 5.5 DISSOLUTION TEST FOR SOLID ORAL DOSAGE FORMS

5.5 DISSOLUTION TEST FOR SOLID ORAL DOSAGE FORMS

This text is based on the internationally-harmonized texts developed by the Pharmacopoeial Discussion Group (PDG). It has been developed in line with the style and requirements used in The International Pharmacopoeia. The additional sections on Suspensions and powders for oral suspension and on monographs of The International Pharmacopoeia are is not part of the PDG text.

For further guidance, see also the chapter Dissolution testing of tablets and capsules in the Supplementary Information section.

This test determines the amount of active ingredient(s) released from a solid oral dosage form, such as a tablet or a capsule, under controlled conditions using a known volume of dissolution medium within a predetermined length of time.

Basket apparatus. The assembly consists of the following: a vessel, which may be covered, made of glass or other inert, transparent material, which should not sorb, react or interfere with the preparation to be tested; a motor; a drive shaft; and a cylindrical basket (stirring element). The vessel is partially immersed in a suitable water-bath of any convenient size or heated by a suitable device such as a heating jacket. The water-bath or heating device permits maintaining the temperature inside the vessel at 37 ± 0.5 °C during the test. No part of the assembly, including the environment in which the assembly is placed, contributes significant motion, agitation or vibration beyond that due to the smoothly rotating stirring element. An apparatus that permits observation of the preparation and stirring element during the test is preferable. The vessel is cylindrical with a hemispherical bottom and a capacity of 1 litre. Its height is 160–210 mm and its inside diameter is 98–106 mm. Its sides are flanged at the top. A fitted cover may be used to retard evaporation. If a cover is used, it provides sufficient openings to allow ready insertion of the thermometer and withdrawal of samples. The shaft is positioned so that its axis is not more than 2 mm at any point from the vertical axis of the vessel and rotates smoothly and without significant wobble that could affect the results. A speed-regulating device is used that allows the shaft rotation speed to be selected and maintained at a specified rate within ± 4%.

Shaft and basket components of the stirring element are fabricated of stainless steel, type 316 or equivalent, to the specifications shown in Figure 1. A basket having a gold coating of about 2.5 µm (0.0001 inch) thick may be used. The dosage unit is placed in a dry basket at the beginning of each test. The distance between the inside bottom of the vessel and the bottom of the basket is maintained at 25 ± 2 mm during the test.
1. Screen with welded seam: 0.22–0.31 mm wire diameter with wire opening of 0.36–0.44 mm. After welding, the screen may be slightly altered.

2. Maximum allowable runout at “A” is 1.0 mm when the part is rotated on centre line axis with basket mounted.

*Figure 1. Basket stirring element*
Dimensions in millimetres.
A and B dimensions do not vary more than 0.5 mm when part is rotated on centre line axis. Tolerances are ± 1.0 mm unless otherwise stated.

*Figure 2. Paddle stirring element*

Dimensions in millimetres.
Paddle apparatus. Use the assembly from the basket apparatus except that a paddle formed from a blade and a shaft is used as the stirring element. The shaft is positioned so that its axis is not more than 2 mm from the vertical axis of the vessel at any point and rotates smoothly without significant wobble that could affect the results. The vertical centre line of the blade passes through the axis of the shaft so that the bottom of the blade is flush with the bottom of the shaft. The paddle conforms to the specifications shown in Figure 2. The distance of 25 ± 2 mm between the bottom of the blade and the inside bottom of the vessel is maintained during the test. The metallic or suitably inert, rigid blade and shaft comprise a single entity. A suitable two-part detachable design may be used provided the assembly remains firmly engaged during the test. The paddle blade and shaft may be coated with a suitable coating so as to make them inert. The dosage unit is allowed to sink to the bottom of the vessel before rotation of the blade is started. A small, loose piece of non-reactive material, such as not more than a few turns of wire helix, may be attached to dosage units that would otherwise float. An alternative sinker device is shown in Figure 3. Other validated sinker devices may be used.

Figure 3. Alternative sinker. A: acid-resistant wire clasp; B: acid-resistant wire support; Dimensions in millimeters.
Recommended procedure

Conventional-release (or immediate-release) dosage forms

Procedure. Place the stated volume of the dissolution medium (± 1%) in the vessel of the specified apparatus. Assemble the apparatus, equilibrate the dissolution medium to 37 ± 0.5 °C and remove the thermometer. The test may also be carried out with the thermometer in place, provided it is shown that results equivalent to those obtained without the thermometer are obtained. Place one dosage unit in the apparatus taking care to exclude air bubbles from the surface of the dosage unit. Operate the apparatus at the specified rate. Within the time interval specified, or at each of the times stated, withdraw a sample from a zone midway between the surface of the dissolution medium and the top of the rotating basket or blade not less than 1 cm from the vessel wall. Agitation/stirring should continue during sampling. Where multiple sampling times are specified replace the samples withdrawn for analysis with equal volumes of fresh dissolution medium at 37 °C or, where it can be shown that replacement of the medium is not necessary, correct for the volume change in the calculation. Keep the vessel covered for the duration of the test and verify the temperature (37 ± 0.5 °C) of the medium at suitable times. Perform the analysis as directed in the individual monograph using a suitable assay method. The samples are filtered immediately upon sampling, preferably by using in-line filtration or a filter in the tip of the sampling probe or both, unless filtration is demonstrated to be unnecessary. Use an inert filter that does not cause adsorption of the active ingredient or contain extractable substances that would interfere with the analysis. Centrifugation is not recommended unless validated for the specific test. The test is to be conducted with six dosage form units in parallel.

If automated equipment is used for sampling or the apparatus is otherwise modified verification is necessary that the modified apparatus will produce results equivalent to those obtained with the apparatus described in this chapter.

Dissolution medium. A suitable dissolution medium is used. The volume specified refers to measurements made between 20 °C and 25 °C. If the dissolution medium is a buffered solution adjust the solution so that its pH is within 0.05 units of the specified pH. Dissolved gases can cause bubbles to form which may change the results of the test. In such cases, dissolved gases must be removed prior to testing.¹

¹ One appropriate method of deaeration is as follows: heat the medium, while stirring gently, to about 41 °C, immediately filter under vacuum using a filter having a pore size of 0.45 µm or less, with vigorous stirring and continue stirring under vacuum for at least 5 minutes, preferably 15 minutes, until no more bubbles are observed. Other validated deaeration techniques for removal of dissolved gases may be used.
**Time.** Where a single time specification is given, the test may be concluded in a shorter period if the requirement for minimum amount dissolved is met. Samples are to be withdrawn only at the stated times, within a tolerance of ± 2%.

Determine the quantity of active ingredient dissolved at the specified time(s) indicated in the individual monograph. The result should be expressed as a percentage of the content stated on the label of the dosage form.

**Sustained-release (or extended-/prolonged-release) solid-dosage forms**

**Procedure.** Proceed as described for conventional-release dosage forms.

**Dissolution medium.** Proceed as described for conventional-release dosage forms.

**Time.** The test-time points, generally three, are expressed in hours.

**Delayed-release solid-dosage forms**

**Procedure.** Use method A or B.

**Method A**

- **Acid stage.** Place 750 mL hydrochloric acid (0.1 mol/L) VS in the vessel and assemble the apparatus. Allow the medium to equilibrate to a temperature of 37 ± 0.5 °C. Place one dosage unit in the apparatus, cover the vessel and operate the apparatus at the specified rate. After 2 hours of operation in hydrochloric acid (0.1 mol/L) VS, withdraw a sample of the fluid and proceed immediately as directed under buffer stage. Perform an analysis of the sample using a suitable assay method.

- **Buffer stage.** Complete the operations of adding and adjusting the pH within 5 minutes. With the apparatus operating at the rate specified, add to the fluid in the vessel 250 mL of a 0.2 M solution of trisodium orthophosphate R that has been equilibrated to 37 ± 0.5 °C. Adjust, if necessary, with hydrochloric acid (~70 g) TS or sodium hydroxide (~80 g/L) TS to a pH of 6.8 ± 0.05. Continue to operate the apparatus for 45 minutes or for the specified time. At the end of the time period, withdraw a sample of the fluid and perform the analysis using a suitable assay method.
Method B

- **Acid Stage.** Place 1000 mL of hydrochloric acid (0.1 mol/L) VS in the vessel and assemble the apparatus. Allow the medium to equilibrate to a temperature of 37 ± 0.5 °C. Place one dosage unit in the apparatus, cover the vessel and operate the apparatus at the specified rate. After 2 hours of operation in hydrochloric acid (0.1 mol/L) VS, withdraw a sample of the fluid and proceed immediately as directed under buffer stage. Perform an analysis of the sample using a suitable assay method.

- **Buffer stage.** For this stage of the procedure, use buffer that has previously been equilibrated to a temperature of 37 ± 0.5 °C. Drain the acid from the vessel and add 1000 mL of pH 6.8 phosphate buffer, prepared by mixing three volumes of hydrochloric acid (0.1 mol/L) VS with one volume of a 0.20 M solution of trisodium orthophosphate R and adjusting, if necessary, with hydrochloric acid (~70 g/L) TS or sodium hydroxide (~80 g/L) TS to a pH of 6.8 ± 0.05. This may also be accomplished by removing from the apparatus the vessel containing the acid and replacing it with another vessel containing the buffer and transferring the dosage unit to the vessel containing the buffer. Continue to operate the apparatus for 45 minutes or for the specified time. At the end of the time period, withdraw a sample of the fluid and perform the analysis using a suitable assay method.

*Time.* All test times stated are to be observed within a tolerance of ± 2%, unless otherwise specified.

**Acceptance criteria**

*Conventional-release (or immediate-release) dosage forms*

Unless otherwise specified in the individual monograph, the requirements are met if the quantities of active ingredient(s) dissolved from the dosage forms tested conform to Table 1. Continue testing through the three levels unless the results conform at either S₁ or S₂. The quantity, Q, is the specified amount of dissolved active ingredient expressed as a percentage of the labelled content; the 5%, 15% and 25% values in the acceptance table are percentages of the labelled content so that these values and Q are in the same terms.
Table 1

<table>
<thead>
<tr>
<th>Level</th>
<th>Samples tested</th>
<th>Acceptance criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>$S_1$</td>
<td>6</td>
<td>Each value is not less than $Q + 5%$.</td>
</tr>
<tr>
<td>$S_2$</td>
<td>6</td>
<td>Average value of the 12 dosage units ($S_1 + S_2$) is equal to or greater than $Q$ and no unit is less than $Q - 15%$.</td>
</tr>
<tr>
<td>$S_3$</td>
<td>12</td>
<td>Average value of 24 dosage units ($S_1 + S_2 + S_3$) is equal to or greater than $Q$; not more than 2 units are less than $Q - 15%$; no unit is less than $Q - 25%$.</td>
</tr>
</tbody>
</table>

Sustained-release (or extended-/prolonged-release) dosage forms

Unless otherwise specified in the individual monograph, the requirements are met if the quantities of active ingredient(s) dissolved from the dosage forms tested conform to Table 2. Continue testing through the three levels unless the results conform at either $L_1$ or $L_2$. Limits on the amounts of active ingredient(s) dissolved are expressed in terms of the labelled content. The limits embrace each value of $Q$, the amount dissolved at each specified fractional dosing interval. Where more than one range is specified, the acceptance criteria apply individually to each range.

Table 2

<table>
<thead>
<tr>
<th>Level</th>
<th>Samples tested</th>
<th>Acceptance criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>$L_1$</td>
<td>6</td>
<td>No individual value lies outside each of the stated ranges and no individual value is less than the stated amount at the final test time.</td>
</tr>
<tr>
<td>$L_2$</td>
<td>6</td>
<td>The average value of the 12 dosage units ($L_1 + L_2$) lies within each of the stated ranges and is not less than the stated amount at the final test time; none is more than 10% of the labelled content outside each of the stated ranges; and none is more than 10% of labelled content below the stated amount at the final test time.</td>
</tr>
<tr>
<td>$L_3$</td>
<td>12</td>
<td>The average value of the 24 dosage units ($L_1 + L_2 + L_3$) lies within the stated ranges and is not less than the stated amount at the final test time; not more than 2 of the 24 dosage units are more than 10% of labelled content outside each of the stated ranges; not more than 2 of the 24 dosage units are more than 10% of labelled content below the stated amount at the final test time; and none is more than 20% of labelled content outside each of the stated ranges or more than 20% of labelled content below the stated amount at the final test time.</td>
</tr>
</tbody>
</table>
Delayed-release dosage forms

*Acid stage.* Unless otherwise stated in the individual monograph, the requirements of this part of the test are met if the quantities, based on the percentage of the labelled content of active ingredient(s) dissolved from the dosage units tested conform to Table 3. Continue testing through the three levels unless the results of both acid and buffer stages conform at an earlier level.

**Table 3**

<table>
<thead>
<tr>
<th>Level</th>
<th>Samples tested</th>
<th>Acceptance criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>A₁</td>
<td>6</td>
<td>No individual value exceeds 10% dissolved.</td>
</tr>
<tr>
<td>A₂</td>
<td>6</td>
<td>Average value of the 12 dosage units ((A₁ + A₂)) is not more than 10% dissolved, and no individual value is greater than 25% dissolved.</td>
</tr>
<tr>
<td>A₃</td>
<td>12</td>
<td>Average value of 24 dosage units ((A₁ + A₂ + A₃)) is not more than 10% dissolved, and no individual value is greater than 25% dissolved.</td>
</tr>
</tbody>
</table>

*Buffer stage.* Unless otherwise specified in the individual monograph, the requirements are met if the quantities of active ingredients dissolved from the units tested conform to Table 4. Continue testing through the three levels unless the results of both stages conform at an earlier level. The value of Q in Table 4 is 75% dissolved unless otherwise specified. The quantity, Q, is the specified total amount of active ingredient dissolved in both the acid and buffer stages, expressed as a percentage of the labelled content. The 5%, 15% and 25% values in the table are percentages of the labelled content so that these values and Q are in the same terms.

**Table 4**

<table>
<thead>
<tr>
<th>Level</th>
<th>Samples tested</th>
<th>Acceptance criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>B₁</td>
<td>6</td>
<td>No value is less than (Q + 5%).</td>
</tr>
<tr>
<td>B₂</td>
<td>6</td>
<td>Average value of the 12 dosage units ((B₁ + B₂)) is equal to or greater than (Q), and no unit is less than (Q - 15%).</td>
</tr>
<tr>
<td>B₃</td>
<td>12</td>
<td>Average value of the 24 dosage units ((B₁ + B₂ + B₃)) is equal to or greater than (Q); not more than 2 units are less than (Q - 15%), and no unit is less than (Q - 25%).</td>
</tr>
</tbody>
</table>
Suspensions and Powders for oral suspension

Procedure. Prepare a suspension from Powders for oral suspension or re-suspend suspensions according to the product information. Avoid the introducing of bubbles into the sample to ensure the precision of dosing. Transfer to the dissolution apparatus, preferably by weight, the amount of sample indicated in the monograph. If no amount is given, use an amount that is equivalent to 1 unit dose or, in case the product has different doses depending on body weight or age, the amount of sample that corresponds to the highest unit dose to be administered at one time. If the product is labeled for single use, each sample should come from a different container/packet.

Monographs of The International Pharmacopoeia

The following additional statements apply to the individual monographs of The International Pharmacopoeia.

Qualification of dissolution test equipment and verification of system performance

Periodically qualify the equipment utilizing an “enhanced mechanical calibration”, such as the procedure described in the international standard procedure ASTM 2503 or a combination of a mechanical calibration to determine conformance of the dissolution apparatus to the dimensions and tolerances as given above and the analysis of suitable reference tablets to verify the performance of the testing system.

Test conditions

The following specifications are given in the individual monographs:

- the apparatus to be used;
- the composition and volume of the dissolution medium;
- the rotation speed of the paddle or basket;
- the preparation of the test and reference solutions;
- the time, the method and the amount of sample to be withdrawn or the conditions for continuous monitoring; the preparation of the sample and the reference solution;
- the method of analysis; and
- the limits of the quantity or quantities of active pharmaceutical ingredient(s) required to dissolve within a prescribed time.

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Dissolution media

If a buffer is added to the dissolution medium, adjust its pH to within ± 0.05 units of the prescribed value. In specific cases, and subject to approval by the relevant regional or national authority, dissolution media may contain enzymes and/or surfactants. The addition of enzymes may be considered, for example, for formulations containing gelatin when dissolution failures can be ascribed to the cross-linking of this excipient (e.g. hard and soft gelatin capsules; gelatin containing tablets). For the testing of preparations containing poorly aqueous-soluble active substances, modification of the medium may be necessary. A surfactant may be added only when the active pharmaceutical ingredient is insoluble over the entire physiological pH range, pH 1.2 to 6.8. In such circumstances, a low concentration of surfactant may be prescribed.

Below are some examples of dissolution media:

- **Dissolution buffer pH 1.2, TS**
  
  Dissolve 2 g of *sodium chloride* R in 800 mL of *water R*, adjust the pH to 1.2 with *hydrochloric acid* (~70 g/L) TS and dilute to 1000 mL with *water R*.

- **Dissolution buffer pH 2.5, TS**
  
  Dissolve 2 g of *sodium chloride* R in 800 mL of *water R*, adjust the pH to 2.5 with *hydrochloric acid* (~70 g/L) TS and dilute to 1000 mL with *water R*.

- **Dissolution buffer pH 3.5, TS**
  
  Dissolve 7.507 g of *glycine* R and 5.844 g of *sodium chloride* R in 800 mL of *water R*, adjust the pH to 3.5 with *hydrochloric acid* (~70 g/L) TS and dilute to 1000 mL with *water R*.

- **Dissolution buffer pH 4.5, TS1**
  
  Dissolve 2.99 g of *sodium acetate* R in 900 mL of water R, adjust the pH to 4.5 by adding about 14 mL of *acetic acid* (~120 g/L) TS and dilute to 1000 mL with *water R*.

- **Dissolution buffer pH 4.5, TS2**
  
  Dissolve 6.8 g of *potassium dihydrogen phosphate* R in 900 mL of *water R*, adjust the pH to 4.5 either with *hydrochloric acid* (~70 g/L) TS or *sodium hydroxide* (~80 g/L) TS and dilute to 1000 mL with *water R*. 
• **Dissolution buffer, pH 6.8, TS**

Dissolve 6.9 g of sodium dihydrogen phosphate R and 0.9 g of sodium hydroxide R in 800 mL of water R, adjust the pH to 6.8 with sodium hydroxide (~80g/L) TS and dilute to 1000 mL with water R.

• **Dissolution buffer, pH 6.8, 0.25% SDS TS**

Dissolve 6.9 g of sodium dihydrogen phosphate R, 0.9 g of sodium hydroxide R and 2.5 g of sodium dodecyl sulfate R in 800 mL of water R, adjust the pH to 6.8 with sodium hydroxide (~80g/L) TS and dilute to 1000 mL with water R.

• **Dissolution buffer pH 7.2, TS**

Dissolve 9.075 g of potassium dihydrogen phosphate R in water R to produce 1000 mL (solution A). Dissolve 11.87 g of disodium hydrogen phosphate R in sufficient water R to produce 1000 mL (solution B). Mix 300 mL of solution A with 700 mL of solution B.

• **Gastric fluid, simulated, TS**

Dissolve 2.0 g of sodium chloride R and 3.2 g of pepsin R in 7.0 mL of hydrochloric acid (~420 g/L) TS and sufficient water R to produce 1000 mL. This test solution has a pH of about 1.2.

• **Intestinal fluid pH 6.8, simulated, TS**

Mix 77.0 mL of sodium hydroxide (0.2 mol/L) VS, 250.0 mL of a solution containing 6.8 g potassium dihydrogen phosphate R and 500 mL of water R. Add 10.0 g pancreatin R, mix and adjust the pH with the buffer components to 6.8 ± 0.1. Dilute to 1000 mL with water R.

***
WHO Biowaiver Project - Preparation for cycle IV (2021): Prioritization exercise of active pharmaceutical ingredients on the WHO Model List of Essential Medicines for solubility determination and Biopharmaceutics Classification System-based classification

DRAFT FOR COMMENTS

Please send your comments to Dr Valeria Gigante, Technical Officer, Norms and Standards for Pharmaceuticals, Technical Standards and Specifications (gigantev@who.int), with a copy to Ms Claire Vogel (vogelc@who.int) before 20 August 2020. Please use our attached Comments Table for this purpose.

Our working documents are sent out electronically and they will also be placed on the WHO Medicines website (http://www.who.int/medicines/areas/quality_safety/quality_assurance/guidelines/en/) for comments under the “Current projects” link.

If you wish to receive all our draft guidelines, please send your email address to jonessi@who.int and your name will be added to our electronic mailing list.
WHO Biowaiver Project - Preparation for cycle IV (2021): Prioritization exercise of active pharmaceutical ingredients on the WHO Model List of Essential Medicines for solubility determination and Biopharmaceutics Classification System-based classification

1. Introduction and scope

In October 2019, the World Health Organization (WHO) Expert Committee on Specifications for Pharmaceutical Preparation (ECSPP) took note of the results achieved within the WHO Biowaiver Project and recommended continuing the Biopharmaceutics Classification System (BCS)-based classification of active pharmaceutical ingredients (APIs) contained in medicines listed in the WHO List of Essential Medicines (EML) (1) and prioritized according to public health priorities, Member States’ and WHO partners’ needs (2).

This document is intended to support the prioritization exercise of APIs that will be characterized in their solubility profile in cycle IV of the WHO Biowaiver Project, to take place in 2021 according to the ECSPP decision (2).

The WHO Biowaiver Project is organized into study cycles. Previous and current cycles are summarized below in order to provide an overview of the project development:

- 2018: cycle I; also referred to as the pilot phase.
- 2019: cycle II.
- 2020: cycle III; current study cycle.
- 2021: cycle IV. Note: this prioritization exercise is propaedeutic to this study cycle.

2. Background

When evaluating multisource (generic) products, the goal is to ensure that they have a comparable bioavailability (BA) with respect to their originator in order to assume comparability in their efficacy and safety profiles.

The WHO recognizes the possibility to waive in vivo bioequivalence studies for immediate-release, solid oral dosage forms APIs belonging to classes I and III according to the BCS, using comparative dissolution studies as surrogate proof of bioequivalence (3).

The aim of WHO biowaiver guidance documents is to reduce the risk of “bioinequivalence” to an acceptable level when granting biowaivers supporting pharmaceutical development and access to medicines. In this context, the solubility, the release from the drug product and the
subsequent absorption phase are considered critical processes underlying the equivalence of the test and reference product.

Equilibrium solubility profiles of APIs contained in medicines in the EML (1) can be used in conjunction with absorption/permeability data, finished pharmaceutical products (FPP) dissolution studies and comparative consideration of FPP-Excipient content in order to provide an informed decision on whether or not a biowaiver could be granted safely.

3. The revised WHO Biowaiver List

According to the recommendations from the Fifty-second, Fifty-third and Fifty-fourth ECSPP, the WHO Secretariat has published the revised WHO Biowaiver List: Proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate-release, solid oral dosage forms (4). The List is published in form of a living document and is meant to be regularly updated with new data and in accordance with the scientific and technical progress in this area. In addition, the List replaces the existing literature-based compilation published in 2006 that is reported in the Proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate-release, solid oral dosage forms (5).

The WHO Protocol to conduct equilibrium solubility experiments for the purpose of biopharmaceutics classification system-based classification of active pharmaceutical ingredients for biowaiver (6) is a tool available to all participants in this research. This protocol was developed with the purpose of providing a harmonized methodology for the equilibrium solubility experiments, thereby minimizing the variability amongst centres and studies.

4. Prioritization exercise of active pharmaceutical ingredients for Biopharmaceutical Classification System-based classification in WHO Biowaiver Project

A fourth set of APIs is proposed for BCS-based classification within the WHO Biowaiver Project. The criteria underpinning the APIs prioritization are as follows:

- the API must be contained in medicines listed in the EML;
- the API must be intended to be formulated as an immediate-release, solid oral dosage form;
- the API must belong to therapeutic areas of major public interest; and
- the specific physical-chemical properties for the API must be known.

Consideration should be given to narrow therapeutic index drugs (NTIs) as the BCS-based biowaiver approach is not considered to be a suitable surrogate for the establishment of bioequivalence of NTIs.
COVID-19 emergency use

During this prioritization exercise, propaedeutic to the study of the solubility profiles of APIs, particular attention has been made of potential candidates currently in clinical trials to address the COVID-19 pandemic. In addition great efforts are being made to conduct an expedite characterization to address this public health emergency. Dexamethasone followed by hydroxychloroquine are therefore suggested as high priority APIs for the solubility characterization.

Note: the inclusion of these substance in the list does not imply any endorsement from WHO but is intended only to promote access to medicines in case they will be deemed suitable for the intended purpose.

Proposed list of active pharmaceutical ingredients for study in cycle IV

The list of APIs to be prioritized for BCS-based classification in the next cycle of the project (cycle IV- 2021) are proposed below (in alphabetic order) and comments are invited. When providing comments, you might wish to indicate their order of priority.

<table>
<thead>
<tr>
<th>N</th>
<th>API contained in medicines on the EML</th>
<th>Therapeutic Area</th>
<th>Indication</th>
<th>Highest therapeutic single dose [mg]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Abacavir</td>
<td>Antiretrovirals</td>
<td>Treatment and prevention of HIV</td>
<td>600 mg</td>
</tr>
<tr>
<td>2</td>
<td>Dexamethasone</td>
<td>(1) Gastrointestinal medicines/ (2) Immunomodulators and antineoplastics/ (3) Medicines for other common symptoms in palliative care</td>
<td>(1) Antiemetic medicines/ (2) Acute lymphoblastic leukaemia (2) Multiple myeloma/ (3) Medicines for other common symptoms in palliative care</td>
<td>(1) (3) 0.75 to 9 mg a day depending on the disease being treated/ (2) 40 mg</td>
</tr>
<tr>
<td>3</td>
<td>Doxycycline</td>
<td>(1) Antiprotozoals (2) Antibacterials</td>
<td>(1) Antimalarial medicines (2) Antibiotics (access group)</td>
<td>(1) and (2) 100 mg (as hyclate)</td>
</tr>
<tr>
<td>4</td>
<td>Ethambutol</td>
<td>Antibacterials</td>
<td>Antituberculosis medicines</td>
<td>2 g</td>
</tr>
<tr>
<td>5</td>
<td>Isoniazid</td>
<td>Antibacterials</td>
<td>Antituberculosis medicines</td>
<td>300 mg</td>
</tr>
<tr>
<td></td>
<td>Drug Name</td>
<td>Category</td>
<td>Description</td>
<td>Dose</td>
</tr>
<tr>
<td>---</td>
<td>-----------</td>
<td>----------</td>
<td>-------------</td>
<td>------</td>
</tr>
<tr>
<td>6</td>
<td>Hydroxy-chloroquine</td>
<td>Medicines for diseases of joints</td>
<td>Disease-modifying agents used in rheumatoid disorders (DMARDs)</td>
<td>400 to 600 mg</td>
</tr>
<tr>
<td>7</td>
<td>Lamivudine</td>
<td>Antiretrovirals</td>
<td>Treatment and prevention of HIV</td>
<td>300 mg</td>
</tr>
<tr>
<td>8</td>
<td>Levonorgestrel</td>
<td>Medicines for reproductive health and perinatal care</td>
<td>Oral hormonal contraceptives</td>
<td>1.5 mg</td>
</tr>
<tr>
<td>9</td>
<td>Nifurtimox</td>
<td>Antiprotozoal medicines</td>
<td>African trypanosomiasis and American trypanosomiasis</td>
<td>10.0 mg/kg</td>
</tr>
<tr>
<td>10</td>
<td>Proguanil</td>
<td>Antiprotozoals</td>
<td>Antimalarial</td>
<td>100 mg (as hydrochloride)</td>
</tr>
</tbody>
</table>

**Note:** For exemption from an in vivo bioequivalence study, an immediate release, multisource product should exhibit very rapid or rapid in vitro dissolution characteristics that are comparable to the reference product. The excipients used in the formulation must be considered together with a risk-based approach in terms of the therapeutic index and clinical indications.
5. References


6. Further reading


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ZANAMIVIR

(ZANAMIVIRUM)

Draft proposal for inclusion for *The International Pharmacopoeia*

**DRAFT FOR COMMENTS**

Please send any comments you may have on this draft working document to **Dr Herbert Schmidt**, Technical Officer, Norms and Standards for Pharmaceuticals, Technical Standards and Specifications (email: schmidt@who.int) by **14 September 2020**.

Working documents are sent out electronically and they will also be placed on the WHO Medicines website (http://www.who.int/medicines/areas/quality_safety/quality_assurance/guidelines/en/) for comments under the “Current projects” link.

If you wish to receive our draft guidelines, please send your e-mail address to jonessi@who.int and your name will be added to our electronic mailing list.

*/Note from the Secretariat.* *It is proposed to include the monograph on Zanamivir in The International Pharmacopoeia. The monograph is based on a submission by a manufacturer and on laboratory investigations.*
ZANAMIVIR (ZANAMIVIRUM)

Molecular formula. $C_{12}H_{20}N_4O_{7,x}H_2O$

Relative molecular mass. 332.3 (anhydrous substance).

Graphic formula.

Chemical name. $(2R,3R,4S)$-3-Acetamido-4-carbamimidamido-2-[(1R,2R)-1,2,3-trihydroxypropyl]-3,4-dihydro-2H-pyran-6-carboxylic acid hydrate; CAS Reg. No. 551942-41-7.

Description. A white, or almost white, slightly hygroscopic powder.

Solubility. Slightly soluble in water R, practically insoluble in ethanol (~750 g/L) TS and dichloromethane R.

Category. Antiviral.

Storage. Zanamivir should be kept in tightly closed containers, protected from light.

Labelling. The designation on the container should state that the substance is in the form of the hydrate.

Additional information. Zanamivir may exhibit polymorphism.
Requirements

Definition. Zanamivir contains not less than 97.0% and not more than 102.0% of C_{12}H_{20}N_{4}O_{7}, calculated with reference to the anhydrous and solvent-free substance.

Identity tests

• Either test A or test B may be applied.

A. Carry out the test as described under 1.7 Spectrophotometry in the infrared region. The infrared absorption spectrum is concordant with the spectrum obtained from zanamivir RS or with the reference spectrum of zanamivir. If the spectra thus obtained are not concordant, repeat the test using the residues obtained by separately dissolving the test substance and zanamivir RS in a small amount of methanol R and evaporating to dryness. The infrared absorption spectrum is concordant with the spectrum obtained from zanamivir RS.

B. Carry out test B.1 or, where a diode array detector is available, test B.2.

B.1 Carry out the test as described under 1.14.4 High-performance liquid chromatography using the conditions given under “Assay”. The retention time of the principal peak in the chromatogram obtained with solution (1) corresponds to the retention time of the peak due to zanamivir in the chromatogram obtained with solution (2).

The absorption spectrum (1.6) of a 6 µg per mL solution of the test substance in phosphate buffer, pH 7.4, TS, when observed between 200 nm and 400 nm, exhibits a maximum at 260 nm.

B.2 Carry out the test as described under 1.14.4 High-performance liquid chromatography using the conditions given under “Assay”. Record the UV spectrum of the principal peak in the chromatograms with a diode array detector in the range of 200 nm to 400 nm. The retention time and the UV spectrum of the principal peak in the chromatogram obtained with solution (1) correspond to the retention time and UV spectrum of the peak due to zanamivir in the chromatogram obtained with solution (2).
Specific optical rotation (1.4). Dissolve 0.250 g in 25.0 mL of water R; sonicate until the substance is dissolved. Calculate with reference to the anhydrous and solvent-free substance; the specific optical rotation is between +36.0 to +38.5.

Sulfated ash (2.3). Not more than 1.0 mg/g, determined on 1.0 g.

Water. Determine as described under 2.8 Determination of water by the Karl Fischer method, Method A. The water content is not less than 40 mg/g and not more than 90 mg/g.

Heavy metals. Use 1.0 g for the preparation of the test solution as described under 2.2.3 Limit test for heavy metals, Procedure 5; determine the heavy metals content according to Method B; not more than 20 μg/g.

Related substances. Carry out the test as described under 1.14.4 High-performance liquid chromatography, using a stainless steel column (25 cm x 4.6 mm) packed with particles of cross-linked polyvinyl alcohol polymer with chemically bonded polyamine (5 μm).³

As the mobile phase, use a mixture of 60 volumes of acetonitrile R and 40 volumes of a 0.7 g/L solution of sulfuric acid (~1760 g/L) TS previously adjusted to pH 5.5 with ammonia (~1.7 g/L) TS.

Operate with a flow rate of 1.5 mL per minute. As a detector, use an ultraviolet spectrophotometer set at a wavelength of 234 nm and, for impurity I, at 210 nm. For identity test B.2, use a diode array detector in the range of 200 nm to 400 nm. Maintain the column temperature at 30 °C. Prior to first use, rinse the column with a 0.7 g/L solution of ammonium sulfate R at 1.5 mL per minute at 30 °C for about 1 hour. Prior to each use, rinse with the mobile phase for at least 8 hours.

³An Asahipak NH2P-50 column has been found suitable.
Prepare the following solutions. For solution (1), dissolve 23.0 mg of the test substance in 20 mL of water R and dilute to 50.0 mL with acetonitrile R[0.46 mg Z/mL]. For solution (2), dilute 1.0 mL of test solution (1) to 100.0 mL with mobile phase. Dilute 1.0 mL or this solution to 10.0 mL with mobile phase[0.1%]. For solution (3), dissolve 5 mg of zanamivir for system suitability RS (containing zanamivir and the impurities A, B, C and E) in 6 mL of water R and dilute to 10 mL with acetonitrile R. For solution (4), dissolve 3.00 mg of zanamivir impurity F RS in mobile phase and dilute to 100.0 mL with mobile phase. Dilute 1.0 mL of this solution to 100.0 mL with mobile phase. Dilute 3.0 mL of this solution to 20.0 mL with mobile phase[0.045 µg imp F/mL]. For solution (5), dissolve 10 mg of imidazole R in 40 mL of water R and dilute to 100 mL with acetonitrile R. Dilute 1.0 mL of this solution to 100.0 mL with mobile phase.

Inject alternately 20 µL of solutions (1), (2), (3), (4) and (5) and record the chromatogram for 3 times the retention time of zanamivir.

Use the chromatogram obtained with solution (3) to identify the peaks due to the impurities A, B, C and E. Use the chromatogram obtained with solution (4) to identify the peak due to impurity F. Use the chromatogram obtained with solution (5) to identify the peak due to impurity I.

The impurities are eluted, if present, at the following relative retention with reference to zanamivir (retention time about 9 minutes): impurity I about 0.26; impurity F about 0.30; impurity B about 0.60; impurity D about 0.71; impurity C about 0.77; impurity E about 0.83; impurity H 1.14; and impurity A about 2.75.

The test is not valid unless, in the chromatogram obtained with solution (3), the peak-to-valley ratio (Hp/Hv) is at least 2.5, where Hp is the height above the baseline of the peak due to impurity E, and Hv is the height above the baseline of the lowest point of the curve separating this peak from the peak due to impurity C. Also, the test is not valid unless, in the chromatogram obtained with solution (4), the peak due to impurity F is obtained with a signal-to-noise ratio of at least 10.

Measure the areas of the peaks corresponding to the impurities in the chromatograms obtained with solutions (1) and (4) and the area of zanamivir in the chromatogram obtained with solution (2).
Determine the percentage content of impurity F, considering the concentration of impurity F in solution (4) and the declared content of impurity F in zanamivir impurity F RS.

- The percentage content of impurity F is not greater than 0.01%.

For impurities other than impurity F, compare the peak areas of the impurities with the peak areas of zanamivir obtained with solution (2).

In the chromatogram obtained with solution (1):

- the area of any peak corresponding to impurity A is not greater than 5 times the area of the peak due to zanamivir in the chromatogram obtained with solution (2) (0.5 %);
- the area of any peak corresponding to impurity B is not greater than 3 times the area of the peak due to zanamivir in the chromatogram obtained with solution (2) (0.3 %);
- the area of any peaks corresponding to impurity E, when multiplied with a correction factor of 0.63, is not greater than 2 times the area of the peak due to zanamivir in the chromatogram obtained with solution (2) (0.2 %);
- the areas of any peaks corresponding to impurity C or D is not greater than 2 times the area of the peak due to zanamivir in the chromatogram obtained with solution (2) (0.2 %);
- the area of any peak corresponding to impurity I, recorded at 210 nm, when multiplied by a correction factor of 0.4, is not greater than the area of the peak due to zanamivir in the chromatogram obtained with solution (2), recorded at 210 nm (0.1 %);
- the area of any other impurity peak is not greater than the area of the peak due to zanamivir in the chromatogram obtained with solution (2) (0.10 %).

- Determine the sum of the areas of all impurity peaks recorded at 234 nm, other than any peak corresponding to impurity I and including the corrected area of any peak corresponding to impurity E. Disregard all peaks with an area of less than 0.5 times the area of the peak due to zanamivir in the chromatogram obtained with solution (2) (0.05%). Calculate the percentage concentration of these impurities using the area of any peak corresponding to zanamivir in the chromatogram obtained with solution (2) as a reference. Calculate the percentage concentration of impurity I using the area of any peak corresponding to zanamivir in the chromatogram obtained with solution (2) and recorded at 210 nm as a reference. Add the percentage concentration of impurity I to the percentage concentration of all other impurities. Disregard impurity I if the percentage concentration is less than 0.05%. The percentage concentration of all impurities is not greater than 1.2%.
**Assay.** Carry out the test as described under 1.14.4 *High-performance liquid chromatography*, using the conditions given above under "Related substances" with the following modifications.

Prepare the following solutions. For solution (1), dissolve 23.0 mg of the test substance in 20 mL of water R and dilute to 50.0 mL with acetonitrile R. Dilute 5.0 mL of this solution to 50.0 mL with mobile phase. For solution (2), dissolve 23.0 mg of zanamivir RS in 20 mL of water R and dilute to 50.0 mL with acetonitrile R. Dilute 5.0 mL of this solution to 50.0 mL with mobile phase.

Inject alternately 20 µL of solutions (1) and (2) and record the chromatogram for 3 times the retention time of zanamivir.

Measure the areas of the peaks corresponding to zanamivir obtained in the chromatograms of solutions (1) and (2) and calculate the percentage content of C₁₂H₂₀N₄O₇ in the sample using the declared content of C₁₂H₂₀N₄O₇ in zanamivir RS.

**Impurities**

A. (2R,3R,4S)-3-acetamido-2-[(1R,2R)-3-[[[(2R,3R,4S)-3-acetamido-6-carboxy-2-[(1R,2R)-1,2,3-trihydroxypropyl]-3,4-dihydro-2H-pyran-4-yl]carbamoyl]oxy]-1,2-dihydroxypropyl]-4-carbamimidamido-3,4-dihydro-2H-pyran-6-carboxylic acid (zanamivir dimer)(synthesis-related impurity).
B. 5-Acetamido-9-O-[4-amino-6-(1H-pyrazol-1-yl)-1,3,5-triazin-2-yl]-2,6-anhydro-3,4,5-trideoxy-4-guanidino-d-glycero-d-galacto-non-2-enonic acid (O-triazinyl zanamivir) (synthesis-related impurity).

C. (2R,3R,4S)-3-acetamido-4-amino-2-[(1R,2R)-1,2,3-trihydroxypropyl]-3,4-dihydro-2H-pyran-6-carboxylic acid (4-amino zanamivir) (synthesis-related impurity).

D. (2R,3R,4S)-3-acetamido-4-(carbamoylamino)-2-[(1R,2R)-1,2,3-trihydroxypropyl]-3,4-dihydro-2H-pyran-6-carboxylic acid (zanamivir urea analog) (synthesis-related impurity).
E. \((2R,3R,4S)-3\text{-acetamido}-4-(N\text{-carbamimidoylcarbamimidamido})-2-[(1R,2R)\text{-1,2,3-trihydroxypropyl}]\text{-3,4-dihydro-2H-pyran-6-carboxylic acid (4-biguanide zanamivir)}\) (synthesis-related impurity).

F. \(1H\text{-pyrazole-1-carboximidamide)}\) (synthesis-related impurity).

H. \((2R,3R,4R)-3\text{-acetamido-4-carbamimidamido}-2-[(1R,2R)\text{-1,2,3-trihydroxypropyl}]\text{-3,4-dihydro-2H-pyran-6-carboxylic acid (talo-zanamivir)}\) (synthesis-related impurity).

I. imidazole (synthesis-related impurity).
Reference substances to be established

Zanamivir for system suitability RS (containing zanamivir and the impurities A, B, C and E)
  • It is intended to refer to the corresponding reference substance established by the European Pharmacopoeia.

Zanamivir impurity F
  • It is intended to refer to the corresponding reference substance established by the European Pharmacopoeia.

Zanamivir RS
  • International Chemical Reference Substance to be established.

Reagents to be established

Ammonia (~1.7 g/L) TS

Ammonia (~17 g/L) TS, diluted to contain about 1.7 g of NH₃ per litre (approximately 0.1 mol/L).
ZANAMIVIR POWDER FOR INHALATION, PRE-METERED
(ZANAMIVIRI PULVIS PRO INHALATIONE)

Draft proposal for inclusion for *The International Pharmacopoeia*

**DRAFT FOR COMMENTS**

Please send any comments you may have on this draft working document to
Dr Herbert Schmidt, Technical Officer, Norms and Standards for Pharmaceuticals,
Technical Standards and Specifications (email: schmidt@who.int) by 14 September 2020.

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If you wish to receive our draft guidelines, please send your e-mail address to jonesi@who.int and your name will be added to our electronic mailing list.

*Note from the Secretariat:* It is proposed to include the monograph on Zanamivir powder for inhalation, pre-metered in The International Pharmacopoeia. *The monograph is based on a submission by a manufacturer and on laboratory investigations. It was developed in collaboration with the British Pharmacopoeia.*
ZANAMIVIR POWDER FOR INHALATION, PRE-METERED
(ZANAMIVIRI PULVIS PRO INHALATIONE)

**Category.** Antiviral, neuraminidase inhibitor.

**Labelling.** The designation of the container should indicate that the active ingredient is Zanamivir. The quantity of active ingredient is stated in terms of the equivalent amount of zanamivir per pre-metered unit.

**Additional information.** Zanamivir inhalation powder is listed on the third invitation to manufacturers of influenza-specific antiviral medicines to submit an Expression of Interest (EOI) for product evaluation to the WHO Prequalification Team: medicines.

**Labelling.** The label states the content of active ingredient per pre-metered unit.

**Manufacture.** The fine-particle characteristics of the aerosol cloud generated by the powder for inhalation is controlled so that a consistent portion is deposited in the lung. The test and limits for the aerodynamic assessment of the fine particles (fine particle dose) should be agreed with the relevant regulatory authority.

**Requirements**
Complies with the monograph on *Powders for Inhalation*.

**Definition.** Zanamivir powder for inhalation, pre-metered consists of Zanamivir, in the form of microfine powder or equivalent, either alone or combined with a suitable carrier. The pre-metered unit is loaded into a dry-powder inhaler to generate an aerosol. It contains not less than 90.0% and not more than 110.0% of the amount of C₁₂H₂₀N₄O₇ per pre-metered unit as stated on the label.
Identity tests
A. Transfer a quantity of the powder, nominally containing 10 mg of Zanamivir, into a 50 mL flask, add 50 mL of a mixture of 1 volume of formamide R and 2 volumes of methanol R and sonicate for five minutes to dissolve excipients. Filter the suspension and dry the residue at 120 °C for about one hour. Carry out the test as described under 1.7 Spectrophotometry in the infrared region. The infrared absorption spectrum is concordant with the spectrum obtained from zanamivir RS similarly treated.

B. Carry out test B.1 or, where a diode array detector is available, test B.2.
B.1 Carry out the test as described under 1.14.4 High-performance liquid chromatography using the conditions given under “Assay”. The retention time of the principal peak in the chromatogram obtained with solution (1) corresponds to the retention time of the peak due to zanamivir in the chromatogram obtained with solution (2). The absorption spectrum (1.6) of a solution of the powder in phosphate buffer, pH 7.5, TS, nominally containing 6 µg of Zanamivir per mL, when observed between 200 nm and 400 nm, exhibits a maximum at 260 nm.

B.2 Carry out the test as described under 1.14.4 High-performance liquid chromatography using the conditions given under “Assay”. Record the UV spectrum of the principal peak in the chromatograms with a diode array detector in the range of 200 nm to 400 nm. The retention time and the UV spectrum of the principal peak in the chromatogram obtained with solution (1) correspond to the retention time and UV spectrum of the peak due to zanamivir in the chromatogram obtained with solution (2).

Uniformity of delivered dose. Complies with the test for Uniformity of delivered dose stated under Powders for Inhalation using the following method of analysis.

Carry out the test as described under 1.14.4 High-performance liquid chromatography, using the conditions given below under “Assay”, with the following modifications.

Prepare as a diluent a mixture of 60 volumes of acetonitrile R and 40 volumes of water R. Prepare the following solutions. For solution (1), dissolve the collected dose in sufficient diluent to produce a solution, nominally containing 0.05 mg of Zanamivir per mL. For solution (2), use solution (2) as described under “Assay”.

504
Inject alternately 10 µL of solutions (1) and (2).

Calculate the content of C₁₂H₂₀N₄O₇ in each delivered dose using the declared content of C₁₂H₂₀N₄O₇ in zanamivir RS.

**Related substances.** Carry out the test as described under *1.14.4 High-performance liquid chromatography*, using the conditions given below under “Assay”, with the following modifications:

Prepare the following solutions. For solution (1), transfer a quantity of the powder, nominally containing 20 mg of Zanamivir, into a 50.0 ml volumetric flask. Add about 45 mL of mobile phase and sonicate for five minutes[BP: 10 mg Z in 25 ml]. Allow to cool to room temperatures and make up to volume with mobile phase[0.4 mg Z/mL]. For solution (2), dilute 1.0 mL of solution (1) to 200.0 mL with mobile phase[0.5%]. For solution (3), dissolve 5 mg of zanamivir for system suitability RS (containing zanamivir and the impurities A, B, C and E) in mobile phase and dilute to 10 mL with the same solvent. For solution (4), dissolve 2.67 mg of zanamivir impurity F RS in mobile phase and dilute to 100.0 mL with mobile phase. Dilute 1.0 mL of this solution to 100.0 mL with mobile phase. Dilute 3.0 mL of this solution to 20.0 mL with mobile phase[0.04 µg imp F/mL]. For solution (5), dilute 1.0 mL of solution (2) to 200.0 mL with mobile phase [0.1%].

Inject alternately 10 [20 ul in the API monograph. GSK advises to inject 10 ul] µL of solutions (1), (2), (3), (4) and (5) and record the chromatogram for 3[4 times BP] times the retention time of zanamivir.

Use the chromatogram obtained with solution (3) and the chromatogram supplied with zanamivir for system suitability to identify the peaks due to the impurities A, B, C and E. Use the chromatogram obtained with solution (4) to identify the peak due to impurity F. The impurities are eluted, if present, at the following relative retention with reference to zanamivir (retention time about 9 minutes): impurity F about 0.30; impurity B about 0.60; impurity D about 0.71; impurity C about 0.77; impurity E about 0.83; impurity H about 1.14; impurity A about 2.75[RR from GSK doc Zanamivir API test methods for WHO].
The test is not valid unless, in the chromatogram obtained with solution (3), the peak-to-valley ratio \((Hp/Hv)\) is at least 2.5, where \(Hp\) is the height above the baseline of the peak due to impurity E and \(Hv\) is the height above the baseline of the lowest point of the curve separating this peak from the peak due to impurity C. Also, the test is not valid unless in the chromatogram obtained with solution (5) the peak due to impurity F is obtained with a signal-to-noise ratio of at least 10.

Measure the areas of the peaks corresponding to the impurities of zanamivir in the chromatograms obtained with solution (1) and (4) and the area of zanamivir in the chromatogram obtained with solution (2).

Determine the percentage content of impurity F, considering the concentration of the impurity in solution (4) and the declared content of impurity F in zanamivir impurity F RS.
- The percentage content of impurity F is not greater than 0.01%.

For impurities other than impurity F, compare the peak areas of the impurities with the peak areas of zanamivir obtained with solution (2).

In the chromatogram obtained with solution (1):
- the area of any peak corresponding to impurity A is not greater than the area of the peak due to zanamivir in the chromatogram obtained with solution (2) (0.5 %);
- the area of any peak corresponding to impurity B is not greater than 0.6 times the area of the peak due to zanamivir in the chromatogram obtained with solution (2) (0.3 %);
- the area of any peaks corresponding to impurities C or D is not greater than 0.4 times the area of the peak due to zanamivir in the chromatogram obtained with solution (2) (0.2 %);
- the area of any peak corresponding to impurity E, when multiplied by a correction factor of 0.63, is not greater than 0.4 times the area of the peak due to zanamivir in the chromatogram obtained with solution (2) (0.2 %).
- The sum of the areas of all impurity peaks, including the corrected area of any peak corresponding to impurity E, is not greater than 2.4 times the area of the peak due to zanamivir in the chromatogram obtained with solution (2) (1.2%). Disregard all peaks with an area or less than the area of the peak due to zanamivir in the chromatogram obtained with solution (2) (0.1%).
**Assay.** Carry out the test as described under 1.14.4 High-performance liquid chromatography, using a stainless steel column (25 cm x 4.6 mm) packed with cross-linked polyvinyl alcohol polymer with chemically bonded polyamine (5 µm). As the mobile phase use a mixture of 60 volumes of acetonitrile R and 40 volumes of a 0.7 g/L solution of sulfuric acid (~1760 g/L) TS previously adjusted to pH 5.5 with ammonia (~1.7 g/L) TS.

Operate with a flow rate of 1.5 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 234 nm. For identity test B.2 use a diode array detector in the range of 200 nm to 400 nm. Maintain the column temperature at 30 °C.

Prepare as a diluent a mixture of 60 volumes of acetonitrile R and 40 volumes of water R. Prepare the following solutions. For solution (1), weigh and powder the contents of 24 pre-metered units. Transfer a quantity of the mixed contents, nominally equivalent to 50.0 mg of Zanamivir to a 100 mL volumetric flask. Add about 90 mL of water R and sonicate for 5 minutes. Allow to cool to room temperature and make up to volume with water R. Dilute 10.0 mL of this solution to 100.0 mL with diluent. For solution (2), dissolve 50.0 mg of zanamivir RS in diluent and dilute to 100.0 mL with the same solvent. Dilute 10.0 mL of this solution to 100.0 mL with diluent.

Inject alternately 10 µL each of solution (1) and (2). Record the chromatogram for 3 times the retention time of zanamivir.

Measure the areas of the peaks corresponding to zanamivir obtained in the chromatograms of solution (1) and (2) and calculate the percentage content of C₁₂H₂₀N₄O₇ per pre-metered unit using the declared content of C₁₂H₂₀N₄O₇ in zanamivir RS.

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4 An Asahipak NH2P-50 column has been found suitable.
Impurities
The impurities limited by the requirements of this monograph include those listed in the monograph on Zanamivir.

Reference substances to be established
Zanamivir for peak identification RS (containing zanamivir and the impurities A, B, C and E)
• It is intended to refer to the corresponding reference substance established for the European Pharmacopoeia.

Zanamivir impurity F
• It is intended to refer to the corresponding reference substance established by the European Pharmacopoeia.

Zanamivir RS
• ICRS to be established.

Reagent to be established
Ammonia (~1.7 g/L) TS

Ammonia (~17 g/L) TS, diluted to contain about 1.7 g of NH₃ per litre (approximately 0.1 mol/L).

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POWDERS FOR INHALATION

(PULVIS AD INHALATIONEM)

Draft proposal for inclusion in The International Pharmacopoeia

DRAFT FOR COMMENTS

Please send any comments you may have on this draft working document to Dr Herbert Schmidt, Technical Officer, Norms and Standards for Pharmaceuticals, Technical Standards and Specifications (schmidt@who.int) by 14 September 2020.

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If you wish to receive our draft guidelines, please send your e-mail address to jonessi@who.int and your name will be added to our electronic mailing list.

[Note from the Secretariat. It is proposed to include a general monograph on Powders for inhalation in The International Pharmacopoeia. The text was drafted based on the corresponding texts in the chapter Preparations for inhalation of the European Pharmacopoeia (Ph.Eur.) and the Japanese Pharmacopoeia (JP), which underwent bilateral harmonization between these pharmacopoeias. During the course of development, the text has undergone changes.]
POWDER FOR INHALATION
(INHALANDA)

This text was drafted based on the corresponding texts in the chapters on Preparation of inhalation of the European Pharmacopoeia and the Japanese Pharmacopoeia. During the course of development, the text has undergone changes.

**Definition**
Powders for inhalation are solid preparations intended to be converted to aerosols and orally administered to the lung using a breath-actuated inhaler.

Powders for inhalation may be supplied in single-dose containers for use in pre-metered inhalers or in multidose containers for use in either pre-metered or device-metered powder inhalers. Pre-metered inhalers are loaded with powders pre-dispersed in capsules or other suitable dosage forms. Device-metered inhalers may use a powder reservoir where the dose is created by a metering mechanism within the inhaler.

Powders for inhalation contain one or more active pharmaceutical ingredients. To facilitate the use of powders for inhalation, the active pharmaceutical ingredients may be combined with suitable excipients, e.g. a carrier substance. These excipients do not adversely affect the functions of the mucosa of the respiratory tract or its cilia.

**Additional information**
The delivered dose is the dose delivered from the inhaler. For some preparations, the labelled dose has been established as a metered dose or as a pre-metered dose. The metered dose is determined by adding the amount deposited on the inhaler to the delivered dose. It may also be determined directly.

**Manufacture**
The manufacturing processes for powders for inhalation should meet the requirements of good manufacturing practices (GMP).

The fine-particle characteristics of the aerosol cloud generated by the powder for inhalation is controlled so that a consistent portion is deposited in the lung.

During the development of a powder for inhalation that contains an antimicrobial preservative, the effectiveness of the chosen preservative shall be demonstrated to the satisfaction of the relevant regulatory authority.
In the manufacture, packaging, storage and distribution of powders for inhalation, suitable measures are taken to ensure their microbial quality. Recommendations on this aspect are provided in the chapter titled *Microbiological quality of non-sterile products: recommended acceptance criteria for pharmaceutical preparations* in the supplementary information section.

For a multidose powder inhaler, uniformity of a delivered dose must be ensured within a device (intra-inhaler) and between devices (inter-inhaler). For intra-inhaler testing, the uniformity of delivered dose tests are described below. For inter-inhaler testing, an example of a suitable procedure is to take 10 inhalers and collect a single dose from each inhaler, collecting the dose at the beginning (from 3 inhalers), middle (from 4 inhalers) and end (from 3 inhalers) of the number of doses stated on the label. Other inter-inhaler testing procedures are possible, where justified and authorized.

*Uniformity of delivered dose*

Powders for inhalation comply with the following test.

The test is carried out using a dose collection apparatus that must be capable of quantitatively capturing the delivered dose. A suitable dose collection apparatus is specified in Figure 1 and Table 1.

*Figure 1. Apparatus suitable for measuring the uniformity of delivered dose for powder inhalers*
Table 1. Specifications of the apparatus used for powder inhalers described in Figure 1.

<table>
<thead>
<tr>
<th>Code</th>
<th>Item</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Sample collection tube</td>
<td>Capable of quantitatively capturing the delivered dose, e.g. dose collection tube with dimensions of 34.85 mm ID × 12 cm length (e.g. product number XX40 047 00, Millipore Corporation, Bedford, MA 01732, USA, with modified exit tube, ID ≥ 8 mm, fitted with Gelman product number 61631), or equivalent.</td>
</tr>
<tr>
<td>B</td>
<td>Filter</td>
<td>47 mm filter, e.g. A/E glass fibre filter (Gelman Sciences, Ann Arbor, MI 48106, USA), or equivalent.</td>
</tr>
<tr>
<td>C</td>
<td>Connector</td>
<td>ID ≥ 8 mm, e.g., short metal coupling, with low-diameter branch to P3.</td>
</tr>
<tr>
<td>D</td>
<td>Vacuum tubing</td>
<td>A length of suitable tubing having an ID ≥ 8 mm and an internal volume of 25 ± 5 mL.</td>
</tr>
<tr>
<td>E</td>
<td>2-way solenoid valve</td>
<td>A 2-way, 2-port solenoid valve having a minimum airflow resistance orifice with ID ≥ 8 mm and an opening time ≤ 100 ms (e.g. type 256-A08, Bürkert GmbH, 74653 Ingelfingen, Deutschland), or equivalent.</td>
</tr>
<tr>
<td>F</td>
<td>Vacuum pump</td>
<td>Pump must be capable of drawing the required flow rate through the assembled apparatus with the powder inhaler in the mouthpiece adapter (e.g. product type 1023, 1423 or 2565, Gast Manufacturing Inc., Benton Harbor, MI 49022, USA), or equivalent. Connect the pump to the 2-way solenoid valve using short and/or wide (≥ 10 mm ID) vacuum tubing and connectors to minimize pump capacity requirements.</td>
</tr>
<tr>
<td>G</td>
<td>Timer</td>
<td>Timer capable of driving the 2-way solenoid valve for the required time period (e.g. type G814, RS Components International, Corby, NN17 9RS, UK), or equivalent.</td>
</tr>
<tr>
<td>P1</td>
<td>Pressure tap</td>
<td>2.2 mm ID, 3.1 mm OD, flush with internal surface of the sample collection tube, centred and burr-free, 59 mm from its inlet. The pressure tap P1 must never be open to the atmosphere. Differential pressure to atmosphere is measured at P1.</td>
</tr>
<tr>
<td>P2</td>
<td>Pressure measurements</td>
<td>Absolute pressures.</td>
</tr>
<tr>
<td>P3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>Flow control valve</td>
<td>Adjustable regulating valve with maximum Cv ≥ 1 (e.g. type 8FV12LNSS, Parker Hannifin plc., Barnstaple, EX31 1NP, UK), or equivalent.</td>
</tr>
</tbody>
</table>
Unless otherwise stated, determine the test flow rate and duration using the dose collection tube, the associated flow system, a suitable differential pressure meter and a suitable volumetric flowmeter, calibrated for the flow leaving the meter, according to the following procedure.

Prepare the inhaler for use as directed in the instructions to the patient and connect it to the inlet of the apparatus using a mouthpiece adapter to ensure an airtight seal. Use a mouthpiece adapter that ensures that the front face of the inhaler mouthpiece is flush with the front face of the sample collection tube. Connect one port of a differential pressure meter to the pressure reading point P1 in Figure 1, and let the other be open to the atmosphere. Switch on the pump, open the 2-way solenoid valve and adjust the flow control valve until the pressure drop across the inhaler is 4.0 kPa (40.8 cm H\(_2\)O) as indicated by the differential pressure meter. Remove the inhaler from the mouthpiece adapter and, without touching the flow control valve, connect a flowmeter to the inlet of the sampling apparatus. Use a flowmeter calibrated for the volumetric flow leaving the meter, or calculate the volumetric flow leaving the meter (\(Q_{\text{out}}\)) using the ideal gas law. For a meter calibrated for the entering volumetric flow (\(Q_{\text{in}}\)), use the following expression:

\[
Q_{\text{out}} = \frac{Q_{\text{in}} \times P_0}{P_0 - \Delta P}
\]

\(P_0\) = atmospheric pressure;
\(\Delta P\) = pressure drop over the meter.

If the flow rate is above 100 L/min, adjust the flow control valve to obtain a flow rate of 100 L/min (± 5%). Note the volumetric airflow rate exiting the meter and define this as the test flow rate, \(Q_{\text{out}}\), in litres per minute. Define the test flow duration, \(T\), in seconds so that a volume of 4 L of air is drawn from the mouthpiece of the inhaler at the test flow rate, \(Q_{\text{out}}\). Ensure that critical flow occurs in the flow control valve by the following procedure: with the inhaler in place and the test flow rate \(Q_{\text{out}}\) measure the absolute pressure on both sides of the control valve (pressure reading points P2 and P3 in Figure 1); a ratio P3/P2 of less than or equal to 0.5 indicates critical flow; switch to a more powerful pump and re-measure the test flow rate if critical flow is not indicated.

*Pre-metered inhalers.* Connect the inhaler to the apparatus using an adapter that ensures a good seal. Draw air through the inhaler using the predetermined conditions. Repeat the procedure until the number of deliveries that constitute the minimum recommended dose have been sampled. Quantitatively collect the contents of the apparatus and determine the amount of active substance. Repeat the procedure for a further 9 doses.
**Device-metered inhalers.** Connect the inhaler to the apparatus using an adapter that ensures a good seal. Draw air through the inhaler under the predetermined conditions. Repeat the procedure until the number of deliveries that constitute the minimum recommended dose have been sampled. Quantitatively collect the contents of the apparatus and determine the amount of active substance. Repeat the procedure for a further 2 doses.

Discharge the inhaler to waste until \((n/2) + 1\) deliveries remain, where \(n\) is the number of deliveries stated on the label. If necessary, store the inhaler to discharge electrostatic charges. Collect 4 doses using the procedure described above.

Discharge the inhaler to waste until 3 doses remain. If necessary, store the inhaler to discharge electrostatic charges. Collect 3 doses using the procedure described above. For preparations containing more than 1 active substance, carry out the test for uniformity of delivered dose for each active substance.

**Requirements.** The preparation complies with the test if 9 out of 10 results lie between 75 % and 125 % of the mean value and all lie between 65 % and 135 %. If 2 or 3 values lie outside the limits of 75 % to 125 %, repeat the test for 2 more inhalers. Not more than 3 of the 30 values lie outside the limits of 75 % to 125 % and no value lies outside the limits of 65 % to 135 %.

In justified and authorized cases, these ranges may be extended but no value should be greater than 150 % or less than 50 % of the mean value. Unless otherwise authorized, the mean value must be between 85 % and 115 % of the label claim for delivered dose.

**Fine particle dose**
Using a suitable and authorized method, calculate the fine particle dose.

**Number of deliveries per inhaler for multidose inhalers** (this test may be combined with the test for Uniformity of delivered dose).

Using the method described in the test for Uniformity of delivered dose above, discharge doses from the inhaler until empty, at the predetermined flow rate. Record the deliveries discharged.

**Requirements.** The total number of deliveries so discharged from the inhaler is not less than the number stated on the label.
Labelling
Every pharmaceutical preparation must comply with the labelling requirements established under Good Manufacturing Practice.

The label should include:
(1) the name of the pharmaceutical product;
(2) the name(s) of the active ingredients; International Nonproprietary Names (INNs) should be used wherever possible;
(3) the amount of active ingredient in the delivered dose or, if justified and authorized (e.g. where the dose has been established as a metered dose or as a pre-metered dose), the metered dose or the pre-metered dose;
(4) where applicable, the number of deliveries from the inhaler to provide the minimum recommended dose;
(5) the number of deliveries per inhaler
(6) the name and concentration of any antimicrobial preservative and the name of any other excipient;
(7) the batch (lot) number assigned by the manufacturer;
(8) the expiry date and, when required, the date of manufacture;
(9) any special storage conditions or handling precautions that may be necessary;
(10) directions for use, warnings, and precautions that may be necessary; and
(11) the name and address of the manufacturer or the person responsible for placing the product on the market.

***
GOOD MANUFACTURING PRACTICES:
WATER FOR PHARMACEUTICAL USE

DRAFT FOR COMMENTS

Please send your comments to Dr Sabine Kopp, Team Lead, Norms and Standards for Pharmaceuticals, Technical Standards and Specifications (kopps@who.int), with a copy to Ms Claire Vogel (vogelc@who.int) before 11 September 2020. Please use our attached Comments Table for this purpose.

Our working documents are sent out electronically and they will also be placed on the WHO Medicines website (http://www.who.int/medicines/areas/quality_safety/quality_assurance/guidelines/en/) for comments under the “Current projects” link.

If you wish to receive all our draft guidelines, please send your email address to jonessi@who.int and your name will be added to our electronic mailing list.
Background

Water quality, including microbiological and chemical quality, throughout production, storage and distribution processes, should be controlled. Unlike other product and process ingredients, water is usually drawn from an on-demand system and is not subject to testing and batch or lot release prior to use. The assurance of water quality to meet the on-demand expectation is, therefore, essential.

In recent years, following extensive consultations with stakeholders, several pharmacopoeias have adopted revised monographs on water for injection (WFI) that allow for production by non-distillation technologies. In 2017, the World Health Organization (WHO) Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP) recommended that the WHO Secretariat collect feedback on whether or not they should revise the WHO specifications and good manufacturing practices (GMP) on WFI, and how to do so. Following discussions during several consultations, the ECSPP agreed that the monograph in *The International Pharmacopoeia (Water for injections)* and the guideline *WHO Good manufacturing practices: water for pharmaceutical use (1)*, should both be revised to allow for technologies other than distillation for the production of WFI. In early 2019, the WHO Secretariat commissioned the preparation of a draft guidance text for the production of WFI by means other than distillation. Following several public consultations, the text was presented to the Fifty-fourth ECSPP. The Expert Committee adopted the *Production of water for injection by means other than distillation* guideline and recommended that it should also be integrated into WHO’s existing guideline on *Good manufacturing practices: water for pharmaceutical use*.

1. **Introduction and scope**

   1.1 This document concerns water for pharmaceutical use (WPU) produced, stored and distributed in bulk form. It provides information on different specifications for WPU; good practices for quality management of water systems; water treatment (production) systems; water storage and distribution systems; commissioning, qualification and validation; sampling and testing; and the routine monitoring of water.

   1.2 The focus of this document is on the treatment, storage and distribution of treated water used in pharmaceutical applications. It excludes the production, storage and usage of water in quality control laboratories.

   1.3 This document does not cover water for administration to patients in the formulated state or the use of small quantities of water in pharmacies to compound individually prescribed medicines.

   1.4 The document can be used in whole or in part, as appropriate, to the section and application under consideration.

   1.5 In addition to this document, the “Further reading” section at the end of this document includes some relevant publications that can serve as additional background material when planning, installing and operating systems intended to provide WPU.

   1.6 This document is supplementary to the *World Health Organization (WHO) Good manufacturing practices for active pharmaceutical ingredients* (2), and the *WHO Good manufacturing practices for pharmaceutical products: main principles* (3).
2. **Background to water requirements and uses**

2.1 Water is a widely used substance in the pharmaceutical industry and other establishments involved in manufacturing pharmaceutical products. It is extensively used as a raw material or starting material in the production, processing and formulation of active pharmaceutical ingredients (APIs), intermediates and finished pharmaceutical products (FPP), in the preparation of solvents and reagents, and for cleaning (e.g. washing and rinsing). Water has unique chemical properties due to its polarity and hydrogen bonds. These include a relatively high boiling point, high specific heat, cohesion, adhesion and density. These include contaminants that may represent hazards in themselves or that may be able to react with intended product substances, resulting in hazards to health. Water should therefore meet the required quality standards to mitigate these risks.

2.2 The microbiological and chemical quality of water should be controlled throughout production, storage and distribution. Water is not usually subjected to testing and batch or lot release before use. It is usually drawn from a system on-demand for use. While chemical test results can normally be obtained without delay, results from microbiological testing are normally available only after water has already been used as microbiological tests may require periods of incubation. The assurance of quality to meet the on-demand expectation of water is therefore essential.

2.3 To reduce the risks associated with the production, storage and distribution of water, and considering the properties and use, it is essential:

- to ensure the appropriate design, installation, operation and maintenance of WPU, pre-treatment, treatment, storage and distribution systems;
- to continuously or periodically perform sanitization;
- to take the appropriate measures in order to prevent chemical and microbial contamination; and
- to prevent microbial proliferation and endotoxin formation, where applicable.

2.4 Different grades of water quality exist. The appropriate water quality, meeting its defined specification (such as described in a pharmacopoeia), should be used for the intended application.

2.5 The application of specific types of water to processes and dosage forms should be considered.
2.6 Pharmaceutical manufacturers should use the appropriate grade of WPU during, for example, the manufacture of APIs and different dosage forms, for different stages in washing and cleaning, and in the synthesis of materials and products.

2.7 The grade of water used should take into account the nature and intended use of the intermediate or FPP and the stage in the manufacturing process at which the water is used.

2.8 Bulk water for injections (BWFI) should be used, for example, in the manufacture of injectable products, such as dissolving or diluting substances or preparations during the manufacturing of parenteral products, and for the manufacture of water for preparation of injections. BWFI should also be used for the final rinse after the cleaning of equipment and components that come into contact with injectable products, as well as for the final rinse in a washing process in which no subsequent thermal or chemical depyrogenization process is applied.

3. **General principles for pharmaceutical water systems**

3.1 Pharmaceutical water production, storage and distribution systems should be designed, installed, commissioned, qualified, validated, operated and maintained to ensure the consistent and reliable production of water of intended quality.

3.2 The capacity of these systems should be appropriate to meet the average and peak flow demand. These systems should be able to operate continuously for significant periods of time in order to avoid the inefficiencies and equipment stresses that occur when equipment cycles turn on and off too frequently.

3.3 Following an initial qualification such as installation qualification (IQ), operational qualification (OQ), performance qualification (PQ) and validation, the release and use of the system should be approved by the quality unit, e.g. quality assurance (QA).

3.4 Water sources and treated water should be monitored regularly for chemical, microbiological and, where appropriate, endotoxin contamination. The performance of water treatment, storage and distribution systems should also be monitored. Records of the results monitored, trend analysis and any actions taken should be maintained.
4. Water quality specifications

4.1 Pharmacopoeial specifications

4.1.1 Pharmacopoeias include specifications for water used in bulk and in dosage forms. Where this document refers to specifications, such as those in pharmacopoeias, the relevant, current publications should be used. This document does not attempt to duplicate such material. Where subtle points of difference exist between pharmacopoeial specifications, the manufacturer should choose the appropriate specification in accordance with the related marketing authorization submitted to the relevant medicine’s regulatory authority. Pharmacopoeial requirements or guidance for WPU are described in national, regional and international pharmacopoeias (4) and limits for various impurities, or classes of impurities, are either specified or recommended. Requirements or guidance are given in pharmacopoeias on the microbiological and chemical quality of water.

4.2 Drinking-water

Note: The requirements for the design, construction and commissioning of drinking water systems are usually controlled through local regulations. Drinking water systems are not usually qualified or validated.5

4.2.1 The quality of drinking-water is covered by the WHO guidelines for drinking-water quality (5) and standards from the International Organization for Standardization (ISO) and other regional and national agencies. Drinking-water should comply with the relevant regulations laid down by the competent authority.

4.2.2 Drinking-water may be derived from a natural or stored source. Examples of natural sources include springs, wells, rivers, lakes and the sea. The condition of the source water should be considered when choosing a treatment to produce drinking-water.

4.2.3 Drinking-water should be supplied under continuous positive pressure by a plumbing system free from any defects that could lead to the contamination of any product.

4.2.4 Drinking-water may be derived from a public water supply system. This includes an off-site source, such as a municipality. The appropriate drinking-water quality should be ensured by the supplier. Tests should be conducted to guarantee that the drinking-water delivered is of drinking quality. This testing is typically performed on water from the water source. Where required, the quality may be achieved through the appropriate processing on-site.

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5 See documents listed under Further reading
4.2.5 Where drinking-water is purchased in bulk and transported to the user by water tanker, controls should be put into place to mitigate any risks associated therewith. Vendor assessment and authorized certification activities, including confirmation of the acceptability of the delivery vehicle, should be undertaken in a way similar to that used for any other starting material.

4.2.6 It is the responsibility of the pharmaceutical manufacturer to assure that the source water supplying the purified water (PW) treatment system meets the appropriate drinking-water requirements. In these situations, the point at which drinking-water quality is achieved should be identified and a water sample taken and tested at defined intervals thereafter.

4.2.7 If drinking-water is used directly in certain stages of pharmaceutical manufacture, such as in the production of APIs or in the feedwater for the production of higher qualities of WPU, then testing should be carried out periodically by the water user’s site; for example, at the point of use, to confirm that the quality meets the standards required for drinking-water. The selection of tests to be performed, and the frequency of testing, should be based on risk assessment.

4.2.8 Where drinking-water is produced through the treatment of raw water by a system on-site, the system configuration and water-treatment steps used should be described.

4.2.9 Examples of typical processes employed to produce drinking-water may include:

- desalination;
- filtration;
- softening;
- disinfection or sanitization (e.g. by sodium hypochlorite (chlorine));
- iron (ferrous) removal;
- precipitation; and
- the reduction of concentration of specific inorganic and/or organic materials.

4.2.10 Controls should be implemented to prevent the microbiological contamination of sand filters, carbon beds and water softeners. The techniques selected should be appropriate and may include backflushing, chemical and/or thermal sanitization and frequent regeneration.

4.2.11 The quality of drinking-water should be monitored routinely to account for environmental, seasonal or supply changes which may have an impact on the source water quality.
4.2.12 Where drinking-water is stored and distributed by the user, the storage and distribution systems should minimize the degradation of the water quality prior to use. After any such storage, testing should be carried out routinely and in accordance with a defined procedure. The storage and distribution of drinking-water should be done in a manner to ensure a turnover or recirculation of the water, if possible.

4.2.13 The equipment and systems used to produce and store drinking-water should be able to be drained or flushed, and sanitized.

4.2.14 Storage tanks should be closed with appropriately protected vents and should allow for visual inspection.

4.2.15 Distribution pipework should be able to be drained or flushed and sanitized.

4.2.16 The scope and extent of commissioning and qualification for the system should be identified and justified.

4.2.17 The results from testing drinking-water should be subjected to statistical analysis in order to identify trends and changes. If the drinking-water quality changes significantly, but is still within specification, the direct use of this water as a WPU, or as the feedwater to downstream treatment stages, should be reviewed for any potential risks. The appropriate action should be taken and documented.

4.2.18 Changes to a system or to its operation should be made in accordance with change control procedures.

4.2.19 Additional testing should be considered if there is any change in the raw water source, treatment techniques or system configuration.

4.3 Bulk purified water

4.3.1 Bulk purified water (BPW) should meet the relevant pharmacopoeial specifications for chemical and microbiological purity.

4.3.2 BPW should be prepared from drinking-water as a minimum-quality feedwater.

4.3.3 Any appropriate, qualified purification technique, or sequence of techniques, may be used to prepare BPW. BPW may be prepared by, for example, a combination of ion exchange, reverse osmosis (RO), RO/electro-deionization (EDI), and ultrafiltration.
4.3.4 The following should be considered when configuring a water purification system or defining user requirement specifications (URS):

- the quality of feedwater and its variation over seasons;
- the quantity of water required by the user;
- the required water-quality specification;
- the sequence of purification stages required;
- appropriately located sampling points designed in such a way so as to avoid potential contamination;
- unit process steps provided and documented with the appropriate instrumentation to measure parameters such as flow, pressure, temperature, conductivity and total organic carbon;
- material of construction;
- sanitization strategy;
- main components;
- interlocks, controls and alarms; and
- electronic data storage, system security and audit trail.

4.3.5 Ambient-temperature systems such as ion exchange, RO and ultrafiltration are especially susceptible to microbiological contamination, particularly when equipment is static during periods of no or low demand for water. Sanitization at defined intervals (e.g. based on the data collected from the system validation and system behaviour), as well as other controls, should be defined to prevent and minimize microbiological contamination.

4.3.6 Methods for sanitizing each stage of purification should be appropriate and validated. Where agents are used for sanitization, their removal should be validated.

4.3.7 The following controls should be considered in order to minimize and prevent microbial contamination:

- the maintenance of water flow at all times in order to prevent water from stagnating;
- control of temperature in the system, for example, by heat exchangers or room cooling in order to reduce the risk of microbial growth;
- the provision of ultraviolet disinfection at appropriate locations in the system;
- the use of water-treatment system components that can periodically be thermally sanitized above 70 °C for a defined period of time, or chemically sanitized using, for example, ozone, hydrogen peroxide and/or peracetic acid; and
- a combination of thermal and chemical sanitization, if required.
4.3.8 BPW should have appropriate alert and action limits for chemical and microbiological purity determined from a knowledge of the system and data trending. BPW should be protected from recontamination and microbial proliferation.

4.4 Bulk water for injections

4.4.1 BWFI should meet the relevant pharmacopoeial specifications for chemical and microbiological purity (including endotoxins). BWFI is the highest quality of pharmacopoeial WPU.

4.4.2 BWFI is not a final dosage form. It is an intermediate bulk product suitable to be used as an ingredient during formulation.

4.4.3 As a robust technique should be used for the production of BWFI, the following should be considered when configuring a water purification system or defining URS:

- the quality of feedwater and its variation over seasons;
- the quantity of water required by the user;
- the required water-quality specification;
- the sequence of purification stages required, where appropriate;
- based on the selection of components, material of construction and type of system, the appropriate URS, qualification and validation;
- the optimum generator size or generators with variable control to avoid over-frequent start/stop cycling;
- blow-down and dump functions;
- cool-down venting to avoid contamination ingress;
- appropriately located sampling points designed in such a way so as to avoid potential contamination;
- appropriate instrumentation to measure parameters as required;
- sanitization strategy;
- interlocks, controls and alarms; and
- electronic data storage, system security and audit trail.

4.4.4 BWFI may be prepared, for example, by distillation as the final purification step. Alternatively, BWFI may be produced by means other than distillation. Techniques such as deionisation, electro deionization, nano filtration, ultrafiltration, water softening, descaling, pre-filtration and degasification, ultraviolet treatment, along with other techniques, may be considered in conjunction with a single or double pass RO system. For full details, see Production of water for injection by means other than distillation as published in the WHO Technical Report Series, No. 1025, Annex 3, 2020 (6).
4.4.5 BWFI should have appropriate microbial and chemical alert and action limits and should also be protected from recontamination and microbial proliferation.

4.5 Other grades of water

4.5.1 When a specific process requires a special non-pharmacopoeial grade of water, its specification must be documented within a company’s quality system. As a minimum, it must meet the pharmacopoeial requirements relating to the grade of WPU required for the type of dosage form or process step.

5. General considerations for water purification systems

5.1 Pharmaceutical manufacturers should apply the current principles of quality risk management (7) in selecting and using the appropriate water purification systems. An appropriate method for the production of WPU should be used.

5.2 Risks and controls should be identified for each stage of the production, storage, distribution, use and monitoring of WPU.

5.3 Risks identified should be evaluated in order to determine the scope and extent of validation and qualification of the system, including the computerized systems used for the production, control and monitoring of WPU.

5.4 Risk management should be an ongoing part of the quality management process for WPU. A mechanism to review or monitor events associated with the production, storage, distribution and use of WPU should be implemented.

5.5 Procedures for managing changes and deviations should be followed. Where applicable, the appropriate risk and impact assessments should be carried out where changes and deviations are managed.
5.6 The chosen water purification system, method or sequence of purification steps must be appropriate in order to ensure the production of water of the intended grade. Based on the outcome of the risk assessment, the following should at least be considered when selecting the water treatment system and method:

- the quality of the available feedwater and the variation over time (seasonal changes);
- the availability of suitable support facilities for the system (e.g. electricity, heating, steam, chilled water and compressed air);
- the extent of pre-treatment required;
- the sequence of purification steps required;
- the design and location of sampling points;
- the sanitization strategy;
- the availability of water-treatment equipment on the market;
- the reliability and robustness of the water-treatment equipment in operation;
- the yield or efficiency of the purification system;
- the ability to adequately support and maintain the water purification equipment;
- the continuity of operational usage considering hours/days/years and planned downtime;
- the total life-cycle of the system (including capital, operation and maintenance);
- the final water quality specification; and
- the minimum, average and maximum quantity of water required by the user.

5.7 The specifications for water purification equipment, storage and distribution systems should take into account the following:

- the location of the plant room;
- the extremes in temperature that the system will encounter;
- the risk of contamination, for example, from materials of construction (contact materials) and the environment;
- the adverse impact of adsorptive contact materials;
- hygienic or sanitary design, where required;
- corrosion resistance;
- freedom from leakage;
- system configuration to avoid or minimize proliferation of microbiological organisms;
- tolerance to cleaning and sanitizing agents (thermal and/or chemical);
- the sanitization strategy;
- system capacity and output requirements; and
- the provision of all necessary instruments, test and sampling points in order to allow for all the relevant critical quality parameters of the complete system to be monitored.
5.8 The design, configuration and layout of the water purification equipment, storage and distribution systems should also take into account the following physical considerations:
- the ability to collect samples;
- the space available for the installation and environment around the system;
- structural loadings on buildings;
- the provision of adequate access for maintenance and monitoring; and
- the ability to safely handle regeneration and sanitization chemicals.

6. Water storage and distribution systems

6.1 Where drinking water is stored and distributed, the appropriate controls should be determined and implemented in order to mitigate risks. This applies to all stages in the supply, storage and distribution of drinking-water.

6.2 The water storage and distribution systems for PW and BWFI should be appropriately designed, installed, qualified, operated and maintained in order to ensure the storage and distribution of water is of consistent quality to the user points.

7. Good practices for water systems

7.1 The components of water systems, including but not limited to pipework, valves and fittings, seals, diaphragms and instruments, should be appropriate and should satisfy the following objectives for the full range of the working temperature and potential chemicals that will come into contact with the system at rest, in operation and during sanitization. The construction materials should be of an appropriate quality.

7.2.1 As a minimum, the following design and construction practices should be considered.

For drinking water storage, supply and distribution systems on-site

Materials of construction should be selected based on the following requirements:
- ability to operate at the temperatures/pressures required;
- lack of impact to the final water quality;
- resistant to any sanitizing chemicals that may be used;
- threaded and flanged joints are permitted; and
- sample valves should preferably be of sanitary design.

Note that the system may have a design life at the end of which it should be replaced/adequately maintained.
For purified water and bulk water for injection systems

Note: Construction standards are generally aligned with potable water standards up to the process stage.

- Materials of construction should be appropriate. It should be non-leaching, non-adsorbing, non-absorbing and resistant to corrosion. Stainless-steel grade 316L or PVDC is generally recommended. The choice of material should take into account the intended sanitization method.
- Stainless steel systems should be orbitally welded, with manual welds where necessary. Inter-weldability between materials should be demonstrated with the maintenance of weld quality through a defined process. Documentation for such a system should be kept and should include, as a minimum, the qualification of the welder, welder set-up, work session test pieces (coupons or weld samples), proof of quality of gas used, welding machine calibration record, weld identification and heat numbers, and logs of all welds. Records, photographs or videos of inspection of a defined proportion of welds (e.g. 100% manual welds, 10% orbital welds).
- Joints should be made using sanitary connections, for example, Tri-clover joints. Threaded joints should not be permitted. Polyvinylidene fluoride or polyvinylidene difluoride (PVDF) systems should be fusion joined and visually inspected.
- Passivation should be considered for stainless steel systems, for example, for non-electropolished surfaces (after initial installation and after significant modification) in accordance with a documented procedure defining the solution to be used, its concentration, the temperature and contact time.
- Internal finish should be smooth.
- Flanges, unions and valves should be of a hygienic or sanitary design. Valves should be diaphragm type forged or machined body, with points of use constructed so that they can drain. Sample valves should be sanitary type with the surface roughness of 1.0 micron for PW and WFI systems and are typically installed between process stages and on the distribution loop return. The appropriate checks should be carried out in order to ensure that the correct seals and diaphragms are used and that they are fitted and tightened correctly.
- The system should be installed to promote drainability with a recommended minimum slope of 1/100.
- Where appropriate, pressure or hydro-tests for leaks, spray-ball functionality test and flow turbulence should be considered.
- Provision should be made for on-line measurement for total organic carbon (TOC), conductivity and temperature.
• Documents should provide evidence of system components and qualification. These include as applicable drawings, original or certified copies of certificates of conformity for materials of construction, records of on-site tests performed, weld/joining records, calibration certificates, system pressure test records and records of passivation.

8. System sanitization and bioburden control

8.1 Water-treatment, storage and distribution systems should be subjected to controls that will reduce the risk of contamination and the proliferation of microbiological organisms.

8.2 Controls may include using chemical and/or thermal sanitization procedures as appropriate (e.g. production, storage and distribution). The procedure and conditions used, such as times and temperatures, as well as the frequency, should be defined and proven to be effective for sanitizing all relevant parts of the system. The techniques employed should be considered during the design stage of the system as the procedure and technique may impact on the components and materials of construction.

8.3 Systems that operate and are maintained at elevated temperatures (e.g. > 70 °C) are generally less susceptible to microbiological contamination than systems that are maintained at lower temperatures. When lower temperatures are required due to the water treatment processes employed, or the temperature requirements for the water in use, special precautions should be taken to prevent the ingress of contaminants including microorganisms (see section 9.2 for guidance).

8.4 Where the chemical sanitization of the water systems is part of the biocontamination control programme, a validated procedure should be followed in order to ensure that the sanitizing process selected is effective and that the sanitizing agent has been effectively removed.

8.5 Records of sanitization should be maintained.
8.6 Other control techniques to be considered may include:
- The maintenance of a continuous circulation of water maintaining turbulent flow evidenced by, for example, a Reynolds number of > 4000.
- Ensuring hygienic design, including the use of zero dead leg diaphragm valves and minimizing dead legs. Areas of possible dead legs should be measured and calculated.
- Installing pipework in a manner to allow for full drainage, if required. A guidance figure for the slope is not less than 1:100.
- Considering the use of ultraviolet lamps in the system where needed with independent monitoring.
- Maintaining the system at an elevated temperature (e.g. > 70 °C), if required.

9. **Storage vessels**

9.1 Storage vessels should be appropriate for their intended use.

9.2 As a minimum, the following should be considered:
- the design and shape;
- the provision for drainage of water from the vessel, when required;
- construction materials;
- capacity, including buffer capacity, between the steady state, water generation rate and the potentially variable simultaneous demand from user points, short-term reserve capacity in the event of failure of the water-treatment system or the inability to produce water (e.g. due to a regeneration cycle);
- prevention of stagnant water in the vessel (e.g. the headspace where water droplets can accumulate) and the need for the use of a spray-ball or distributor devices to wet the inner surfaces of the vessel;
- limitation and design of nozzles within the storage vessels;
- the fitting of bacteria-retentive, hydrophobic vent filters which are tested for their integrity at appropriate intervals;
- the fitting of sanitary design bursting discs provided with external rupture indicators to ensure that loss of system integrity is detected;
- the design and sanitation, as required, of level indicators;
- the design and location of valves, sampling points and monitoring devices and sensors; and
- the need for heat exchangers or jacketed vessels. Where these are used, double tube sheet or double plate heat exchangers should be used, ideally with the utility pressure less than the system pressure to minimise the risk of contamination.
10. Water distribution

10.1 The water distribution system should be designed as a loop, with continuous circulation of BPW and BWFI. Where this is not the case, the appropriate justification for using a non-recirculating one-way system should be provided as well as robust measures implemented to monitor these.

10.2 As a minimum, the following should be considered:
   - controls to minimize proliferation of contaminants;
   - material of construction, joints and impact as a result of sanitization; and
   - the design and location of devices, sensors and instruments such as flow meters, conductivity sensors, TOC analysers and temperature sensors.

10.3 Filtration should not be used in distribution loops or at take-off user points.

10.4 Where heat exchangers are used, they should be arranged in continually circulating loops or sub-loops in order to avoid unacceptable static water in the system.

10.5 When the temperature is reduced for processing purposes, the reduction should occur for the minimum necessary time. The cooling cycles and their duration should be proven satisfactory during the qualification of the system.

10.6 Circulation pumps should be of a sanitary design with the appropriate seals to prevent contamination of the system.

10.7 Where stand-by pumps are provided, they should be configured or managed to avoid dead zones trapped within the system.

10.8 Consideration should be given to preventing contamination in systems where parallel pumps are used, especially if there is stagnant water when one of the pumps is not being used.
11. **Operational considerations including some qualification and validation principles**

11.1 Water systems should be appropriately qualified and validated \(^{(8)}\). The scope and extent of qualification should be determined based on risk assessment.

11.2 When commissioning work is done, this should be documented. Commissioning is not a replacement for qualification.

11.3 In order to demonstrate the reliability and robustness of a system and its performance, a three-phase approach should be used for validation, covering at least one year of operation over different seasons. Tests on the source water (drinking-water) should be included within the validation programme and continued as part of the routine monitoring, and these results should meet specifications.

**Phase 1**

Phase I should cover a period of at least two weeks.

Operational procedures and schedules should cover at least the following activities and testing approaches:

- chemical and microbiological testing in accordance with a defined plan;
- sample, test and monitoring of the incoming feedwater to verify its quality;
- sample, test and monitoring after each step in the purification process;
- sample, test and monitoring at each point of use and at other defined sample points including the end of the distribution loop;
- verification of operating ranges;
- demonstrate performance of operating, cleaning, sanitizing and maintenance procedures;
- demonstrate the consistent production and delivery of product water of the required quality and quantity;
- provisional alert and action levels; and
- test-failure procedure.

The system should be monitored intensively for its performance. Water should not be used for product manufacturing during this phase.
Phase 2

Phase 2 should cover at least a further test period of two weeks after the satisfactory completion of Phase 1. The system should be monitored while deploying all the standard operating procedures (SOPs). The sampling program should be generally the same as in Phase 1. The use of the water for product manufacturing purposes during this phase may be acceptable, provided that Phase 1 and Phase 2 data demonstrate the appropriate water quality and the practice is approved by QA.

The approach should also:
- demonstrate consistent system operation within established ranges; and
- demonstrate consistent production and delivery of water of the required quantity and quality when the system is operated in accordance with the SOPs.

Phase 3

Phase 3 should cover at least a further 12 months after the satisfactory completion of Phase 2. The sample locations, sampling frequencies and tests may be reduced according to a routine plan which should be based on the established procedures and data from Phase 1 and Phase 2. Data should be trended, for example, quarterly and a system review should be undertaken after the completion of Phase 3 as part of the evaluation of system performance capability. The appropriate action should be taken where such a need is identified.

Water can be used during this phase. The data and information obtained during Phase 3 should demonstrate the reliable performance of the system over this period of time covering the different seasons.

12. Continuous system monitoring

12.1 The system should be subject to continuous monitoring.

12.2 A monitoring plan should be followed where samples are collected in accordance with a written procedure.

12.3 A combination of online and offline instruments, linked to appropriately qualified alarm systems, should be used. Parameters such as flow, pressure, temperature, conductivity and TOC should be monitored with online devices with periodic offline testing to confirm the results. Other parameters may be monitored through offline testing.
12.4 Offline testing (including physical, chemical and microbiological attributes) should be done in accordance with a predetermined programme.

12.5 Samples should be taken from points of use and dedicated sample points where required. All water samples should be taken using the same methodology as detailed in production procedures, for example, using a hose and with a suitable flushing and drainage procedure in place.

12.6 Tests should be carried out to ensure that the relevant pharmacopoeia specification (and approved company specification, where applicable) has been met. This may include the microbiological quality of water, as appropriate.

12.7 The results for identified quality attributes should be subjected to statistical analysis at defined intervals, for example, monthly, quarterly and annually, in order to identify trends. The results should be within defined control limits, such as 3 sigma.

12.8 Alert and action levels should be established based on historically reported data.

12.9 Adverse trends and out-of-limit results should be investigated for the root cause, followed by the appropriate corrective and preventive actions.

13. **Maintenance of water systems**

13.1 WPU systems should be maintained in accordance with an approved and documented maintenance programme. Records should be kept.

13.2 The programme should take into account at least the following:
  * defined frequency for system elements;
  * the calibration programme;
  * SOPs for specific tasks;
  * the control of approved spare parts;
  * preventive maintenance and maintenance plan and instructions, including cleaning after maintenance;
  * a review and approval of systems for use upon completion of work; and
  * a record and review of problems and faults during maintenance.
14. **System reviews**

14.1 WPU systems should be reviewed at described intervals.

14.2 The review team should be comprised of representatives from, for example, engineering, utilities, validation, QA, quality control, microbiology, production and maintenance.

14.3 Examples of matters to be included in the review are:
- changes made since the last review;
- system performance trends and capability;
- quality trends;
- failure events and alarm history;
- investigations;
- out-of-specification and out-of-limit results;
- alert and action limits;
- assessing compliance with current GMP requirements for WPU systems;
- verification of documentation being current;
- records such as log books and electronic data; and
- the appropriateness of the software and the computerized system linked to the water system, for example, SCADA (Supervisory Control and Data Acquisition), including audit trail, authorized users with access and privileges.

15. **Inspection of water systems**

15.1 WPU (BPW and BWFI) systems are subjected to regulatory inspections. Users should conduct audits and self-inspection of water systems at regular intervals. Records should be maintained.

15.2 This document can be used as the basis of an audit and inspection. A tour of the water system, treatment system, storage and distribution system, as well as visible pipework and user points, should be performed to ensure that the system is appropriately designed, installed, qualified, validated, maintained and monitored.
Glossary

Commissioning. The setting up, adjustment and testing of equipment or a system to ensure that it meets all the requirements, as specified in the user requirement specification, and capacities as specified by the designer or developer. Commissioning is carried out before qualification and validation.

References


Further reading

[Note from WHO Secretariat: will be updated further]

- European Pharmacopoeia: see website for the publishers of the European Pharmacopoeia and supplements (http://www.pheur.org/).
WHO Drug Information, Vol 34, No. 3, 2020

Consultation Documents


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REVISION OF CHAPTER 2.1: GENERAL IDENTIFICATION TESTS

Draft proposal for revision in The International Pharmacopoeia

DRAFT FOR COMMENTS

Please send any comments you may have on this draft working document to Dr Herbert Schmidt, Technical Officer, Norms and Standards for Pharmaceuticals, Technical Standards and Specifications (schmidt@who.int) by 18 September 2020.

Working documents are sent out electronically and they will also be placed on the WHO Medicines website (http://www.who.int/medicines/areas/quality_safety/quality_assurance/guidelines/en/) for comments under the “Current projects” link.

If you wish to receive our draft guidelines, please send your e-mail address to jonessi@who.int and your name will be added to our electronic mailing list.

[Note from the Secretariat. It is proposed to revise chapter 2.1: General identification tests. Changes from the current text are indicated in the text by insert or delete.]
REVISION OF CHAPTER 2.1: GENERAL IDENTIFICATION TESTS

2.1 General identification tests

**Acetylated substances**
Place a quantity of the test substance as specified in the monograph in a test tube (of maximum 18 mm diameter) and treat it with 3 drops of phosphoric acid (~1440 g/L) TS. Close the tube with a stopper through which passes a smaller test tube filled with water and, on the outside of which, hangs a drop of lanthanum nitrate (30 g/L) TS. Heat the apparatus in a boiling water bath for 5 minutes. Transfer the drop of lanthanum nitrate to a white porcelain spot plate and mix with a drop of iodine (0.02 mol/L) VS. Place at the edge of the mixture a drop of ammonia (~100 g/L) TS. A blue colour slowly appears at the interface of the two liquids and persists for a short time.

**Amines, primary aromatic**
Dissolve a quantity of the test substance as specified in the monograph in 2 mL of hydrochloric acid (~70 g/L) TS with the aid of heat, if necessary. Cool in ice, treat it with 4 mL of sodium nitrite (10 g/L) TS and pour the mixture into 2 mL of 2-naphthol TS1 containing 1 g of sodium acetate R. A heavy precipitate, coloured as specified in the monograph, is produced.

**Ammonia and volatile aliphatic amines**
Dissolve a quantity of the substance as specified in the monograph, place the solution in a test-tube and add 1 g of magnesium oxide R; warm, if specified in the monograph. Alkaline vapours evolve gradually and turn manganese/silver paper R black, the reagent paper being placed in the upper part of the test-tube.

**Ammonium**
Carry out the test in an apparatus consisting of stoppered test-tubes A and B connected by a bent glass tube to permit a stream of air to pass consecutively through test-tubes A and B. Place the solution as specified in the monograph and 0.2 g of magnesium oxide R into test-tube A, and 1 mL of hydrochloric acid (0.1 mol/l) VS containing 1 drop of methyl red/ethanol TS in test-tube B. Bubble air through the apparatus. Evolved ammonia turns the colour of the solution in test-tube B to yellow. On the addition of 1 mL of sodium cobaltinitrite (100 g/l) TS to this solution a yellowish-brown precipitate is formed.
Bismuth
A. Prepare the solution in hydrochloric acid (~250 g/l) TS as specified in the monograph and dilute 10 times with water. A white precipitate is formed, which turns dark brown on the addition of sodium sulfide TS.

B. Treat the solution in nitric acid (~1000 g/l) TS as specified in the monograph with potassium iodide (80 g/l) TS. A black precipitate is formed, which is soluble in an excess of the reagent to give a yellowish brown or orange solution. Dilute this solution with several volumes of water and heat; an orange or copper-coloured precipitate is obtained. The black precipitate that is first formed on the addition of potassium iodide (80 g/l) TS also becomes orange or copper-coloured when heated with water.

Bromides
A. Prepare a solution as specified in the monograph, acidify with nitric acid (~130 g/L) TS and add silver nitrate (40 g/L) TS. A yellowish curdy precipitate is produced, which is partially soluble in ammonia (~260 g/L) TS, but almost insoluble in ammonia (~100 g/L) TS and in nitric acid (~1000 g/L) TS.

B. NOTE: For testing bromides or hydrobromides of insoluble or sparingly soluble bases. Prepare the solution as specified in the monograph, add ammonia (~100 g/L) TS, filter, acidify the filtrate with nitric acid (~130 g/L) TS and proceed with test A.

C. Prepare the solution as specified in the monograph, acidify with sulfuric acid (~100 g/L) TS, and mix with chlorine TS. A brown solution results; after shaking with dichloromethane chloroform R, it becomes colourless whereas the dichloromethane chloroform layer turns reddish.

Calcium
A. Prepare the solution as specified in the monograph and add to it ammonium oxalate (25 g/L) TS. A white precipitate is formed, which is soluble in hydrochloric acid (~250 g/L) TS but is practically insoluble in acetic acid (~300 g/L) TS.

B. Treat 1 drop of a solution as specified in the monograph with 4 drops of glyoxal bis(2-hydroxyanil) TS, and 1 drop of sodium hydroxide (~80 g/L) TS. A reddish brown precipitate is formed which dissolves in dichloromethane chloroform R to give a red solution.
Chlorides
A. Prepare a solution as specified in the monograph, acidify with nitric acid (~130 g/L) TS and add silver nitrate (40 g/L) TS. A white curdy precipitate is produced, which is soluble in ammonia (~100 g/L) TS but is practically insoluble in nitric acid (~1000 g/L) TS.

B. **NOTE: For testing chlorides or hydrochlorides of insoluble or sparingly soluble bases.** Prepare the solution as specified in the monograph, add ammonia (~100 g/L) TS, filter and acidify the filtrate with nitric acid (~130 g/L) TS and proceed with test A.

C. Mix the quantity of the test substance as specified in the monograph with an equal quantity of manganese dioxide R, moisten with sulfuric acid (~1760 g/L) TS and heat gently. The evolved chlorine is recognizable by its greenish colour and produces a blue coloration of moistened starch/iodide paper R. Carry out the reaction preferably under a hood.

Citrate
A. Treat at ambient temperature a neutral solution as specified in the monograph with calcium chloride (55 g/L) TS. No precipitate is formed but, on boiling, a white solid is produced which is soluble in acetic acid (~300 g/L) TS.

B. Boil a solution with mercuric sulfate TS as specified in the monograph and filter if necessary. After the addition of a few drops of potassium permanganate (10 g/l) TS to the filtrate, the colour is discharged and a white precipitate is produced.

B. To 10 mg of the test substance or the solution described in the monograph, add 4 mL of pyridine R and 2 mL of acetic anhydride R, and shake; a yellow colour is immediately produced. Heat on a water bath for 2 minutes; a light pink to red colour is produced.

/Note from the Secretariat./ **Identity test C in the monograph on Diethycarbamazine dihydrogen citrate tablets describes a colour reaction using mercuric sulfate. It is proposed to replace the text by the following:** Filter the aqueous layer obtained from identity test B. The filtrate yields reaction B described under 2.1 General identification tests as characteristic of citrates.

Ferric salts:
Dissolve a quantity of the test substance to be examined equivalent to not less than 1 mg of iron (Fe³⁺) in 1 mL of water R or use 1 mL of the prescribed solution. Add 1 mL of potassium ferrocyanide (~53 g/L) TS. A blue precipitate is formed that does not dissolve on addition of 5 mL of hydrochloric acid (~70 g/L) TS.
**Ferrous salts**

A. Prepare a solution as specified in the monograph and add potassium ferricyanide (10 g/L) TS. A dark-blue precipitate is formed which is practically insoluble in hydrochloric acid (~70 g/L) TS.

B. Prepare a solution as specified in the monograph, acidify with sulfuric acid (~100 g/L) TS and treat with o-phenanthroline (1 g/L) TS. An intense red colour is produced which is discharged by the addition of ceric sulfate (35 g/L) TS.

**Iodides**

A. Prepare a solution as specified in the monograph, acidify with nitric acid (~130 g/L) TS and add silver nitrate (40 g/L) TS. A yellow curdy precipitate is formed which is practically insoluble in ammonia (~100 g/L) TS and in nitric acid (~1000 g/L) TS.

B. **NOTE: For testing iodides of insoluble or sparingly soluble bases.** Prepare a solution as specified in the monograph, add ammonia (~100 g/L) TS, filter and acidify the filtrate with nitric acid (~130 g/L) TS and proceed with test A.

C. Prepare a solution as specified in the monograph, acidify with sulfuric acid (~100 g/L) TS and add potassium nitrite (100 g/L) TS. A brown solution results; after shaking with dichloromethane chloroform R, it becomes colourless whereas the dichloromethane chloroform layer turns violet.

**Nitrates**

A. Prepare a solution as specified in the monograph and treat it with ferrous sulfate (15 g/L) TS. No brown colour appears unless sulfuric acid (~1760 g/L) TS is cautiously added to form a lower layer. A brown colour is then produced at the interface of the two liquids.

B. Add 2 mg of the finely ground test substance to a mixture of 0.1 mL of nitrobenzene R and 0.2 mL of sulfuric acid (~1760 g/L) TS. Allow to stand at room temperature for 5 minutes, cool in ice, and add slowly while mixing 5 mL of water and 3 mL of sodium hydroxide (~400 g/L) TS. Add 5 mL of acetone R, shake and allow to separate. An intense violet colour is produced in the upper phase.
Orthophosphates
A. Add, drop by drop, a quantity of nitric acid (~130 g/L) TS to 5 mL of ammonium molybdate (95 g/L) TS until any precipitate that may appear dissolves. Divide this solution into 2 portions, add to one portion a test solution acidified with nitric acid (~130 g/L) TS as specified in the monograph and boil both portions. A yellow precipitate is formed with the test solution while the other shows no more than a slight opalescence.
B. Prepare a neutral solution as specified in the monograph and add silver nitrate (40 g/L) TS. A yellow precipitate is produced which does not darken upon heating the solution to boiling. The precipitate is soluble in ammonia (~100 g/L) TS and in nitric acid (~130 g/L) TS.

Potassium
Prepare an alkaline solution as specified in the monograph and treat it with sodium tetraphenylborate (30 g/L) TS. A white precipitate is produced.

Salicylates
Treat a neutral solution as specified in the monograph with ferric chloride (25 g/L) TS. An intense reddish violet colour appears which remains on the addition of a small amount of acetic acid (~300 g/L) TS but disappears on the addition of hydrochloric acid (~70 g/L) TS, with separation of a white crystalline precipitate.

Sodium
A. Moisten a quantity of the substance with hydrochloric acid (~250 g/L) TS. An intense yellow colour is produced when the solution is introduced into a nonluminous flame.

NOTE: Perform test B or C if, for technical reasons, test A cannot be carried out.
B. Acidify a solution as specified in the monograph with acetic acid (~60 g/l) TS, filter, if necessary, and treat it with uranyl/zinc acetate TS. A yellow crystalline precipitate is produced.
B. Dissolve 0.1 g of the test substance in 2 mL of water R or use 2 mL of the solution described in the monograph. Add 2 mL of potassium carbonate (150 g/L) TS and heat to boiling. No precipitate is formed. Add 4 mL of potassium pyroantimonate (13 g/L) TS and heat to boiling. Allow to cool in iced water and, if necessary, rub the inside of the test tube with a glass rod. A dense white precipitate is produced.
C. Dissolve a quantity of the substance to be examined equivalent to about 2 mg of sodium (Na+) in 0.5 mL of water R or use 0.5 mL of the prescribed solution. Add 1.5 mL of methoxyphenylacetic R and cool in ice-water for 30 min. A voluminous, white, crystalline precipitate is produced. Place in water at 20 °C and stir for 5 min. The precipitate does not disappear. Add 1 mL of ammonia (~100 g/L) TS. The precipitate dissolves completely. Add 1 mL of ammonium carbonate solution R. No precipitate is produced.
Sulfates
A. Prepare a solution as specified in the monograph and add barium chloride (50 g/L) TS. A white precipitate is formed which is practically insoluble in hydrochloric acid (~250 g/L) TS.
B. To a solution as specified in the monograph, add lead acetate (80 g/L) TS. A white precipitate is formed which is soluble in ammonium acetate (80 g/L) TS and in sodium hydroxide (~80 g/L) TS but practically insoluble in hot water.

Tartrates
A. Acidify a solution as specified in the monograph with acetic acid (~300 g/L) TS and add 1 drop of ferrous sulfate (15 g/L) TS, a few drops of hydrogen peroxide (~60 g/L) TS and enough sodium hydroxide (~80 g/L) TS to make the solution alkaline. A purple or violet colour is produced.
B. Mix a few mL of sulfuric acid (~1760 g/L) TS with a few drops of resorcinol (20 g/L) TS and a few drops of potassium bromide (100 g/L) TS and add 2 or 3 drops of a solution as specified in the monograph. Warm the liquid in a water-bath for 5 to 10 minutes. An intense blue colour is produced. Cool the liquid and pour it into water. The solution becomes red.

Reagents to be added:
Ammonium carbonate (158 g/L) TS
Ammonium carbonate dissolved in water R to contain 158 g of ammonium carbonate R in 1000 mL.

Methoxyphenylacetic R
Procedure. Dissolve 2.7 g of methoxyphenylacetic acid R in 6 mL of tetramethylammonium hydroxide (~100 g/L) TS and add 20 mL of dehydrated ethanol R.
Storage. Store in a polyethylene container.

Methoxyphenylacetic acid R
C9H10O3
Description. White, crystalline powder or white or almost white crystals.
Solubility. Sparingly soluble in water, freely soluble in ethanol (~750 g/L) TS.
Melting point. About 70° C.

Potassium carbonate (150 g/L) TS
Procedure. Dissolve 15 g of anhydrous potassium carbonate R in 100 mL of water R.
Potassium pyroantimonate (13 g/L) TS
Dissolve 1.95 g of potassium pyroantimonate R in 95 mL of hot water R. Cool quickly and add a solution containing 2.5 g of potassium hydroxide R in 50 mL of water R and 1 mL of dilute sodium hydroxide (~85 g/L) TS. Allow to stand for 24 hours, filter and dilute to 150 mL with water R.

Potassium pyroantimonate R
K₅Sb(OH)₆

*Description.* White or almost white, crystals or crystalline powder.

*Solubility.* Sparingly soluble in water R.
POLICY:
EVALUATING AND PUBLICLY DESIGNATING REGULATORY AUTHORITIES AS WHO LISTED AUTHORITIES

DRAFT FOR COMMENTS

Please send any comments you may have to Mr Mohamed Refaat, Technical Officer, Regulatory Systems Strengthening, Regulation and Safety Unit (refaatm@who.int), with a copy to Yvonne Melounou (melounouy@who.int) by 15 September 2020. Please use our attached Comments Table for this purpose.

Our working documents are sent out electronically and they will also be placed on the WHO Medicines website (http://www.who.int/medicines/areas/quality_safety/quality_assurance/guidelines/en/) for comments under the “Current projects” link.

If you wish to receive all our draft guidelines, please send your email address to jone@who.int and your name will be added to our electronic mailing list.
POLICY:
EVALUATING AND PUBLICLY DESIGNATING REGULATORY AUTHORITIES AS WHO LISTED AUTHORITIES

1. Introduction

This policy on the evaluation and designation of regulatory authorities as WHO Listed Authorities (WLA) was developed following broad public consultation and the review of written comments received from the publication of a concept note (1), which informed the drafting of a first version of the WLA policy and operational guidance, as well as international consultative meetings with Member States and interested stakeholders (2, 3). It also considers recommendations from the fifty-second meeting of the World Health Organization (WHO) Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP) on the replacement of the term “stringent regulatory authority” with “WHO-listed Authority” (4). The ECSPP recommendations were based on comments received on the proposed elements of a replacement definition for Stringent Regulatory Authorities (SRAs) posted by WHO for public comment in August 2017 that was intended to provide a more transparent, robust and equitable measure of regulatory performance (5).

2. Context

World Health Assembly Resolution 67.20 (WHA 67.20) on Regulatory system strengthening for medical products (6) recognizes that effective regulatory systems are an essential component of health system strengthening, necessary for the implementation of universal health coverage and, ultimately, contribute to better public health outcomes. Resolution WHA 67.20 also recognizes that inefficient regulatory systems can be a barrier to access to safe, effective and quality medical products. Several WHO regional committee resolutions on regulatory system strengthening have also been adopted, including, for example, Regional Committee Resolution (CD50.R9), 2010, in the WHO Regional Office for the Americas (AMRO/PAHO) (7), Regional strategy for improving access to essential medicines in the Western Pacific Region (2005-2010) (8), and document AF/RC63/7 of the WHO Regional Office for Africa (AFRO) (9). The road map for access to medicines, vaccines and other health products highlights regulatory system strengthening as an integral part of a health systems approach to improving access to safe and effective medical products of assured quality (10).
Resolution WHA 67.20 calls upon WHO to:

a) apply evaluation tools to generate and analyse evidence of regulatory system performance;

b) facilitate the formulation and implementation of institutional development plans; and

c) provide technical support to national regulatory authorities and governments.

The WHO supports Member States in strengthening regulatory systems as a means of promoting equitable access to and availability of quality assured medical products. To assist countries in reaching and sustaining a level of medical product regulatory oversight that is effective, efficient and transparent, WHO has implemented a regulatory system strengthening programme. Its objectives are to:

a) promote regulatory cooperation, convergence and transparency through networking, work-sharing and reliance; and

b) build regulatory capacity in Member States consistent with good regulatory practices.

In order to reach these objectives, WHO has established the framework, principles, tools and processes to, among others, a) evaluate regulatory systems and establish maturity levels by applying the Global Benchmarking Tool (GBT) (11) and b) evaluate regulatory performance in order to designate authorities responsible for regulation of medical products as WLA.

3. Purpose

The principle of reliance is central to WHO’s approach to regulatory system strengthening and effective regulation, regardless of the size and maturity of the authority (12). Regulatory cooperation and reliance are built on trust and confidence which, in turn, depend on greater knowledge and transparency of the regulatory systems and the performance of the regulatory authority upon which others may rely.

The introduction of a framework for designating and publicly listing a regulatory authority as a WLA provides a transparent and evidence-based pathway for regulatory authorities to be globally recognized as meeting and applying WHO and other internationally recognized standards and guidelines, as well as good regulatory practices. The main purpose of the introduction of the WLA designation is the replacement of the concept of an SRA which was initially developed to guide global procurement of medicines. This concept has been used by the WHO Secretariat and the Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund) to guide medicine procurement decisions and has subsequently become widely recognized by the international regulatory and procurement community.
The definition of an SRA, first published by the Global Fund in 2008, was based on membership in the International Conference (now Council) of Harmonization (ICH) (13) but the utilization of this concept has been documented since 2003. An interim definition adopted by ECSPP in 2017 restricted eligibility to ICH membership prior to 23 October 2015 while awaiting the development of a more suitable definition and approach based on the WHO benchmarking of regulatory systems (14).

The WLA framework is also replacing the concept and procedure for recognizing regulatory authorities exhibiting ‘a high level of performance’ in vaccine regulation based on criteria defined in the WHO Technical Report Series (TRS) 978 (15).

The GBT is and remains the foundation for assessing the regulatory systems based on inputs, processes and outputs. Based on this, the WLA framework is meant to provide a more detailed picture of how a regulatory system operates through an additional performance evaluation process that examines key regulatory outputs and consistency in adherence to international standards and guidelines as well as good regulatory practices.

It should be noted that in 2019, an estimated 75% of the 194 Member States were estimated to not have a stable and well-functioning regulatory system corresponding to maturity level (ML) 3 or 4, with ML 3 being the target of Resolution WHA 67.20. Bringing these regulatory systems to ML 3 will require significant and sustained efforts and a ‘smart’ regulatory approach based on reliance on other mature and trusted reference regulatory authorities – the WLAs – whenever possible.

The designation of a regulatory authority as a WLA is ultimately meant to promote access and the supply of safe, effective and quality medical products by facilitating the use of reliance on the work products and decisions of trusted agencies in the regulatory decision-making of regulatory authorities and the procurement decisions of the United Nations (UN) and other agencies to reduce the redundancy and waste of limited regulatory and financial resources.

4. Scope

This policy describes the purpose, definitions and operating principles related to the evaluation and public listing of authorities responsible for the regulation of medical products as WHO Listed Authorities or WLAs. The initial scope of the WLA designation will be limited to medicines and vaccines, with an option to expand to other categories of products in the future in line with the expansion of the scope of the GBT.
5. **Policy statement**

Independent, efficient, science-based and transparent regulatory systems are essential to health care systems, access to safe, effective and quality medical products and the implementation of universal health coverage. A system for publicly designating regulatory authorities as WLAs provides an evidence-based mechanism to evaluate, recognize and transparently classify and list well-performing regulatory systems. It thereby, where appropriate, intends to:

a) promote trust, confidence and reliance between regulatory authorities;
b) encourage continuous improvement of regulatory systems and the efficient use of regulatory resources;
c) expand the pool of regulatory authorities beyond SRAs for users such as regulatory authorities or the WHO Prequalification (PQ) Programme;
d) promote the supply of safe, effective and quality assured medical products for use by UN procurement agencies and countries; and
e) create an enabling environment for innovation and local production of medical products by facilitating the implementation of reliance approaches and therefore accelerating access to safe, effective and quality assured medical products.

6. **Definition of a WHO Listed Authority**

A WHO Listed Authority (WLA) is a regulatory authority\(^6\) or a regional regulatory system which has been documented to comply with all the indicators and requirements specified by WHO for listing based on an established benchmarking and performance evaluation process.

7. **Operating principles**

The following principles define in broad terms how the WLA framework is to be implemented. Details are provided in the *WLA Operational Guidance* and accompanying procedures.

a) The process to establish a WLA is initiated by a request from the Member State; for a regional regulatory system (RRS), the request should come from a regional body, where it exists, or another institution representing the RRS, following coordination with the individual authorities that are part of the system, as appropriate.

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\(^6\) A regulatory authority is meant to cover all the institutions, working together in an integrated and effective manner, that are responsible for the regulatory oversight of medical products in a given country or region.
b) The GBT forms the basis for evaluating the ML. The WLA performance evaluation process assesses the consistent performance including adherence to international standards and guidelines, as well as good regulatory practices of the regulatory authority or RRS over time against the requirements established for the scope of listing being sought.

c) A regulatory authority or RRS can be listed for one or more product categories and/or for one or more regulatory functions.


d) Regulatory authorities or RRSs must at least have attained overall ML 3 as established by the GBT to be eligible for consideration as a WLA.

e) A WLA is expected to have the capacity and established track record of performing the regulatory functions for the product categories relevant to the scope of the WLA listing. A WLA can rely in a targeted way based on a defined approach on others for these functions and/or products categories, but full reliance cannot be used as a substitute for reliable performance of regulatory functions/for product categories which are assessed as part of the listing.

f) After the WHO confirms eligibility criteria are met, the regulatory authority or the RRS and WHO agree to a written plan of performance evaluation and commit the necessary resources to execute the plan, which may be adjusted from time to time. The plan agreed, the resources involved and the time for execution of the plan will depend on the requested scope, the completeness of the documentation as well as the readiness of the regulatory authority or RRS.


g) In considering the extent and depth of the evaluation process, factors such as existing evidence and track record of regulatory function and performance, including from previous benchmarking/audit exercises undertaken by WHO or other organizations such as, for example, the Pharmaceutical Inspection Co-operation Scheme (PIC/S), Benchmarking of European Medicines Agencies (BEMA) or the International Organization for Standardization (ISO) of the regulatory authority or RRS, should be taken into consideration when determining compliance with the requirements for designation as a WLA in order to make best use of limited resources for performance evaluation and avoid unnecessary burden and ensure optimal use of resources.

h) The degree of integration on the basis of a common framework varies between different regional regulatory systems which should also be taken into account in the designation of these systems.

i) All non-public information provided is kept confidential.

j) Following the successful completion of the WLA evaluation process, a regulatory authority or RRS is publicly listed as a WLA in the list of reference authorities (16). The listing as a WLA includes the scope of the designation (product categories and/or regulatory functions); evidence reviewed, and the process undertaken to support the listing; the original date and the period of validity of the initial listing.
k) A listing will initially be valid for a period of 5 years unless extended. A risk-based process will be used to renew the initial listing. Once renewed, the listing will no longer be subject to a validity period but to a continuous monitoring based on risk management principles to ensure that requirements for the listing continue to be met.

l) Changes or events that could cause sufficient concern that the requirements for the listing are no longer met will trigger a re-evaluation of the WLA. The re-evaluation will be risk-based and will focus on the issues of concern.

m) To ensure impartiality of the WLA process, a recommendation to list or delist a regulatory authority or RRS is made following a review of the evaluation report on the candidate WLA by an advisory committee. This committee will be set up by WHO based on established and transparent criteria such as ensuring equitable geographical representation, gender balance and professional competencies in order to provide a representation of different approaches and practical experience from all regions of the world. The review process provides an additional level of assurance that due process was followed and that decisions are supported by findings.

n) WHO reserves the right to delist a WLA should, upon evaluation and subsequent discussion with the regulatory authority or RRS, it be concluded that the basis for supporting the listing is no longer valid. Delisting and the rationale for delisting are published on the WHO website. The decision to delist would follow a meeting with the regulatory authority or the RRS during which the authority would have an opportunity to present its case.

o) The ultimate responsibility and decision for use of the list resides with the users (e.g. regulatory authorities, WHO Prequalification Programme, procurement agencies) and depends on the specific context of its intended use.

The designation of WLAs is meant to substantiate the maturity level using an international benchmark, as defined by the GBT and the performance of regulatory authorities and RRSs using the WLA performance evaluation process. It is not meant to make any inference regarding the maturity or performance of a regulatory authority or RRS that has been evaluated by other institutions or through other procedures.
8. Glossary

Common regulatory framework. A common regulatory framework is a unified set of requirements, processes and controls applied in the supervision of medical products. For a common legal framework this is, in addition, underpinned by common legislation.

International standards and guidelines. For the purpose of this document, the term includes relevant WHO standards and guidelines and any other relevant internationally recognized standards (e.g. ISO or pharmacopoeial standards) and guidelines (e.g. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) or PIC/S guidelines).

Maturity level (ML). The maturity of regulatory systems is divided into four levels, characterized as follows:

- **ML1**: some elements of regulatory systems exist;
- **ML2**: evolving national regulatory systems that partially perform essential regulatory functions;
- **ML3**: stable, well-functioning and integrated regulatory systems; and
- **ML4**: regulatory systems operating at advanced level of performance and continuous improvement.

Product category(ies). Refers to “medical products” which may include the following product categories: vaccines, medicines, medical devices including in-vitro diagnostics, blood and blood products and vector control products.

Regional regulatory system (RRS). A system composed of individual regulatory authorities, or a regional body composed of individual regulatory authorities, operating under a common regulatory framework including or excluding a common legal framework. The common framework must at least ensure equivalence between the members in terms of regulatory requirements, practices and quality assurance policies. The system or regional body, where it exists, may have enforcement powers to ensure compliance with the common regulatory framework. A RRS so described may be considered a single entity and therefore eligible for listing as a WLA, as well as each of the individual authorities that are part of the system. In cases where a RRS is further underpinned by a common legal framework, it should be considered as a single entity and, as such, eligible for listing as a WLA, as well as each of the individual authorities that are part of the system.
**Regulatory function(s).** The term refers to the regulatory functions as components of a regulatory system for medical products defined in the GBT being national regulatory systems, registration and marketing authorization, vigilance, market surveillance and control, licensing establishments, regulatory inspection, laboratory testing, clinical trials oversight, and national regulatory authorities (NRA) lot release.

**Reliance.** The act whereby the (national) regulatory authority in one jurisdiction may take into account and give significant weight to assessments performed by another (national) regulatory authority or trusted institution, or to any other authoritative information in reaching its own decision. The relying authority remains independent, responsible and accountable for decisions taken, even when it relies on the decisions and information of others.

**Stringent regulatory authority** (*interim definition ECSPP*). A regulatory authority which is:

a) a member of the ICH, being the European Commission, the United States (U.S.) Food and Drug Administration and the Ministry of Health, Labour and Welfare of Japan, also represented by the Pharmaceuticals and Medical Devices Agency (as before 23 October 2015); or

b) an ICH observer, being the European Free Trade Association, as represented by Swissmedic, and Health Canada (as before 23 October 2015); or

c) a regulatory authority associated with an ICH member through a legally-binding, mutual recognition agreement, including Australia, Iceland, Liechtenstein and Norway (as before 23 October 2015) (6).
References


12. WHO Good Reliance Practices (GReIP) (link to document to be added after start of public consultation).


16. "List of reference authorities"

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Good regulatory practices
for regulatory oversight of medical products

DRAFT FOR COMMENTS

Please send your comments to Dr Marie Valentin, Technical Officer, Regulatory Convergence and Networks, Regulation and Safety (valentinm@who.int), with a copy to Mrs Carolyn Doucelin (doucelinc@who.int) by 11 September 2020.

Please use our attached Comments Table for this purpose.
Our working documents are sent out electronically and they will also be placed on the WHO Medicines website (http://www.who.int/medicines/areas/quality_safety/quality_assurance/guidelines/en/) for comments under the “Current projects” link.

If you wish to receive all our draft guidelines, please send your email address to jonessi@who.int and your name will be added to our electronic mailing list.
Good regulatory practices
for regulatory oversight of medical products

Acronyms

APEC  Asia-Pacific Economic Cooperation
ASEAN  Association of Southeast Asian Nations
GGP  Good Governance Practices
GRP  Good Regulatory Practices
GReIP  Good Reliance Practices
GRevP  Good Review Practices
OECD  Organisation for Economic Co-operation and Development
QMS  Quality Management System
QRM  Quality Risk Management
WHO  World Health Organization
WLAs  WHO-Listed Authorities
Executive Summary

A fundamental role of government is to protect and promote the health and safety of the public, including the delivery of health care. A well-functioning health care system depends upon the availability and affordability of medical products that are safe, effective and of consistently assured quality.

The medical products sector is one of the most regulated of all industries as a consequence of the impact of the diverse range of medical products on health, the difficulty in assessing their quality, safety and efficacy, and the complexities associated with their development, production, supply and surveillance. It is therefore essential that the interests and safety of the public be entrusted to a regulatory body responsible for ensuring that only products in legal trade are available and that marketed products are safe, perform as claimed and are of assured quality.

Regulatory authorities have a duty to ensure that they regulate in a manner that achieves public policy objectives. A coherent legal framework should be established and implemented that provides the required level of oversight while also facilitating innovation and access to safe, effective and quality medical products. This also means building the necessary flexibilities and responsiveness to manage public health emergencies, address new technologies and practices and promote international regulatory cooperation.

Governments incur costs by establishing and maintaining regulatory systems to protect and promote the health of its citizens. Regulated parties incur costs in complying with regulation. However, additional impacts (health system, socio-economic and economic impacts) can accrue from inefficient regulatory systems - with potentially significant implications for disease morbidity/mortality, health care costs and the economy.

A sound legal framework, the adoption of international norms and standards and the recruitment and development of competent staff are necessary but not sufficient conditions to ensure ‘good regulatory oversight’. These measures must be combined with good regulatory practices (GRP) that guide all individuals within organizations entrusted to regulate in the application of requirements and the formulation of decisions so that they are clear, consistent, impartial, proportionate, timely and based on sound science and legislation. GRP can be defined as a set of principles and practices that are applied to the development, implementation and maintenance of regulatory instruments – including laws, regulations and guidelines – in order to achieve a public health policy objective in the most efficient way.
The successful application of GRP is the hallmark of a modern, science-based and responsive regulatory system that translates the practice of regulation into desired outcomes. GRP provide a means of establishing and implementing sound, affordable and efficient regulatory oversight of medical products as an important part of health system performance and sustainability.

This document is intended to present Member States with widely-recognized principles of GRP. The principles presented in this document derive from an extensive review of public documents developed by governments and multi-lateral organizations on the subject, as well as many consultative workshops, benchmarking exercises and interactions with Member States. The nine principles presented in this document, such as, legality, consistency, independence, impartiality, proportionality, flexibility, clarity, efficiency and transparency, are relevant to all authorities responsible for the regulatory oversight of medical products, irrespective of resources, sophistication or regulatory model.

GRP serve as a foundation within a suite of related guidance documents on best regulatory practices. Taken together, this expanding set of guidance documents is intended to provide regulatory authorities comprehensive guidance on improving their performance. This document will be supplemented by practical ‘how to’ guides and tools designed to facilitate the implementation of GRP.
1. Introduction

This document responds to requests from national authorities responsible for the regulatory oversight of medical products for guidance in addressing common gaps in regulatory practices identified during benchmarking exercises.

This document draws upon documents from multilateral bodies such as the Asia-Pacific Economic Cooperation (APEC), the Organisation for Economic Co-operation and Development (OECD), the World Bank and the Association of Southeast Asian Nations (ASEAN) (1) (2) (3) (4) (5) as well as guides published by a number of governments. The document also takes account of earlier World Health Organization (WHO) documents that touch on aspects of GRP (6) (7) (8) (9) (10) (11) (12) (13) (14) and from WHO experience in applying the WHO Global Benchmarking Tool (GBT) and promoting the various principles of good regulatory practices (GRP).

When the principles of GRP are properly implemented through the GRP enablers across the regulatory system, desired regulatory outcomes and impact can be achieved.

2. Background

A fundamental role of government is to protect and promote the health and safety of the public, including in the delivery of health care. A well-functioning health care system depends upon the availability and affordability of medical products that are safe, effective and of assured quality.

Medical products are essential to the prevention, diagnosis and treatment of disease and the consequences of substandard and falsified medical products can be therefore life-threatening. This reality is of particular concern as users of medical products are typically not in a position to judge their quality. It is therefore essential that the interests and safety of the public be entrusted to a regulatory body or bodies responsible for ensuring that only products in legal trade are available and that marketed products are safe, perform as claimed and are of assured quality.

The regulatory oversight of medical product has become increasingly complex given the globalization of product development, production and supply, coupled with the rapid pace of technological and social change in a context of limited financial and human resources.
The importance of robust regulatory systems was recognized by the Sixty-Seventh World Health Assembly in endorsing Resolution WHA 67.20 Regulatory system strengthening for medical products. The Resolution notes that “effective regulatory systems are an essential component of health system strengthening and contribute to better public health outcomes”, that “regulators are an essential part of the health workforce”, and that “inefficient regulatory systems themselves can be a barrier to access to safe, effective and quality medical products” (15).

A sound system of oversight requires that regulatory authorities are supported by an effective framework of laws, regulations and guidelines, and that they have the competence, capacity and science-based knowledge to conduct their mandate in an efficient and transparent manner. The degree to which the regulatory framework fulfils policy objectives depends on the quality of its development and implementation processes.

GRP are critical to the efficient performance of the regulatory system and, consequently, to the public’s confidence in the system. A sound regulatory framework, including the adoption of international norms and standards and the recruitment and development of competent staff, are necessary but not sufficient conditions to ensure ‘good oversight’. These measures must be combined with GRP that guide all individuals from regulatory authorities to set appropriate requirements and formulate decisions that are clear, consistent, impartial, proportionate, timely and based on sound science.

3. Purpose

This document presents the high-level principles of GRP. The principles are intended to serve as a benchmark and thereby assist Member States in the application of good practices for the regulatory oversight of medical products. This document is also meant to assist Member States in prioritizing the functions of a regulatory system based on available resources, national goals, medical products policies and the medical product environment. This principles-based document will be supplemented by practical ‘how to’ guides and tools designed to facilitate the implementation of GRP within organizations responsible for the regulatory oversight of medical products.

This foundational document is complemented by a suite of related guidance on best regulatory practices, including but not limited to good governance practices (GGP) (16), good reliance practices (GRelP) (17), good review practices (GRevP) (18) and the implementation of quality management systems (QMS) for national regulatory authorities (NRAs) (19). Taken together, this expanding body of work is intended to provide regulatory authorities with comprehensive guidance on improving performance.
4. **Scope**

This document is relevant to all regulatory authorities irrespective of resources, maturity or regulatory model. These GRP high-level principles are equally applicable to regulatory systems that are supranational (e.g. regional), national and/or subnational in nature, or involve multiple institutions charged with regulating certain products or activities within a country or jurisdiction.

This document presents principles and considerations in the development and implementation of regulatory instruments which underpin regulatory activities. Broader practices and attributes are presented that define well-performing regulatory systems for medical products.

This document is intended for a number of related audiences: institutions and policy-makers responsible for the formulation of health policies, laws, regulations and guidelines; institutions that, together, form national or supranational systems for regulatory oversight of medical products; regulatory networks and parties affected by or otherwise interested in regulatory frameworks; for example, industry or other developers of medical products.

5. **Objectives**

GRP provide a means of establishing sound and effective oversight of medical products as an important part of health system performance and sustainability. If consistently and effectively implemented, they can lead to higher quality regulation, improved regulatory decision-making and compliance, increased efficiency of regulatory systems, and better public health outcomes. They help to ensure that regulatory systems remain current as technologies and the systems in which they are used continue to evolve.

Within the context of an increasingly complex and interconnected regulatory environment, GRP are also an important enabler in promoting trust between regulatory authorities and thereby facilitating international cooperation and the adoption of more effective and efficient approaches to ensuring the quality, safety and efficacy of medical products within the global regulatory community.

The ultimate aim of GRP is to serve and protect public health and patients’ interest, respecting all applicable ethical principles.
6. Key considerations

The medical products sector is one of the most regulated of all industries as a consequence of the impact of the diverse range of medical products on health and society, the difficulty in assessing their quality, efficacy and safety, lessons learned from public health tragedies, and the complexities associated with developing, producing, supplying and monitoring medical products to ensure they consistently perform as intended. This has led many countries to put into place an increasingly sophisticated set of laws, regulations and guidelines that control all aspects of the medical product life-cycle.

While providing the necessary authorities, prohibitions and tools necessary to fulfil publicly entrusted mandates, regulatory authorities have a duty to ensure that they regulate in a manner that achieves public policy objectives. This means establishing and implementing a coherent regulatory framework that provides the required level of oversight and control while also facilitating the innovation and access to safe, effective and quality medical products. It also means building the necessary flexibilities and responsiveness to manage public health emergencies, address new technologies and best practices, and promote international regulatory cooperation.

Increasingly, policy makers and regulatory authorities must adopt modern and responsive models of regulation that consider resource constraints in the face of the challenges posed by scientific development, globalization, rising public expectations and public health emergencies.

Weak or inefficient regulatory systems can be a barrier to access to safe, effective and quality medical products and a threat to public health. At the same time, countries strengthen regulatory capacity regulatory systems need to be science-based, respect international standards and to adopt an approach that leverages the work of other trusted regulatory authorities and institutions whenever possible. Towards this end, countries are encouraged to formulate and implement policies and strategies that promote convergence, harmonization, information and work-sharing, and reliance as part of GRP (17). An ongoing initiative at WHO aims at establishing and implementing a framework for evaluating NRAs and regional regulatory systems as well as designating those that meet a specific standard as WHO-Listed Authorities (WLAs) (20).
For reasons of public health protection noted earlier in the document, the need for regulatory controls over medical products is fully acknowledged. The issue is more how to regulate in an effective, efficient and transparent manner, such that the interests of the health care system are served. The consistent application of GRP in all aspects of oversight is essential in ensuring that these interests are met and providing the foundation on which a well-performing, respected regulatory system is built.

GRP can be defined as a set of principles and practices that are applied to the development, implementation and maintenance of regulatory instruments – including laws, regulations and guidelines – in order to achieve a public health policy objective in the most efficient way.

GRP is about instilling a culture of best practices across institutions responsible for regulatory oversight to ensure that regulation is fairly, consistently and effectively applied.

7. Overview of regulatory system for medical products

Definitions are essential to a common understanding of concepts. While a more extensive set of terms is provided in the Glossary, an elaboration of the terms regulatory framework, legal framework, regulatory authority, regulatory system, and regulatory outputs is provided below to ensure a proper understanding of their usage in this document.

Components of the regulatory framework

In this document, the terms “law” and “regulation” are used for the components of the legal framework (binding legislation). It is acknowledged that other terms may be used in different jurisdictions, such as “act” (instead of law) or “ordinance” (instead of regulation).

Laws are generally used to set out at a high level the roles and responsibilities of institutions; in this case, the regulatory authority, the ministry of health and other relevant organizations. They define the products, persons and activities that are to be regulated and state what is permitted and what is not. More importantly, laws authorize the institution to make lower level (or subordinate) regulations.

Regulations are a diverse set of instruments by which governments place requirements on enterprises and citizens. The regulations usually state at high level the conditions to be met and detail the requirements defined in the laws.
For instance, a law may prohibit the manufacturer, importation or sale of a medical product in the absence of specific authorisation. The regulations would set out the conditions for obtaining authorisation; for example, the need to provide certain types of information - such as clinical trial and manufacturing and control data - that would allow the regulatory authority to establish the quality, safety and efficacy of a medical product.

*Guidelines (and other guidance documents)* provide further detail on how the regulated stakeholders can comply with the laws and regulations. Guidelines may also provide details on the processes that enforce the respective legislation (laws and regulations). Within a regulatory framework for medical products, these documents are usually non-binding and are generally more detailed and scientific in nature. This makes them appropriate for describing approaches generally considered suitable for satisfying regulatory requirements but unsuitable to be embedded into legislation.

![Architecture of a Regulatory Framework](image)

**Figure 1: Architecture of a Regulatory Framework**

Components of the regulatory system

A *regulatory authority* is a public institution(s) or governmental body/bodies authorized by law to independently exercise regulatory powers concerning the development, production, marketing and surveillance of medical products. Although the term implies that a single organization is responsible for all regulatory functions, indeed these functions may be undertaken by one or more institutions reporting to the same or different senior official. The regulatory authority plays a critical role in ensuring the quality, safety, efficacy and performance of medical products as well as the relevance and accuracy of product information.
The regulatory framework is the collection of laws, regulations, guidelines and other regulatory instruments through which a government and a regulatory authority controls particular aspects of a specific activity.

The legal framework is the part of the regulatory framework that refers to (binding) pieces of legislation, such as laws and regulations.

Regulatory outputs are the results or products coming from the regulatory authority (e.g. inspection/assessment reports, decisions, product label, and so on).

The term regulatory system is used to describe the combination of the institutions, processes, regulatory framework and resources which, taken together, are integral to the effective regulatory oversight of medical products in a given country or multi-country jurisdiction. GRP should be considered and applied for the whole regulatory system.

Figure 2: Principles and enablers of Good Regulatory Practices (GRP) and Components of the regulatory system
When looking at the overall regulatory system, three main components (inputs) can be seen as the main contributors to regulatory functions and activities: (1) regulatory framework composed of legal framework (laws and regulations) along with guidelines and other guidance documents, (2) regulatory institutions which may be represented by one or more entities including the national regulatory authority (NRA), the national control laboratory, pharmacovigilance centre(s), research ethics committee(s) and others, and (3) all types of resources including human and financial resources, infrastructure and equipment and information management systems. There are several regulatory outputs depending on the concerned functions and activities (e.g. regulatory and marketing authorization inspection/assessment reports). The concepts and principles of GRP cover and address the overall regulatory system as explained above. For the purpose of application and implementation of GRP, several enablers are essential (see 10. Enablers for Good Regulatory Practices). When the principles of GRP are properly implemented through the enablers, a desired regulatory outcome and impact can be achieved.

WHO classifies the spectrum of regulatory activities according to seven common regulatory functions applicable to the regulation of all medical products: clinical trials oversight, registration and marketing authorization, vigilance, market surveillance and control, licensing establishments, regulatory inspection and laboratory testing (21). In addition, a number of non-common functions apply to certain medical products, such as official lot release for vaccines and other biologicals.

The term regulatory authority implies that a single organization is responsible for all regulatory functions. This is not always the case. For example, different organizations may be legally responsible for the regulation of medicines and vaccines as compared to medical devices. Even when one body is responsible for all regulatory functions, aspects critical to certain functions may lay outside the authority, such as those performed by pharmacovigilance centres that have a formal relationship with the authority in collecting adverse event reports. Certain regulatory functions may also be undertaken by third parties, as in the case of auditing organizations in relation to medical devices.

Regulatory activities may also be undertaken at a supranational (e.g. regional), national and/or subnational level. Examples include the supranational evaluation of certain products for the purpose of granting a marketing authorization valid across multiple countries, or the GMP inspections of multi-source medicines performed at the state level.
8. Principles of good regulatory practices

There is no universal model for the regulatory oversight of medical products. Each approach will reflect national health policies and priorities, the country’s level of socioeconomic development, the availability of resources and infrastructure, the health system, the national legal system, the research and development capacity, as well as the local production capacity. Nonetheless, as in other regulated sectors, there is a growing international consensus on best practices that may be applied to regulatory oversight.

A review of public documents (1) (4) (5) (22) on GRP reveals common themes that should be adopted by all institutions responsible for or involved in the regulatory oversight of medical products. These principles apply equally to the development and implementation of regulatory oversight and to daily regulatory business.

GRP are guided by overarching principles. There are nine principles which are listed below and are described in this section, together with considerations relevant to the regulatory oversight of medical products.

Further elaboration of the principles, practices and examples is foreseen in supplemental ‘how to’ guidance complementing this document.

<table>
<thead>
<tr>
<th>Principles of Good Regulatory Practice</th>
<th>Description</th>
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<tbody>
<tr>
<td>Legality</td>
<td>Regulatory systems and the decisions that flow from them must have a sound legal basis.</td>
</tr>
<tr>
<td>Consistency</td>
<td>Regulatory oversight of medical products should be consistent with existing government policies and legislation and be applied in a consistent and predictable manner.</td>
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<tr>
<td>Independence</td>
<td>Institutions executing regulatory oversight of medical products should be independent.</td>
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<tr>
<td>Impartiality</td>
<td>All regulated parties should be treated equitably, fairly and free from bias.</td>
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<tr>
<td>Proportionality</td>
<td>Regulation and regulatory decisions should be proportional to risk and the regulator’s capacity to implement and enforce.</td>
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<tr>
<td>Flexibility</td>
<td>Regulatory oversight should not be prescriptive but rather allow for flexibility in responding to a changing environment and unforeseen circumstances. Responsiveness in a timely manner to public health emergencies should be built into the regulatory system.</td>
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<tr>
<td>Clarity</td>
<td>Regulatory requirements should be accessible to and understood by users.</td>
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<tr>
<td><strong>Efficiency</strong></td>
<td>Regulatory systems should achieve their goals within the required time and at reasonable effort and cost. International collaboration promotes efficiency by allowing the best use for resources.</td>
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<tr>
<td><strong>Transparency</strong></td>
<td>Regulatory systems should be transparent; requirements and decisions should be made known, and input sought on regulatory proposals.</td>
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### 8.1 Legality
Regulatory systems and the decisions that flow from them must have a sound legal basis.

**Key elements:**
- The regulatory framework should provide the necessary authorities, scope and flexibilities to safeguard and promote health.
- The delegation of power and responsibilities to different levels of the regulatory system should be clear and explicit.
- Regulatory frameworks should support and empower regulatory authorities to contribute to and benefit from international cooperation.
- Systems should be in place to ensure that regulatory decisions and sanctions can be reviewed.
- Regulatory framework should afford for the integrity of the regulatory system with clear scope and lines of authority of institutions forming the regulatory system.
- A legal framework must hold the regulatory authority accountable to the public, those regulated and the government for their actions and decisions.

The principle of legality means that the regulatory system is structured so that all regulatory actions and decisions are based on clear legal authority, thus respecting the “rule of law”.

A regulatory body exists to achieve objectives deemed by the government to be in the public interest. It must operate within and in accordance of the powers conferred by the legal framework (23). The law or act establishing the regulatory authority should be clear on the objectives of the enabling legislation, the powers of the authority, the scope of products and general activities the authority is mandated to regulate, and the provisions for making regulations.

The delegation of power and responsibilities to different levels of the regulatory system should be explicit and clear. When more than one institution or level of government is involved in the regulation of medical products, the functions and responsibilities of the various institutions should be clear and complementary (see 9.2 Consistency).
Given the need for all regulatory authorities to cooperate to manage increasingly complex and cross-jurisdictional issues, it is essential that a modern legal framework for medical products supports and encourages such cooperation in all its forms - including convergence, harmonization, information- and work-sharing, reliance and recognition. Ideally, this would take the form of explicit provisions in law and/or regulations, with further operational detail provided in policies and procedural guidance. At a minimum, the legal framework should not prohibit all forms of regulatory cooperation, including the use of assessments and decisions of other trusted regulatory authorities and institutions in performing its own work. Cooperation does not alter the sovereign responsibility and accountability of each regulatory authority to protect the health and safety of its citizens but allows for the exchange of good practices and may help save resources and avoid duplication.

Legislation has to be in place to control and perform all required regulatory activities under common and non common regulatory functions. Policies, guidelines and procedures cannot compensate for the absence of legislation.

A legal framework should support the integrity of the regulatory system with clear authority, power, roles and responsibilities of institutions forming the regulatory system. Conflict in organizational authority or responsibilities should be avoided.

All regulatory authorities must be accountable to the public, those regulated, and the government for their actions and decisions as part of good governance and accountability frameworks. Within the context of GRP, accountability means that regulatory authorities are: (i) responsible for acting according to certain standards and commitments; (ii) answerable for their actions; and (iii) willing to face the consequences when standards or commitments are not met.

Regulatory actions and decisions should be consistent with authorities and controls provided for by the legal framework. Processes should therefore be put in place for the review of regulatory decisions. This includes internal appeal mechanisms and the right to judicially appeal decisions of regulators – including on the grounds of procedural fairness and due process – in addition to scientific and administrative grounds.
8.2 Consistency

Regulatory oversight of medical products should be consistent with existing government policies and legislation and be applied in a consistent and predictable manner.

Key elements:

- The regulatory framework for medical products should fit coherently into the national legal and policy framework.
- New regulations should complement, and not conflict with, existing regulatory instruments.
- Regulatory requirements should be consistently implemented and enforced across medical product sectors and stakeholders.

Regulatory oversight of medical products must be performed in the context of, and in ways coherent with, the national legal framework, general government policies and public health policy objectives. This also includes any treaties, conventions and regional or international agreements to which the country is a party as well as any supranational legislation having an effect on constituent Member States.

Overlap and conflicts with existing laws and regulations should be avoided since this causes confusion and the duplication of mandates, unnecessary regulatory burden and the likelihood of noncompliance. Manufacturers, importers, distributors and other stakeholders should be able to consistently identify which authority is responsible for what.

This is especially important where the regulation of medical products is decentralized – when, for instance, there may be central and state/provincial-level authorities. Effective systems of mutual consultation, cooperation and coordination between the different levels of government should be put in place in order to promote the national uniformity of regulatory requirements while respecting local responsibilities. It is essential that all the different regulatory functions and activities are efficiently integrated allowing for the uniformity of the regulatory system.

The same considerations are equally important when more than one institution or department within the same level of government is responsible for different, or the same, regulatory functions and products – a situation which is not uncommon. The problems associated with unclear or conflicting mandates and requirements can and do result from complex regulatory systems, compounded by challenges in effective communication and coordination.
In all instances, formal mechanisms should be established to ensure proper coordination during the drafting and execution of the regulatory instruments and the ongoing operations of bodies charged with the regulatory oversight of medical products.

Consistency in regulatory actions and decisions means that the same or similar circumstances should lead to the same or similar outcomes. It is therefore important for the regulatory system to build an institutional memory to keep records of decisions made in order to offer similar and fair treatment to future similar situations. Consistency is supported when the regulatory framework provides for appealing regulatory decisions through an impartial appeals process. The enforcement of such, and corrective measures, should also be consistent across sectors.

Consistency is also supported by having sufficient and clear regulatory guidance based, whenever possible, on international guidelines; the orientation and training programmes for staff; and regular discussions with regulated parties and other key stakeholders that serve as mechanisms for the identification and resolution of issues.

The application of a well-functioning quality management system that spans all regulatory activities (24) is critical for achieving regulatory consistency. This includes, among others, the adoption of a process approach involving the systematic definition and management of regulatory processes, and their interactions, so as to achieve the intended results in accordance with the quality policy and strategic direction of the organization.

Performance based indicators, internal reviews and external audits can also play an important role in ensuring consistency in the application of regulations and regulatory operations.

<table>
<thead>
<tr>
<th>8.3 Independence</th>
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<tr>
<td>Institutions executing regulatory oversight of medical products should be independent.</td>
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Key elements:
- The regulatory system must operate, and be seen to operate, in an independent and authoritative manner, discharging its duties independently from politicians, government and regulated entities.
- Regulatory activities and decisions should avoid improper and undue influence from stakeholders (also known as regulatory capture).
- The appropriate funding and clarity on funding processes is essential.
- Independence of leadership should be put in place in order to support independent behaviour while in employment and upon exiting.
According to an OECD publication entitled *Creating a culture of independence* (20) “regulatory agencies (authorities) often find themselves under various pressures from different stakeholders and interest groups which can subject them to different forms of influence. To ensure they conduct their activities correctly and achieve the right policy outcomes they must take on board legitimate interests and protect themselves from inappropriate or undue influence”.

Good governance and anti-corruption measures (16) should be built into the regulatory framework to avoid actual or perceived conflicts of interest, unfounded bias or improper influence by stakeholders (also known as regulatory capture). To maintain public confidence, the regulatory authority must operate, and be seen to operate, in an independent, authoritative and impartial manner, discharging its duties independently of those regulated entities (e.g. independence from researchers and industries).

For regulators that are funded through fees, an appropriate cost-recovery mechanism is essential to set the “right” fee and avoid a regulator that is under-funded, captured by industry or undermined by the executive. It can be easier to influence a regulator funded through general government revenues by reducing the resources at its disposal. Annual appropriations can make it easier to influence the regulator than multi annual appropriations that are less susceptible to short-term shocks, such as political/electoral imperatives. Adequate safeguards can protect the budget process from being used to unduly direct the regulator.

The nomination and appointment of the regulator’s leadership should be based on transparent and accountable processes. Clear conflict of interest rules should be in place to support independent behaviour while in employment and upon exiting.

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<th>8.4 Impartiality</th>
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<tr>
<td>All regulated parties should be treated equitably, fairly and free from bias.</td>
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**Key elements:**
- Regulatory activities and decisions should avoid conflicts of interest or unfounded bias.
- The regulatory system must operate in an impartial manner.
- The regulatory authority should not be engaged in activities it regulates nor be at a hierarchal level that is subordinate to institutions that perform regulated activities.
- Regulatory decision should be science- and evidence-based and the decision-making process should be robust, according to defined criteria.
Regulatory instruments must be written so that regulatory activities and decisions made on the basis of such instruments are legitimate, evidence-based and ethical. Public and private bodies, domestic and foreign entities should all be regulated equitably using the same principles and framework so that competitive neutrality is achieved.

The regulatory authority must operate in an impartial manner, discharging its duties independently of those regulated entities (see 9.3 Independence).

This principle also extends to researchers and other experts sitting on scientific and advisory committees convened to provide recommendations to the regulatory authority on matters related to regulatory policy or the authorisation of medical products. Declarations of interest have to be completed and reviewed, and rules for withdrawal need to be defined prior to discussions to maintain the integrity and impartiality of the committee and its recommendations.

Furthermore, the regulatory authority should not be engaged in the activities it regulates nor be at a hierarchal level that is subordinate to those institutions that perform regulated activities, including the procurement of medical products by a ministry of health or other government institution.

Regulators can avoid actual or perceived influence by being open and transparent about their decisions and decision-making process. This will help ensure impartiality, better regulatory outcomes and increased public confidence in the use of the regulated products.

Regulatory activities and decisions should be science-driven, evidence-based and predictable. While there will always be a need for good regulatory judgement and discretion in enforcement, actions and decisions should be based on regulatory requirements and on the evidence or circumstances of the situation (also supports 9.2 Consistency).

### 8.5 Proportionality

Regulatory oversight and regulatory decisions should be proportional to risk and the regulator’s capacity to implement and enforce.

<table>
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<th>Key elements:</th>
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<tbody>
<tr>
<td>Regulatory oversight should be adequate to achieve the objectives without being excessive.</td>
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<tr>
<td>Regulatory measures should be proportionate to the risk of the product or activity or service.</td>
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<tr>
<td>Regulation should not exceed the national capacity to implement and enforce the regulation.</td>
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<tr>
<td>The assessment of medical products should be based on a benefit/risk evaluation and continuous monitoring of the benefit/risk profile through a robust vigilance system.</td>
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The principle of proportionality means that an action does not go beyond what is needed to achieve an intended objective. This principle should be applied to all elements of a regulatory system. Regulation should be created only when necessary and should be adequate to the aim being pursued without being excessive. The content and form of regulation should be appropriate to both the issue being addressed and the risk it poses. For instance, extensive pre-clinical and clinical studies are needed to support the safety and efficacy for the marketing authorization of a new medicine, whereas, limited safety/efficacy studies, usually in a form of a single in vivo bioequivalence study or, where appropriate, in vitro studies, are sufficient for generic medicines.

Regulatory enforcement and inspection regimes should also be proportionate to the risk and severity of the infraction with an aim to reduce or mitigate the health risk posed by the infraction. A proportionate, risk-based approach allows the regulator to allocate resources where the need is greater. It also ensures that the cost of complying with regulation is proportionate to the nature of the risk.

The principle of proportionality also applies to the policies and processes by which regulation is made. The regulation-making process should be flexible and proportionate to the complexity and/or impact of the problem that it addresses. For instance, a rigorous cost/impact analysis may be required for a new complex regulatory framework but not for simple regulations or where the policy alternatives are limited. Regulation should not exceed national capacity to implement and enforce the regulation. “If there are no strategies, facilities and resources for implementation and enforcement, legislation on its own will achieve nothing. A law with modest aims and objectives that is properly enforced is preferable to a more comprehensive one that cannot be implemented”(12). Furthermore, the lack of resources or ability to implement and enforce represents a liability for the government.

The assessment of medical products should be based on a benefit/risk evaluation. All the demonstrated benefits from the medical products should be weighed against the identified risks in order to determine if the benefit outweighs the risks. Regulatory systems should have appropriate vigilance processes in place in order to monitor the benefit/risk profile and to take any regulatory actions if required.
8.6 Flexibility

Regulatory oversight should allow for flexibility in responding to a changing environment and unforeseen circumstances.

Key elements:

- The regulatory system, including regulatory frameworks, should provide sufficient flexibility to reflect/respond to changes in the regulated environment, including evolving science and technology.
- The regulatory system should be prepared and provide for timely response to urgent situations, including public health emergencies and shortages of medical products.
- The language of regulation should be performance-based whenever possible, allowing for alternative approaches that achieve the same result.
- The regulatory system should provide the flexibility to apply good judgement.

Flexibility is essential to ensure that regulatory frameworks and regulatory systems remain “fit for purpose”. This requires the appropriate design and use of regulatory instruments.

In developing a meaningful, understandable and enforceable regulatory framework, there is a need to provide sufficient detail to ensure clarity. At the same time, the regulatory framework should allow flexibility to respond to new technologies and innovation, to changes in the regulated environment and to enable a timely response to unforeseen public health threats. It should provide for the regulator’s administrative and enforcement discretion – that is, the flexibility to apply good judgement within the regulatory framework. This discretion must be subject to the appropriate controls and oversight. Flexibility in regulatory oversight should also be risk-based and must not compromise the ability to ensure the quality, safety and efficacy and performance of the product (19).

Responsiveness is an extended principle of flexibility, however slightly different. Responsiveness is time-bound and temporary in nature due to the fact that it addresses urgent situations such as public health emergencies, serious shortages of medical products with no alternatives, unmet medical needs and rare disorders, and the use for compassionate and donation purposes. Regulatory systems should be well prepared and equipped with the necessary regulatory instruments to respond to and manage these unforeseen situations. Flexible and responsive provisions are critical for providing the authority with the ability to make decisions based on best available science and benefit/risk considerations, often in the face of less-than-complete information (e.g. compassionate use, emergency use authorization or listing). The lack of necessary regulatory tools and the flexibilities they afford can pose real and significant impediments to public safety, particularly in times of public health emergencies.
During times when regulatory responsiveness is urged, a regulatory authority should consider the prioritization of its activities using a risk-based approach. The involvement of policy and decision-makers, as well as regulatory collaboration and coordination within the international regulatory community, significantly contributes to regulatory responsiveness.

Flexibility and responsiveness within regulatory framework should aim to accommodate continuing evolution in science and technology. The language of the regulations that support the law should normally be performance-based rather than prescriptive (6), thus allowing regulated parties to use alternative approaches that achieve the same outcome.

Guidelines and other guidance documents are the most detailed, most flexible and most amendable of the regulatory framework instruments. These attributes allow the regulatory framework to respond to new risks in a timely manner and allow for the possibility that an unforeseen technology may be used in a future medical product. Unlike laws and regulations, guidelines in themselves usually do not have the force of law. However, guidelines are very effective if appropriately anchored to the regulation and used to describe how compliance with the regulation may be achieved. They should also allow for other scientifically justified approaches to compliance. Alternate approaches to the principles and practices described in a guidance may be acceptable provided they are supported by adequate scientific justification. The flexibility and amendable attributes that guidelines offer is lost if such detailed texts are put into regulation.

In circumstances where science is rapidly evolving and not sufficiently mature to justify the development of regulatory guidelines, ‘points to consider’ type documents can provide useful principles-based guidance and definitions that promote best practices, a common regulatory understanding, international convergence, and prepare the ground for eventual guidelines. Existing international guidelines and standards should always be considered when new guidance documents are being developed.

The regulation of medical products is complex and ever-evolving. New technologies and practices will continue to pose challenges to regulatory systems and redefine the boundaries of what can and should be regulated. Prior to the possible development of regulations designed to deal with new technologies or address certain practices, regulators will often need to generate the necessary regulatory flexibility through the appropriate interpretation of existing legislation and regulations.
8.7 Clarity
Regulatory requirements should be accessible to and understood by users.

Key elements:
• Regulatory instruments should be written in language that is understood by users.
• Terminology should be defined and consistent with international norms whenever possible.
• Consultation, education and training on new requirements contribute to clarity and compliance.
• Guidelines and good guidance practices are instrumental to proper interpretation of regulations.
• The process and basis for taking regulatory decisions and enforcement actions should be clear.

The compliance with and consistent application of regulatory requirements and processes require a clear understanding of what is expected. Both the regulator and the regulated party should understand the conduct that is expected and the consequences of non-compliance.

Proposed regulatory instruments should be written in language that can be understood by intended users. This will require the collaboration of regulatory programme personnel and legal drafters, taking into consideration the objectives of the legal instrument, the intended audience and other potentially impacted stakeholders, as well as feedback from internal and external consultations. Clear, unambiguous and precise instruments that are drafted in a language and form consistent with other laws and regulations reduce the potential for disputes or misinterpretation and also promote compliance.

As an initial step in the process, the authority drafting medical product regulations should conduct a review to identify areas that lack clarity and resolve any inconsistencies – whether within the regulation itself or between regulations. This also serves as an opportunity to review the “regulatory stock” – the accumulated body of applicable regulations – to identify the need for future updating and better integration of regulatory requirements with a view to eliminating inconsistencies, redundancies and complexity or adapting to new requirements.

Providing interested parties, including the public, the opportunity to be informed of and contribute to the process of regulatory development and regulatory impact analysis is critical to improving the quality and language of the regulatory instrument, promoting a clear understanding of what is intended, and increasing the likelihood of buy-in and future compliance. The means by which interested parties can contribute should be made clear.
Regulatory impact analysis is a valuable tool for systematic assessment of the expected effects of regulatory proposals. It is usually undertaken by the policy analysts of the regulatory departments, agencies or ministries that sponsor the proposal and is primarily aimed at assisting decision-makers in their consideration of a recommended proposal. The product of the regulatory impact analysis process is a document that summarizes the regulatory proposal, the potential alternatives and the implementation aspects and impacts of the proposal.

Terminology should be defined whenever possible to avoid ambiguity or misinterpretation. Where possible, terminology should be consistent with established international norms, standards and harmonized guidelines. As noted, international standards and guidelines are particularly important as vehicles to promote a common regulatory language, convergence and international cooperation.

The principle of clarity is equally important and applicable to the development of regulatory and administrative guidelines which are instrumental in interpreting and providing operational clarity to regulations. Guideline development should follow good guidance practice to ensure that guidelines are written in a clear and concise manner and are consistent with other guidelines and the underlying regulations. This includes the use of standard templates and formats, writing style guides, editors, and experts with a good knowledge of the regulatory framework.

Draft guidelines, as with regulations, should be subject to internal and external consultation. Consultation will help confirm if language is clear or if it requires some refinement to improve comprehension. Plain language and simple sentence structure should be the goal as well as to give illustrative examples where possible.

Education, awareness sessions and training, along with clear timelines for the adoption of new regulations and guidelines, should also be considered as tools to promote clarity and compliance when introducing or amending regulations and guidelines, particularly when complex in nature.

Regulations and supporting guidelines should be reviewed periodically to ensure that they still reflect the authority’s current practices and expectations, are adapted to the scientific and technological developments, and are aligned with current international standards and guidelines, where applicable. When reviewing and revising any guideline, one must consider the consequential changes in other existing guidelines that will need simultaneous revision.

From an operational perspective, the process and basis for taking regulatory decisions and enforcement actions should be clear and accessible to those directly impacted or otherwise affected (see 7.9 Transparency).
In summary, clarity is essential in all aspects of regulatory oversight (requirements, procedures, decisions and communications) if regulatory programmes are to have the desired effect.

### 8.8 Efficiency

Regulatory systems should achieve the intended results within the required time and at reasonable effort and cost.

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<th>Key elements:</th>
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<tr>
<td>• Efficient regulatory oversight are those that achieve the intended public health goals.</td>
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<tr>
<td>• A sound regulatory framework, competent staff and the effective use of resources and information from other authorities are the key elements of an efficient regulatory system.</td>
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<tr>
<td>• Policy-makers should seek the most efficient and least burdensome means of achieving their regulatory purposes and confirm actual effectiveness once implemented.</td>
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<tr>
<td>• In considering a regulatory approach, the total burden and resource needs of cumulative regulation should be evaluated.</td>
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<tr>
<td>• Regulatory authorities should continually explore ways of improving efficiency in fulfilling their mandate.</td>
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<tr>
<td>• Alignment of regulatory requirements with other countries and international collaboration promote efficiency.</td>
</tr>
<tr>
<td>• Regulated entities play a critical role in contributing to the efficiency of regulatory systems.</td>
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<tr>
<td>• The efficiency of regulatory instruments and regulatory operations should be assessed using performance-based indicators.</td>
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An efficient regulatory system must be science- and evidence-based, apply the principles of risk assessment and management, and embed a strategy of international regulatory cooperation into daily business. A regulatory system that is unable to make sound decisions in a timely and consistent fashion is not effective. This is not only a matter of having sufficient resources but also having the right resources and using them effectively, irrespective of size. In this context, lack of integrity of the overall regulatory system is a barrier to regulatory efficiency.

Less resourced regulatory systems can be as effective as more resourced systems if risk-based and if advantage is taken of the work and decisions of other regulatory authorities while focusing resources on essential, value-added activities which only the regulatory authority is in a position to perform (17).
Regulatory oversight cannot be considered efficient if it creates unjustified barriers to access, trade and international regulatory cooperation. The successful establishment of effective regulatory controls on medical products depends on a number of factors as previously described, including:

- The analysis of options that includes the results of consultation with stakeholders. Regulations are more likely to be effective if those impacted have provided input.
- Regulations that are proportional to perceived risk.
- Early-stage planning for implementation and the practicalities of future enforcement. Application and enforcement should not be after-thoughts.

When new regulatory instruments are being developed and subjected to regulatory impact analysis, the regulatory authority should develop "strategies for education, assistance, persuasion, promotion, economic incentives, monitoring, enforcement, and sanctions" (24). The authority must decide which compliance strategies will be established and whether or not consumer awareness and market forces can reasonably be used, in addition to the threat of penalties. The role of civil society in monitoring adherence to regulation should also be considered, if appropriate.

Co-regulation may also be considered in certain circumstances. In such situations, a government would issue regulations and enter into a non-statutory agreement with a body to develop and administer a compliance program. While a government works with and through the body in regulating the activity, it has not delegated its oversight of the activity.

The use of third parties can also be considered by regulatory authority to conduct their activities, a model prevalent in the regulation of medical devices; for example, the use of recognized auditing organizations to conduct audits of manufacturers’ quality management systems to an international standard and applicable regulatory requirements. Regulatory resources are directed at establishing and maintaining oversight of audit organizations, providing more effective use of limited regulatory resources (25).

A government incurs costs by establishing and maintaining regulatory systems. Industry and other regulated parties incur costs in complying with regulation; for example, in undertaking studies, preparing application dossiers, maintaining records and paying fees – the cost of doing business.
Additional costs accrue from inefficient regulatory systems. If the cost of complying with regulation is disproportionately high, companies may decide against placing products on the market. For instance, a mandatory requirement to conduct local clinical trials as a condition for marketing authorisation could be a disincentive to enter a market, especially if trials conducted elsewhere reflect the patient profiles of the intended market and demonstrate safety and efficacy of the product. Similarly, lengthy product review times translate into lost revenue and unnecessary delays in the availability of products for patients – with potentially significant negative implications in terms of morbidity/mortality, health care costs and the economy (healthy economies require healthy people).

Inefficiency also costs regulatory authorities in terms of sub-optimal impact for available resources, reputation, job satisfaction and time spent addressing complaints related to performance. Regulatory frameworks reflecting the principles of proportionality, flexibility and consistency are more likely to be effective. They allow for resources to be allocated to the regulatory activities where they are most needed.

**International collaboration.** Regulatory frameworks that are consistent and aligned with those of other countries and regions encourage the investment needed to bring appropriate and affordable products to that market. Internationally consistent frameworks also enable the regulatory authority to participate in work-sharing networks and other forms of regulatory cooperation (including convergence, harmonization, information- and work-sharing, reliance and recognition). When properly anchored in the regulatory framework, reliance on the work of other authorities eliminates or reduces the inefficient duplication of regulatory evaluations of medical products and the inspection/audit of facilities.

Regulatory authorities should continually explore the means of improving efficiency while maintaining standards for evaluating the quality, safety and efficacy/performance of medical products. For example, this could include the introduction or refinement good review practices (18) and a quality management system (19); greater and more effective use of information technology; consultations with industry on common deficiencies and how best to address them; risk-based criteria for scheduling and conducting inspections; addressing gaps in guidance; performance measurement; and – as highlighted above – regulatory cooperation and reliance.

Industry also plays a critical role in contributing to the efficiency of regulatory systems. As an example, high quality applications for marketing authorization reduce the overall review time by reducing the number of deficiencies and review cycles. Similarly, a manufacturer with a good compliance record should not require the same frequency and depth of inspection as a poorly performing manufacturer. Consultations and training can be effective complements to enforcement actions in achieving the desired level of compliance.
As part of the regulatory impact analysis process, policy-makers should seek the most efficient and least burdensome means of achieving their regulatory purposes at a minimum reasonable cost, including non-regulatory options. In considering a regulatory approach, there should be consideration of the total burden and resource needs of cumulative regulation.

Periodic performance assessments should evaluate the actual efficiency of regulatory instruments that are implemented in order to ensure that the foreseen benefits have been achieved and, if so, what the direct and indirect costs are.

### 8.9 Transparency

Transparency is the hallmark of a well-functioning regulatory system and essential to building public trust and enabling international cooperation.

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<tr>
<td>• Transparency requires investment and a culture of openness, supported by government policy, commitment and action.</td>
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<tr>
<td>• The process of developing new or revising existing regulatory instruments should include stakeholder consultation.</td>
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<tr>
<td>• Regulatory requirements, processes, fees, assessments, decisions and actions should be accessible as much as possible.</td>
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<tr>
<td>• The regulatory authority’s disclosure policies should be consistent with national laws on access to information.</td>
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"Informed opinion and active co-operation on the part of the public are of the utmost importance in the improvement of the health of the people." – World Health Organization Constitution

Transparency is a hallmark of a well-functioning regulatory system. It is in the interests of patients, consumers, governments, health care workers and manufacturers as it increases the level of public trust and confidence in the regulatory oversight of medical products. Transparency in regulatory requirements and actions allows for better-informed investment decisions in the public and private sectors and discourages discriminatory, corrupt or abusive practices.

Transparency means that all affected and potentially interested parties – domestic, foreign, public and private – have meaningful opportunities to be informed of new or amended regulations and guidelines and to make their views known before they are enacted.
Transparency means that, once adopted, medical product regulations and guidelines are readily available and accessible to stakeholders and the general public. Relevant laws, regulations and guideline documents should be posted on the authority’s website. Additionally, national industry and professional associations will often work with regulatory authorities to disseminate new regulatory texts or to provide opportunities for the exchange of relevant information.

The assessments, decisions (positive and also, when possible, negative ones) and actions of the regulatory authority should be documented and made publicly available. Such information is important to a broad range of stakeholders - including industry, researchers, health professionals, patients and consumers - who will use the information for a variety of purposes. It is also an essential element to building trust and confidence in the regulatory system.

Regulated parties should be able to access the full product assessment or site inspection reports that pertain to them. In addition to providing an insight into the basis for comments and decisions, it also serves as an educational tool that can help improve regulatory compliance and the quality of future submissions. This practice can also be beneficial to the regulatory authority by fostering a culture of transparency and accountability at the operational and management level. Furthermore, it can lead to higher quality reports by ensuring that reports clearly explain how such assessments led to decisions.

Transparency requires investment and a culture of openness that, in turn, must be supported by government policy, commitment and action. While it may not be possible for all regulatory authorities to implement the full range of measures that define an optimally transparent regulatory system, a step-wise approach can be adopted. Given the prevalence of smart devices and the internet, efforts could be directed towards establishing and maintaining an up-to-date, searchable public website that contains certain basic information, including:

- Information on the regulatory authority – roles, responsibilities, organization, and contact information.
- Access to laws, regulations, guidelines and procedures necessary to satisfy regulatory requirements and improve the safety and quality of medical products.
- A searchable product registry of approved, suspended and withdrawn products.
- Product information for health care professionals and patients.
- Licensing status of manufacturing sites.
- Health advisories, safety information, quality or substandard and falsified medical product alerts, recalls and other time-sensitive information of public health interest.
- Performance targets/results and annual reports.
- Proposed new regulatory instruments, including comment periods and how to provide input.
The findings of all audits or oversight reviews of the performance and functioning of the regulatory authority should be made public. Such reviews are an important element of public accountability, as is the establishment and ongoing reporting of performance against regulatory targets and the publication of annual reports.

As it fulfils its responsibilities, the regulatory authority will necessarily create or come into possession of proprietary or confidential information. Examples include personal identifiable information from clinical trials or reports of adverse events, specifications of medical product compounds or materials, and key manufacturing processes. Measures should be established to prevent the inappropriate disclosure of such specific information. There should be a mechanism to address instances when the proprietary nature or confidentiality of the information is in dispute.

In general, national law and regulation should favour transparency and public access in both the process and the criteria of regulatory decision-making. The regulatory authority’s disclosure policies should be consistent with the national laws on public access to government information or “freedom of information”. Procedures and contact points to obtain information held by the regulatory authority should be accessible and clear.

Transparency is a key enabler to adopting new, more efficient ways of conducting regulatory operations. It is incumbent upon regulators to practice transparency in regulatory operations and decisions as a fundamental principle of GRP but also towards building trust and maximizing opportunities for cooperation and reliance as part of a shared regulatory community responsibility.

9. Enablers for good regulatory practices

An enabling environment will facilitate a successful implementation of GRP. The non-exhaustive list of GRP key enablers include:

9.1 Political and government-wide support

A sustained support at the highest political and government levels, including policy makers, is essential for the proper implementation of the concept and principles of GRP.

GRP should form an integral part of government-wide policies on regulatory system and, in addition, be backed by strong political support.
9.2 Effective organization and good governance supported with leadership

The structure and line of authority among and within all institutions of the regulatory system should be well defined. The integrity of the overall regulatory system is critical to the effective and efficient performance of all institutions composing the regulatory system. If more than one institution is involved in the regulatory system, the legislation or institutional regulation should provide for clear coordination and avoid an overlap of the regulatory activities. Leadership is critical for setting and carrying out the organizational vision, mission, policies and strategies which in turn significantly contribute to organizational efficiency.

9.3 Inter-and-intra-organizational communication, collaboration and coordination

Adequate and effective communication plays a fundamental role for exchanging information within and outside the institutions forming the regulatory system. When regularly communicating both internally and externally, regulatory authorities remain more transparent and accountable. Communicating correct information prevents the potential misunderstandings and dissemination of misleading information to patients and the public. Communication is a powerful tool for collaboration and coordination with relevant stakeholders at national and international levels which in turn feed into an effective and efficient use of resources and better regulatory outcomes.

9.4 A robust and well-functioning quality management system

QMS (19), which includes the application of quality risk management (QRM) principles, is a valuable tool that helps regulatory authorities to achieve greater credibility for their decisions, and greater stability and consistency in their operations. QMS contributes to systematic planning, control and improved quality in all processes throughout all regulatory functions and ensures a comprehensive approach for all.

9.5 Sufficient and sustainable financial resources

Investment in regulatory systems is critical to a well-functioning health care system. Securing financial resources to effectively carry out the regulatory mandate and to continuously improve the performance of regulatory activities is an essential enabler for regulatory system independence, impartiality, consistency and efficiency. The financial resources of all institutions of the regulatory system should be sustainable, apart from donors’ or philanthropic entities donations.
9.6 Competent human resources

An array of knowledge and the skills of regulatory staff contribute to the development, implementation and maintenance of a regulatory system for medical products. Personal and career development policies and measures (e.g. training programmes, competitive remuneration schemes) are critical for regulatory authorities to attract and recruit competent staff and, in addition, to retain staff in the service.

9.7 Pre-set organizational ethics and values

Regulatory activities should abide by ethical principles, organizational values, and professionalism. All regulatory staff should be made aware and be trained on the ethics and values as set by the regulator authorities (e.g. code of conduct). A system should be established, within or external to the regulatory system, to manage situations of departure from the organizational ethics and values.

9.8 Science- and data-driven decision-making process

Regulatory decisions, along with their making process, should be based on scientific foundations and accurate data rather than intuitions or arbitrariness. Science-based decisions provide for the consistency and predictability of regulatory outcomes.

The above-listed enablers do not work in a stand-alone mode. Rather, they work in harmony to realize the application and implementation of GRP; for example, the sufficient and sustainable financial resources contribute to the recruitment, development and maintenance of competent human resources. Similarly, financial resources shall be managed following good governance practices.

10. Implementing good regulatory practices

WHO Member States are encouraged to implement GRP in their regulatory systems with due consideration to their legal and regulatory system realities. Transparent and predictable processes should aim to develop high-quality regulatory oversight that achieves intended objectives while also minimizing negative impact and costs.

At the same time, there should be sufficient flexibility to allow the processes to be applied proportionately to the scope, magnitude and complexity of the issue. Sustained support at the highest levels, along with adequate resourcing, is essential.

Further guidance will be developed to assist Member States both in establishing new regulatory systems for medical products and in updating existing ones.
11. Acknowledgements

WHO wishes to acknowledge all the authors, stakeholders and organizations who contributed to the preparation of this document.

12. Glossary

The definitions given below apply to the terms as used in this document. They may have different meanings in other contexts. Readers are also encouraged to consult related WHO guidances for a more complete set of definitions relevant to best regulatory practices (see References).

public health emergency. A public health emergency (the condition that requires a governor to declare a state of public health emergency) is defined as "an occurrence or imminent threat of an illness or health condition, caused by bioterrorism, epidemic or pandemic disease, or (a) novel and highly fatal infectious agent or biological toxin that poses a substantial risk of a significant number of human facilities or incidents or permanent or long-term disability (WHO/DCD, 2001). The declaration of a state of public health emergency permits a governor to suspend state regulations and change the functions of state agencies (26).

quality management system (QMS). An appropriate infrastructure encompassing the organizational structure, procedures, processes and resources and systematic actions necessary to ensure adequate confidence that a product or service will satisfy given requirements for quality.

recognition. The acceptance of the regulatory decision of another regulator or other trusted institution. Recognition should be based on evidence of conformity that the regulatory requirements of the reference regulatory authority is sufficient to meet the regulatory requirements of the relying authority.

regulatory convergence. A voluntary process whereby the regulatory requirements in different countries or regions become more similar or “aligned” over time. The process results from the gradual adoption of internationally recognized technical guideline documents, standards and scientific principles, common or similar practices and procedures, or the establishment of appropriate domestic regulatory mechanisms that align with shared principles to achieve a common public health goal (27).
**regulatory cooperation.** A practice between regulatory authorities aimed at the efficient and effective regulation of medical products. Regulatory cooperation can be practised by an agency or institution or on a government-wide basis. The range of formal mechanisms include the creation of joint institutions and treaties and conventions such as mutual recognition agreements, while less formal practices include the sharing of information, scientific collaboration, common risk assessment, joint reviews and inspections and the development of standards. Regulatory cooperation may also include work with international counterparts to build regulatory capacity or provide technical assistance, thus contributing to the improvement of international regulatory governance practices (28) (29) (30) (31).

**regulatory harmonization.** The process whereby technical guidelines are developed in order to be uniform across participating authorities in multiple countries (32).

**regulatory impact analysis.** The process of examining the likely impacts of a proposed regulation and alternative policy options to assist the policy development process (33).

**regulatory stock.** The collection or inventory of accumulated regulations.

**regulatory system.** The combination of institutions, processes and the regulatory framework through which a government controls the particular aspects of an activity (34).

**reliance.** The act whereby the NRA in one jurisdiction may take into account and give significant weight to assessments performed by another NRA or trusted institution, or to any other authoritative information in reaching its own decision. The relying authority remains independent, responsible and accountable regarding the decisions taken, even when it relies on the decisions and information of others.
13. References


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3.6 TEST FOR HISTAMINE-LIKE SUBSTANCES (VASODEPRESSOR SUBSTANCES)

Draft proposal for revision in The International Pharmacopoeia

DRAFT FOR COMMENTS

Please send any comments you may have on this draft working document to Dr Herbert Schmidt, Technical Officer, Norms and Standards for Pharmaceuticals, Technical Standards and Specifications (schmidt@who.int) by 18 September 2020.

Working documents are sent out electronically and they will also be placed on the WHO Medicines website (http://www.who.int/medicines/areas/quality_safety/quality_assurance/guidelines/en/) for comments under the “Current projects” link.

If you wish to receive our draft guidelines, please send your e-mail address to jonessi@who.int and your name will be added to our electronic mailing list.

[Note from the Secretariat. Comments are sought on the proposal to suppress chapter 3.6 Test for histamine-like substances (vasodepressor substances) in The International Pharmacopoeia and the references to this chapter in the monographs on Bleomycin sulfate, Spectinomycin hydrochloride, Streptomycin sulfate. The proposals follows the strategy to phase-out animal testings where possible and justified.

The test for vasodepressor substances is carried out in cats by comparing the depression of arterial pressure caused by the test solution with that obtained after administration of a solution of histamine. Changes from the current chapter are indicated in the text by insert or delete.]
3.6 TEST FOR HISTAMINE-LIKE SUBSTANCES
(VASODEPRESSOR SUBSTANCES)

3.6 Test for histamine-like substances (vasodepressor substances)
The test for vasodepressor substances is carried out in cats by comparing the depression of arterial pressure caused by the test solution with that obtained after administration of a solution of histamine.

Recommended procedures
Use healthy, adult cats, either males or non-pregnant females.

Determine the weight of the animal and place under general anaesthesia by injection of chloralose R or a suitable barbiturate that allows the maintenance of uniform blood pressure. Protect the animal from loss of body heat and maintain it so that the rectal temperature remains within physiological limits. Introduce a tube into the trachea. Surgically expose the common carotid artery and by blunt dissection separate it completely from all surrounding structures, including the vagus nerve. Insert a cannula filled with heparinized saline TS into the artery and connect it to a mercury manometer or another suitable device arranged for making a continuous record of blood pressure. Surgically expose the jugular or the femoral vein and insert into it another cannula filled with heparinized saline TS through which can be injected solutions of histamine and of the test substance.

Determine the sensitivity of the animal to histamine in the following way: Start the recording kymograph or a similar recording device and inspect the tracings for amplitude of excursion and relative stability of blood pressure. Inject into the jugular or femoral vein histamine TS, in doses of 0.05 μg (dose A), 0.1 μg (dose B) – repeated at least 3 times – and 0.15 μg (dose C) of histamine base per kg of animal weight. Administer the second and subsequent injections not less than 1 minute after the blood pressure has returned to the level recorded immediately before the previous injection. Repeat this series of injections until, disregarding the first series of readings, a relatively uniform decrease in blood pressure is obtained after doses B of histamine. The animal should be used for the test only if the decrease after doses B is not less than 2.7 kPa (20 mm Hg) and, moreover, if dose A causes smaller responses than doses B whereas dose C gives greater responses than doses B.

Prepare the test solution as described in the monograph. During the course of the test, take care to maintain a uniform rate of injection for both the test solution and the standard solution. If the jugular vein is used, care should also be taken that the injection of test solution and histamine standard are given in equal volumes to avoid volume effects on blood pressure. When a common cannula is used for both the standard and test solutions, each injection of the standard and test solution should be immediately followed by an injection of approximately 2.0 mL of saline TS to flush any residues from the tubing.
Inject a dose B of the standard solution followed by an injection of the specified amount of the test solution and then another dose B of the standard solution. The second and third injections are given not less than 1 minute after the blood pressure has returned to the level recorded immediately before the preceding injection. If the response to the test solution is greater than that given previously by dose A, repeat the series of injections twice and conclude the test by giving dose C of standard solution. If the response to dose C is not greater than that to dose B, the test is invalid.

The animal may be used in the test as long as it remains reasonably stable and responsive to histamine and provided that (a) an injection of test substance did not cause a greater depressor response than that caused by dose C and (b) the response to dose C of the standard solution given after the administration of the test substance does not become lower than the mean response to doses of B previously injected.

The substance passes the test if the response or the mean of the responses after the injection of the amount specified in the monograph is smaller than the mean of the corresponding responses to dose B of the standard solution (0.1 μg of histamine base per kg of animal weight), and no one single dose of the test solution causes a greater depressor response than dose C of the standard solution (0.15 μg of histamine base per kg of animal weight).

Reference to 3.6 Test for histamine-like substances in monographs:

Bleomycin sulfate (Bleomycini sulfas)

Manufacture. The method of manufacture is validated to demonstrate that the product, if tested, would comply with the following test.

Histamine-like substances. Carry out the test as described under 3.6 Test for histamine-like substances (vasodepressor substances) using 1 mL per kg of body mass of a solution in saline TS containing a quantity equivalent to 500 IU per mL.

Spectinomycin hydrochloride (Spectinomycini hydrochloridum)

Histamine-like substances. Carry out the test as described under 3.6 Test for histamine-like substances (vasodepressor substances) using 1 mL per kg of body mass of a solution in saline TS containing 25 mg of the substance to be examined per mL.

Streptomycin sulfate (Streptomycini sulfas)

Manufacture. The method of manufacture is validated to demonstrate that the product, if tested, would comply with the following test.

Histamine-like substances. Carry out the test as described under 3.6 Test for histamine-like substances (vasodepressor substances) using, per kg of body weight, a solution containing 3 mg of streptomycin base in 1 mL of saline TS.

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ALBENDAZOLE CHEWABLE TABLETS
(ALBENDAZOLI COMPRESSI MANDUCABILI)

Draft proposal for revision for The International Pharmacopoeia

DRAFT FOR COMMENTS

Please send any comments you may have on this draft working document to Dr Herbert Schmidt, Technical Officer, Norms and Standards for Pharmaceuticals, Technical Standards and Specifications (email: schmidt@who.int) by 30 September 2020.

Working documents are sent out electronically and they will also be placed on the WHO Medicines website (http://www.who.int/medicines/areas/quality_safety/quality_assurance/guidelines/en/) for comments under the “Current projects” link.

If you wish to receive our draft guidelines, please send your e-mail address to jonessi@who.int and your name will be added to our electronic mailing list.

[Note from the Secretariat. It is proposed to revise the Dissolution test in monograph on Albendazole chewable tablets based on information received by a manufacturer. Comments are invited on the revised section.

Manufacturers of Albendazole chewable tablets and Albendazole tablets are invited to submit samples of their products so that the applicability of the revised dissolution procedure for their product(s) can be tested.

For further information regarding the submission of samples, please contact Dr Herbert Schmidt at schmidt@who.int.
Changes from the current monograph are indicated in the text by insert or delete.]
ALBENDAZOLE CHEWABLE TABLETS
(ALBENDAZOLI COMPRESSI MANDUCABILI)

Category. Anthelminthic.

Storage. Albendazole chewable tablets should be kept in a tightly closed container.

Labelling. The designation on the container should state that the tablets may be chewed, swallowed whole or crushed and mixed with food or liquid, and that the tablets should be crushed before being given to a young child.

Additional information. Strengths in the current WHO Model List of Essential Medicines (EML): 400 mg. Strengths in the current EML for children: 400 mg.

Requirements
Comply with the monograph for Tablets.

Definition. Albendazole chewable tablets contain Albendazole in a suitable basis that may contain suitable flavouring agents. They contain not less than 90.0% and not more than 110.0% of the amount of Albendazole (C₁₂H₁₅N₃O₂S) stated on the label.

Identity tests
• Any two of tests A, B and C may be applied.

A. Carry out the test as described under 1.14.1 Thin-layer chromatography using the chromatographic conditions given under “Related substances”, Test B. Apply separately to the plate 10 µL each of the following solutions in a mixture of 9 volumes of dichloromethane R and 1 volume of glacial acetic acid R. For solution (A), shake a quantity of the powdered tablets containing about 2.5 mg of Albendazole with 25 mL, filter and use the filtrate. For solution (B), use 0.1 mg of albendazole RS per mL. For solution (C), use 0.1 mg of albendazole RS and 0.1 mg of oxibendazole R per mL. After removing the plate from the chromatographic chamber, allow the plate to dry in a current of warm air and examine the chromatogram under ultraviolet light (254 nm). The test is not valid unless the chromatogram obtained with solution (C) shows two clearly separated spots. The principal spot obtained with solution (A) corresponds in position, appearance and intensity with that obtained with solution (B).

B. See the test described below under “Assay”, Method A. The retention time of the principal peak in the chromatogram obtained with solution (1) is similar to the retention time of the peak due to albendazole obtained with solution (3).
C. See the test described under “Assay”, Method B. The absorption spectrum (1.6) of the test solution, when observed between 220 and 340 nm, exhibits maxima at about 231 nm and at 308 nm; the absorbance at 308 nm is about 0.59.

**Dissolution**

*For 200 mg tablets:* carry out the test as described under 5.5 Dissolution test for solid oral dosage forms using 900 mL of hydrochloric acid (~3.65 g/L) TS as the dissolution medium and rotating the paddle at 75 revolutions per minute. At 30 minutes, withdraw a sample of about 10 mL of the dissolution medium through an in-line filter. Cool the filtered sample to room temperature and dilute 2.0 mL of the obtained solution to 25.0 mL with the dissolution medium. Use this solution as solution (1). For solution (2), dissolve 44.0 mg of albendazole RS in 10.0 mL of sulfuric acid/methanol (1%) TS and immediately dilute to 100.0 mL with of hydrochloric acid (~3.65 g/L) TS. Dilute 2.0 mL of this solution to 50.0 mL with hydrochloric acid (~3.65 g/L) TS.

Measure the absorbance (1.6) of a 1.0 cm layer of solutions (1) and (2) at about 291 nm, using hydrochloric acid (~3.65 g/L) TS as the blank. For each of the six tablets tested, calculate the total amount of albendazole (C₁₂H₁₅N₃O₂S) in the medium using the absorptivity value of 74.2 (\(\varepsilon_{291\text{nm}} = 742\)). The amount of albendazole released is not less than 80% (Q) of the amount declared on the label.

*For 400 mg tablets:* carry out the test as described under 5.5 Dissolution test for solid oral dosage forms using 900 mL of hydrochloric acid (~10 g/L) TS as the dissolution medium and rotating the paddle at 75 revolutions per minute. At 30 minutes, withdraw a sample of about 10 mL of the dissolution medium through an in-line filter. Cool the filtered sample to room temperature and dilute 2.0 mL of the obtained solution to 50.0 mL with hydrochloric acid (~10 g/L) TS. Use this solution as solution (1). For solution (2), dissolve 44.0 mg of albendazole RS in 10.0 mL of sulfuric acid/methanol (1%) TS and immediately dilute to 100.0 mL with hydrochloric acid (~10 g/L) TS. Dilute 2.0 mL of this solution to 50.0 mL with hydrochloric acid (~10 g/L) TS.

Measure the absorbance (1.6) of a 1.0 cm layer of solutions (1) and (2) at about 291 nm, using hydrochloric acid (~10 g/L) TS as the blank. For each of the six tablets tested, calculate the total amount of albendazole (C₁₂H₁₅N₃O₂S) in the medium using the absorptivity value of 74.2 (\(\varepsilon_{291\text{nm}} = 742\)). The amount of albendazole released is not less than 80% (Q) of the amount declared on the label.
Carry out the test as described under 5.5 Dissolution test for solid oral dosage forms using 900 mL of hydrochloric acid (~3.65 g/L) TS as the dissolution medium and rotating the paddle at 75 revolutions per minute. At 30 minutes withdraw a sample of about 15 mL of the dissolution medium through an in-line filter. Cool the filtered sample to room temperature. Transfer 1.0 mL of the clear filtrate to a 50 mL volumetric flask and dilute to volume with sodium hydroxide (0.1 mol/L) VS. Measure the absorbance (1.6) of a 1 cm layer of the resulting solution at the maximum at about 308 nm, using sodium hydroxide (0.1 mol/L) VS as the blank.

For each of the six tablets tested calculate the total amount of albendazole (C₁₂H₁₅N₃O₂S) in the medium using the absorptivity value of 74.2 \( \left( \frac{A_{1000}}{c \cdot l = 742} \right) \). The amount in solution for each tablet is not less than 80% (Q) of the amount declared on the label.

Related substances

- Either method A or method B may be applied.

A. Carry out the test as described under 1.14.4 High-performance liquid chromatography using the conditions given below under “Assay”, Method A.

Prepare the following solutions.

Solvent mixture: dilute 1 volume of sulfuric acid R with 99 volumes of methanol R. 

For solution (1), transfer a quantity of the powdered tablets containing about 25 mg of Albendazole to a 50 mL volumetric flask. Add 5 mL of the solvent mixture and 20 mL of methanol R and shake to dissolve for about 15 minutes. Dilute to volume with methanol R. For solution (2), dilute 1.0 mL of solution (1) to 100.0 mL with methanol R. For solution (3), dissolve about 20 mg of albendazole RS and about 20 mg of oxibendazole R in 5 mL of solvent mixture and dilute to 100.0 mL with methanol R. Inject separately 20 µL each of solutions (1), (2) and (3). Record the chromatogram for about 25 minutes.

In the chromatogram obtained with solution (3), the peak due to oxibendazole is eluted at a retention time of about 9.9 min and the peak due to albendazole at a retention time of about 13.6 minutes. The test is not valid unless the resolution factor between the peak due to oxibendazole and the peak due to albendazole is at least 3.0.

In the chromatogram obtained with solution (1):

- the area of any peak, other than the principal peak, is not greater than the area of the peak due to albendazole in the chromatogram obtained with solution (2) (1.0%); and

- the area of not more than one such peak is greater than 0.75 times the area of the peak due to albendazole in the chromatogram obtained with solution (2) (0.75%).
B. Carry out the test as described under 1.14.1 Thin-layer chromatography using silica gel R5 as the coating substance and a mixture of dichloromethane R, glacial acetic acid R and ether R (30:7:3 v/v) as the mobile phase. Apply separately to the plate 10 µL each of the following solutions in a mixture of 9 volumes of dichloromethane R and 1 volume of glacial acetic acid R. For solution (A), shake a quantity of the powdered tablets containing about 250 mg of Albendazole with 25 mL, filter and use the filtrate. For solution (B), use 0.1 mg of albendazole RS per mL. For solution (C), use 0.075 mg of albendazole RS per mL. For solution (D), use 0.1 mg albendazole RS and 0.1 mg oxibendazole R per mL. After removing the plate from the chromatographic chamber, allow the plate to dry in a current of warm air. Examine the chromatogram in ultraviolet light (254 nm). The test is not valid unless the chromatogram obtained with solution (D) shows two clearly separated spots.

In the chromatogram obtained with solution (A), any spot, other than the principal spot, is not more intense than the principal spot obtained with solution (B) (1.0%) and not more than one spot is more intense than the principal spot obtained with solution (C) (0.75%).

Assay

• Either method A or method B may be applied.

A. Carry out the test as described under 1.14.4 High-performance liquid chromatography using a stainless steel column (25 cm × 4.6 mm) packed with octadecylsilyl base-deactivated silica gel for chromatography R (5 µm). As the mobile phase, use a solution prepared as follows: dissolve 1.67 g of monobasic ammonium phosphate R in 1000 mL of water R, mix and filter. Mix 300 mL of this solution with 700 mL of methanol R. Make adjustments if necessary. Prepare the following solutions.

Solvent mixture: dilute 1 volume of sulfuric acid R with 99 volumes of methanol R. For solution (1), weigh and powder 20 tablets. Transfer a quantity of the powdered tablets containing about 100 mg of Albendazole, accurately weighed, to a 50 mL volumetric flask. Add 5 mL of the solvent mixture and 20 mL of methanol R and shake for about 15 minutes. Dilute to volume with methanol R, mix and filter, discarding the first 15 mL of the filtrate. Dilute 5.0 mL of this solution to 50.0 mL with methanol R. For solution (2), transfer 25.0 mg of Albendazole RS to a 25 mL volumetric flask, add 5 mL of the solvent mixture and 15 mL of methanol R and shake to dissolve. Dilute to volume with methanol R. For solution (3), dilute 2.0 mL of solution (2) to 10.0 mL with methanol R. For solution (4), dissolve about 20 mg of oxibendazole R in 5 mL of solvent mixture in a 100 mL volumetric flask, add 20 mL of solution (2), mix and dilute to volume with methanol R. Operate with a flow rate of 0.7 mL per minute. As a detector, use an ultraviolet spectrophotometer set at a wavelength of 254 nm.
Inject separately 20 µL each of solutions (1), (3) and (4). The test is not valid unless, in the chromatogram obtained with solution (4), the resolution factor between the peaks due to albendazole and due to oxibendazole is at least 3.0.

Measure the areas of the peak responses obtained in the chromatograms from solutions (1) and (3) and calculate the content of Albendazole (C₁₂H₁₅N₃O₂S) in the tablets using the declared content of C₁₂H₁₅N₃O₂S in albendazole RS.

B. Weigh and powder 20 tablets. Transfer a quantity of the powdered tablets containing about 20 mg of Albendazole, accurately weighed, to a 50 mL volumetric flask, add 30 mL of hydrochloric acid/methanol (0.01 mol/L) VS, shake for 15 minutes and dilute to volume with the same solvent. Mix and filter, discarding the first 10 mL of the filtrate. Transfer 1.0 mL of the subsequent filtrate to a 50 mL volumetric flask and dilute to volume with sodium hydroxide (0.1 mol/L) VS. Measure the absorbance of the resulting solution at the maximum at about 308 nm, using sodium hydroxide (0.1 mol/L) VS as the blank. Calculate the content of Albendazole (C₁₂H₁₅N₃O₂S), using the absorptivity value of 74.2 (A¹% = 742).

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Good reliance practices in regulatory decision-making for medical products: high-level principles and considerations

Please send your comments to Mrs Marie Valentin, Technical Officer, Regulatory Convergence and Networks, Regulation and Safety (valentinm@who.int), with a copy to Mrs Carolyn Doucelin (doucelinc@who.int) before 18 September 2020. Please use our attached Comments Table for this purpose.

Our working documents are sent out electronically and they will also be placed on the WHO Medicines website (http://www.who.int/medicines/areas/quality_safety/quality_assurance/guidelines/en/) for comments under the “Current projects” link.

If you wish to receive all our draft guidelines, please send your email address to jonessi@who.int and your name will be added to our electronic mailing list.
Good reliance practices in regulatory decision-making for medical products: high-level principles and considerations

Acronyms

ACSS     Australia-Canada-Singapore-Switzerland Consortium
AMRH     African Medicines Regulatory Harmonisation
APEC     Asia-Pacific Economic Cooperation
API      Active Pharmaceutical Ingredient
ASEAN    Association of Southeast Asian Nations
ASEAN    ASEAN Pharmaceutical Products Working Group
PPWG     
AVAREF   African Vaccine Regulatory Forum
CARICOM  Caribbean Community and Common Market
CEP      Certificate of Suitability to the monographs of the European Pharmacopoeia
CPP      Certificate of Pharmaceutical Product
CPQ      Confirmation of active pharmaceutical ingredient Prequalification
CRP      Collaborative Registration Procedure
CRS      Caribbean Regulatory System
CTD      Common Technical Document
EAC      East African Community
ECOWAS   Economic Community of West African States
ECSPP    Expert Committee on Specifications for Pharmaceutical Preparations
eCTD     Electronic Common Technical Document
EMA      European Medicines Agency
EU       European Union
EU-M4 all European Union Medicines for all
GBT      Global Benchmarking Tool
GCC      Gulf Cooperation Council
GCP      Good Clinical Practices
GDP      Good Distribution Practices
GEON     General European OMCL Network
GHC      Gulf Health Council
GMP      Good Manufacturing Practices
GRP      Good Regulatory Practices
GRelP    Good Reliance Practices
GVP      Good Vigilance Practices
HC       Health Canada
HSA      Health Sciences Authority
ICH      International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICDRA    International Conference of Drug Regulatory Authorities
<table>
<thead>
<tr>
<th>Acronym</th>
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<tr>
<td>ICMRA</td>
<td>International Coalition of Medicines Regulatory Authorities</td>
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<td>ICSR</td>
<td>Individual Case Safety Report</td>
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<td>IMDRF</td>
<td>International Medical Device Regulators Forum</td>
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<td>IPRP</td>
<td>International Pharmaceutical Regulators Programme</td>
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<td>ISO</td>
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<td>IVD</td>
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<td>National Control Laboratory</td>
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<td>National Regulatory Authority; for the purpose of this document, this term also includes regional regulatory authorities such as the European Medicines Agency (EMA)</td>
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<td>OECD</td>
<td>The Organisation for Economic Co-operation and Development</td>
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<td>ZAZIBONA</td>
<td>Zambia, Zimbabwe, Botswana and Namibia; initial participants of the SADC collaborative procedure for the joint assessment of medicines</td>
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1. Background

The World Health Organization (WHO) supports the implementation of reliance on other regulators’ work as a general principle in order to make the best use of available resources and expertise. This principle enables leveraging the output of others whenever possible while placing a greater focus at the national level on value added regulatory activities that cannot be undertaken by other authorities, such as, but not limited to, in-country vigilance and market surveillance and control activities and oversight of local manufacturing and distribution. Reliance approaches facilitate timely access to safe, effective and quality-assured medical products (see 5. Scope) and can help in regulatory preparedness and response, particularly during public health emergencies.

Good Reliance Practices (GReIP) are anchored in the overarching Good Regulatory Practices (GRP) (1) which provide a means for establishing sound, affordable and effective regulatory oversight of medical products as an important part of health system strengthening. If implemented effectively, GRP can lead to consistent regulatory processes, sound regulatory decision-making, increased efficiency of regulatory systems and better public health outcomes. National regulatory authorities (NRAs) are encouraged to adopt these best practices in order to ensure that they are using the most efficient regulatory processes possible.

An ongoing initiative at WHO aims at establishing and implementing a framework for evaluating regulatory authorities and designating them as WHO-Listed Authorities (WLAs) (2). Based on benchmarking using the WHO Global Benchmarking Tool (GBT) (3), along with a performance evaluation process, WHO will assess the regulatory authority’s performance and maturity level in order to qualify a regulatory authority as a WLA and thereby provide a globally recognized, evidence-based and transparent system that can be used by NRAs as a reference for the selection of reference regulatory authority(ies) to practice reliance. A list of reference regulatory authorities is available on the WHO Website for NRAs to refer to (4).

The WHO held a consultative meeting in September 2019 in order to solicit input on the nature, structure and overall content of a document outlining GReIP. The meeting concluded that the Pan American Health Organization (PAHO)/Pan American Network for Drug Regulatory Harmonization (PANDRH)’s concept note and recommendations on regulatory reliance principles (5) should be used as a starting point for the development of a WHO GReIP document. The high-level document would be complemented in a second step by a repository of case studies, practice guides and examples of practical applications of GReIP.
2. Introduction

The United Nations Sustainable Development Goals and the drive for Universal Health Coverage (UHC) require that patients have access to quality-assured and safe medical products, hence, strong regulatory systems for medical products remain a critical element of well-functioning health systems and an important contributor to improving access and ultimately achieving UHC.

Establishing and sustaining mature regulatory systems is an enterprise that requires adequate resources including skilled and capable human resources and significant public investments. Moreover, the globalization of markets, the sophistication of health technologies, the rapid evolution of regulatory science and the increasing complexity of supply chains have led regulators to recognize the importance of international cooperation in order to ensure the safety, quality and efficacy of locally used products. In view of the extent and complexity of regulatory oversight required to address these challenges, NRAs must consider enhanced, innovative and more effective forms of collaboration in order to make the best use of the available resources and expertise, avoid duplication and concentrate their regulatory efforts and resources where most needed.

Reliance represents a smarter and more efficient way of regulating medical products in a modern regulatory world. Towards this end, countries are encouraged to formulate and implement strategies to strengthen their regulatory systems consistently with GRP, including pursuing regulatory cooperation and convergence, as well as reliance. Reliance brings benefit to patients and consumers, the industry, national governments, as well as the donor community, and international development partners by facilitating and accelerating access to quality-assured, effective and safe medical products.

There is a long history of enhancing the efficiency of regulatory systems through reliance. The WHO Certification scheme on the quality of pharmaceutical products moving in international commerce (6), introduced by WHO in 1969, is a form of reliance providing assurance to countries participating in the Scheme about the quality of pharmaceutical products. The European Union (EU) introduced the mutual recognition procedure for marketing authorizations between Member States in 1995, and outcomes of Good Manufacturing Practice (GMP) inspections have been shared for years in the context of the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Cooperation Scheme (PIC/S) (7) and mutual recognition agreements.

The use of reliance was more recently investigated by WHO through a survey conducted on behalf of the International Pharmaceutical Regulators Programme (IPRP) (8). The results showed that regulatory reliance is a broadly accepted and widely practised approach in the area of medical products, especially among the participating well-resourced regulatory authorities. At the same time, responses also reflected an evolving situation marked by varying degrees of experience and promise in the use of reliance-based approaches. While the
use of reliance in some regions may be characterized as an emerging trend, the commonly stated goals are to bring efficiency, to help strengthen regulatory systems and to optimize the use of resources. The results and suggestions from this survey were taken into account for the preparation of this document.

Given the increased prevalence and importance of reliance in the regulatory oversight of medical products, countries have requested WHO to develop practical guidance on the topic while ensuring that approaches meet the intended objectives. This document, and the companion documents that will follow, are intended to assist countries in implementing a sound, evidence-based, practical and effective approach to reliance.

3. Purpose

The objective of this document is to promote a more efficient approach to regulatory oversight, thereby promoting access to quality-assured, effective and safe medical products.

The document aims at presenting the overarching principles of regulatory reliance in the field of oversight of medical products and the use of reliance as a tool for enhancing efficiency of regulatory oversight.

This document is intended to provide high-level guidance, definitions, key concepts and considerations in order to guide reliance mechanisms and activities, illustrative examples of reliance approaches and conclusions. It will be complemented by a “reliance toolbox” consisting of practice guides, case studies and a more comprehensive repository of examples.

4. Scope

This document covers reliance activities in the field of regulatory oversight of medical products (i.e. medicines, vaccines, blood and blood products and medical devices including in vitro diagnostics and other health products), addressing all regulatory functions as defined in the GBT spanning the full life cycle of a medical product - namely registration and marketing authorization, vigilance, market surveillance and control, licensing establishments, regulatory inspection, laboratory testing, clinical trials oversight, and NRA lot release (3).

In addition, this document is intended for all NRAs, irrespective of their level of maturity or resources, as well as policy makers, governments, the industry and other developers of medical products, and other relevant stakeholders.

The concept of reliance can cover all types of medical products and regulatory activities. Special consideration could be given to using reliance approaches for medical products addressing priority diseases with unmet medical needs, medical products to be used in public health emergencies or during shortages as well as for orphan medical products.
5. Definitions and key concepts

5.1 Definitions

Definitions are essential to ensure a common understanding of concepts and clarity in interpreting guidance related to reliance. In addition to the definitions provided below, reference is made to the WHO good regulatory practices document (1), which includes definitions for harmonization, convergence and other relevant terms.

**abridged regulatory pathways.** Abridged regulatory pathways are regulatory procedures facilitated by the use of reliance, whereby the regulatory decision is solely or widely based on the application of reliance. Normally this would also involve some degree of work by the relying NRA (see 6.2.4 Risk-based approach). The expectation is that the use of reliance in these pathways would save resources and shorten the timelines compared to the standard pathways, while ensuring that the standards for regulatory oversight are maintained.

**assessment.** For the purpose of this document, the term “assessment” covers the outcome of any evaluation conducted for a regulatory function (e.g. evaluation for a clinical trial application, evaluation of an initial authorization for a medical product or any subsequent post-authorization changes, evaluation of safety data, evaluation as part of an inspection, etc.).

**equivalence of regulatory systems.** Equivalence of regulatory systems implies a high degree of similarity between two regulatory systems as mutually established and documented through objective evidence. Equivalence can be established using criteria and approaches such as similarity of the regulatory framework and practices, adherence to the same international guidelines and standards, experience gained through the use of assessments for regulatory decision-making, joint activities and exchange of staff, among others. The expectation is that equivalent regulatory systems should lead to similar standards and levels of regulatory oversight or “levels of control”.

**international standards and guidelines.** For the purpose of this document, the term includes relevant WHO standards and guidelines and any other relevant internationally recognized standards (e.g. International Organization for Standardization (ISO) or pharmacopoeial standards) and guidelines (e.g. International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) or PIC/S guidelines).

**mutual recognition agreement.** According to a definition issued by the Organisation for Economic Co-operation and Development (OECD), mutual recognition agreements are “a principle of international law whereby states party to mutual recognition agreements recognize and uphold legal decisions taken by competent authorities in another member state. Mutual recognition is a process which allows conformity assessments (of qualifications, product…) carried out in one country to be recognized in another country” (9).
recognition. The acceptance of the regulatory decision of another regulator or trusted institution. Recognition should be based on evidence of conformity that the regulatory requirements of the reference regulatory authority is sufficient to meet the regulatory requirements of the relying authority. Recognition may be unilateral or mutual and may, in the latter case, be the subject of a mutual recognition agreement.

reference regulatory authority. For the purpose of this document, the reference regulatory authority is a national or regional authority or a trusted institution such as WHO prequalification (WHO PQ) being relied upon by another regulatory authority.

regional regulatory system. A system composed of individual regulatory authorities, or a regional body composed of individual regulatory authorities, operating under a common regulatory framework including or excluding a common legal framework. The common framework must at least ensure equivalence between the members in terms of regulatory requirements, practices and quality assurance policies. The system or regional body, where it exists, may have enforcement powers to ensure compliance with the common regulatory framework.

reliance. The act whereby the NRA in one jurisdiction may take into account and give significant weight to assessments performed by another NRA or trusted institution, or to any other authoritative information in reaching its own decision. The relying authority remains independent, responsible and accountable regarding the decisions taken, even when it relies on the decisions and information of others.

sameness of product. For the purpose of this document, the sameness of product means that two products have identical essential characteristics (i.e. the product being submitted to the relying authority and the product approved by the reference regulatory authority). All relevant aspects applicable to drugs, medical devices and in vitro diagnostics have to be considered in order to confirm that the product is the same or sufficiently similar (e.g. same qualitative and quantitative composition, same strength, same pharmaceutical form, same intended use, same manufacturing process, same active pharmaceutical ingredient suppliers, etc.). Additionally, supporting safety, efficacy and quality studies, indications and conditions of use, and so on, should be the same. The impact of potential justified differences should be assessed by the manufacturer (for the purpose of this document, manufacturer also means marketing authorization holder) and the relying NRA in determining the merit of using foreign regulatory assessments or decisions.
**stringent regulatory authority.** A regulatory authority which is: (a) a member of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), being the European Commission, the US Food and Drug Administration and the Ministry of Health, Labour and Welfare of Japan also represented by the Pharmaceuticals and Medical Devices Agency (as before 23 October 2015); or (b) an ICH observer, being the European Free Trade Association, as represented by Swissmedic, and Health Canada (as before 23 October 2015); or (c) a regulatory authority associated with an ICH member through a legally-binding, mutual recognition agreement, including Australia, Iceland, Liechtenstein and Norway (as before 23 October 2015) (10).

**work-sharing.** Work-sharing is a process by which NRAs of two or more jurisdictions share activities to accomplish a specific regulatory task. The opportunities for work-sharing include, but are not limited to: jointly assessing applications for authorization of clinical trials, marketing authorizations or good practices inspections, joint work in the post-marketing surveillance of medical product quality and safety, joint development of technical guidelines or regulatory standards, and collaboration on information platforms and technology. Work-sharing also entails the exchange of information consistent with the provisions of existing agreements and compliant with each agency’s or institution’s legislative framework for sharing such information with other NRAs.

A **joint activity** is a form of work-sharing whereby a regulatory task is conducted by two or more NRAs in collaboration in order to share their assessments, benefit from each other’s expertise and discuss any shortcomings of the data being evaluated. For example, a joint assessment is a procedure in which the same application is simultaneously submitted to two or more NRAs in order for the (assigned) NRAs to conduct their evaluations in parallel and share their respective scientific assessments with each other (e.g. the different modules for quality, nonclinical and clinical data can be assigned to different NRAs for review). The NRAs participating in the joint assessment can combine their list of questions or deficiencies to send to the manufacturer and base their respective independent regulatory decision on the outcome of these assessments. Similarly, a joint inspection is an inspection involving two or more NRAs sharing the activities and assessment performed during an inspection.

### 5.2 Key concepts

The diagram below illustrates some of the key concepts explained in the document, notably how NRAs can gain efficiencies in their regulatory operations and how they avoid duplication by using reliance approaches.
5.2.1 Reliance versus recognition

Reliance may take many forms and reflect varying degrees of application in recognizing or taking account of the assessments, decisions or any other authoritative information available from other authorities and institutions. Recognition may be seen as a special and more formalized approach to reliance whereby one regulatory authority recognizes the decisions of another regulatory authority, system or institution, obviating the need for additional regulatory assessment in reaching its own decision. Recognition usually requires formal and binding legal provisions.
5.2.2 Unilateral vs. mutual reliance/recognition

Reliance and recognition can be unilateral, for example, when a country chooses to rely on or formally recognize the assessment from another country unilaterally and without reciprocity. In other cases, mutual reliance or recognition may be based on binding mutual agreements or treaties negotiated at the level of governments. These agreements may take considerable time and resources to set up as the regulatory systems involved need to be mutually assessed and shown to be equivalent before implementation. The demonstration of equivalence of regulatory systems is normally a prerequisite to mutual reliance or recognition.

5.2.3 Life cycle approach

The concept of reliance for regulatory oversight of medical products should be applied across the full life cycle of medical products and all regulatory functions (see 5. Scope). While reliance approaches are widely used for the initial authorization of medical products, it is equally important to consider the use of reliance for vigilance and other post-authorization activities given the substantial regulatory resources required for evaluating safety and post-approval changes over the product life cycle. Reviewing post-approval changes to a product approved by a different authority may present some challenges. Therefore, if an NRA has relied upon another NRA’s assessment for its initial approval, there is a strong benefit for similar reliance measures for post-approval changes and vigilance activities. This also avoids the situation of different changes being accepted in the originating and receiving countries over time.

5.2.4 Risk-based approach

Each NRA should define its own strategy regarding the appropriate risk-based approach to reliance that considers factors, such as the type and source of products evaluated, the level of resources and expertise available in the NRA, the public health needs and priorities of the country, and opportunities for reliance. Using marketing authorization as an example, one could envisage four different approaches and levels of reliance involving an increasing degree of additional assessment by the relying NRA:

i. Verification of sameness of the product to ensure that the medical product is the same as the one that has been assessed by the reference regulatory authority (see 8.1e Sameness of the product in different jurisdictions).
ii. Confirmation of applicability of the assessment outcomes of another authority for regulatory decision-making in the national context, for example, in terms of legal and regulatory settings, benefit-risk assessment, co-morbidities, unmet medical needs, risk management plans and any quality-related specificities such as climatic zones for product stability. In case of differences, such as in target population, epidemiology and other features of the disease, concomitantly used medicines and other factors that can substantially affect the benefit-risk profile of a medicine as well as quality parameters, especially in relation to the stability under different climatic conditions, appropriate justification should be provided by the Applicant.

iii. Abridged assessment of the quality, safety and efficacy/performance data taking into account information in the assessment reports of the reference regulatory authority.

iv. Joint assessment or work-sharing between two or more regulatory authorities. This could take various forms, including a primary review by one authority followed by a joint assessment session to finalize the assessment report and comments, or a distribution of the different modules (quality, non-clinical and safety/efficacy) between authorities.

Regardless of the approach, the expectation is that reduced timelines compared to standard timelines are applied when using reliance.

Similar models can also be developed or used for other regulatory functions (e.g. inspection).

### 5.2.5 Regional reliance mechanisms

In some regions, an assessment for medical products can be conducted centrally based on a regional regulatory system for a group of countries. In some regional reliance mechanisms, the regional decision is binding on the member states (e.g., EU processes). In others, the regional decisions are recommendations that member states take into consideration when making their national regulatory decisions (e.g. Southern African Development Community (SADC) collaborative procedure (ZAZIBONA, which stands for Zambia, Zimbabwe, Botswana and Namibia), the Gulf Health Council (GHC) and the Caribbean Regulatory System (CRS)).
6. Principles underpinning good reliance practices

In developing a strategy on the use of reliance in regulatory functions and activities, an NRA should consider possible approaches in the context of the needs and characteristics of the national health and regulatory system. The decision to practice reliance should take into consideration the existing capacities, regulatory systems’ needs, the availability of an authority that the NRA can rely upon with confidence, and how reliance can complement their own capacities to drive efficiencies and the optimal use of resources. Reliance is not a lesser form of regulatory oversight but rather a strategy seeking to make the best use of the available resources in any given setting. This would allow the allocation of resources to other areas of regulatory functions, such as in-country vigilance and post-authorization activities and increase the effectiveness of the local regulatory oversight. In addition, reliance can lead to more evidence-based and better-quality decisions.

The following principles are meant to complement and expand upon the basic principles of GRP and are based on the principles presented in the PAHO/PANDRH concept note and recommendations on regulatory reliance principles (5).

6.1 Universality

Reliance applies to all NRAs irrespective of their levels of maturity or resources. Lack of resources or capacity are not the exclusive drivers for reliance. Different NRAs use reliance for different reasons, either to increase or build capacity when they have the requisite expertise in house, but just not enough of it to perform their regulatory work as efficiently as they would like. Other NRAs use reliance to increase expertise to which they otherwise would not have local access to. Indeed, reliance is relevant for all resource settings, representing an increasingly important mechanism for improving regulatory efficiency.

6.2 Sovereignty of decision-making

The decision to practice reliance, and how best to implement reliance, rests with the health regulatory authority of the country. Reliance does not imply dependence. In applying reliance in their daily practice, NRAs maintain independence, sovereignty and accountability in regulatory decision-making.

6.3 Transparency

Transparency is a key enabler to adopting new, more efficient ways of conducting regulatory operations, both locally and internationally. NRAs should be transparent regarding the standards, processes and approaches adopted in implementing reliance measures. In addition, the basis and rationale for relying on a specific entity should be disclosed and fully understood by all parties. NRAs should engage with all stakeholders including industry to ensure the appropriateness and awareness of the reliance processes.
Furthermore, NRAs should conduct transparent regulatory operations and decision-making, not only as a fundamental principle of GRP, but also towards building trust and maximizing opportunities for cooperation and reliance as part of a shared regulatory community responsibility. In other words, regulatory authorities are an increasingly important audience and beneficiaries of measures that promote transparency in regulatory oversight through the publishing and sharing of regulatory information. NRAs seeking to act as reference agencies are encouraged to issue public assessment reports in a common language documenting their regulatory decisions. Relying NRAs should use these reports where available as the primary source to inform assessment. If no public assessment reports are available or when additional information of a confidential nature is required, the manufacturer should provide such assessment report. If the relying NRA insists to obtain the non-public assessment reports from the reference agency, those reports may be provided by the reference agency with the consent of the manufacturer, if needed.

6.4 Respect of national and regional legal basis

Reliance practices should be coherent with national and regional legal frameworks and medical products’ policy and supported by clear mandates and regulations that enable the efficient implementation of reliance as part of government policy on good regulation. The driving force behind the adoption of these legal frameworks should be the efficiencies and capacity to be gained by reliance, not the minimization of resources for regulatory functions. Where regulations including explicit provisions regarding the application of reliance do not exist, reliance may still be adopted through the interpretation of existing regulations provided that the legal framework does not explicitly preclude the application of reliance approaches by the NRA. Implementing reliance can be done through policy changes as long as it is broadly consistent with the legislation. If prohibitions to apply reliance exist, they should be considered for revision within a reasonable timeframe.

6.5. Consistency

Reliance on a specific assessment or decision from another authority should be established for specific and well-defined categories of products and processes. The scope of regulatory activities where reliance may be practised should be clearly defined and the process for practising reliance should be transparent and predictable. Thus, the expectation is that reliance shall be applied consistently for products/processes in the same predetermined categories.
6.6 Competency

The implementation of reliance approaches requires that NRAs have built the necessary competencies for critical decision-making. Setting up the reliance approach will normally require the involvement of senior regulatory staff, managers and experts who are competent to make the best use of foreign information in the local context. NRAs should also maintain the appropriate scientific expertise of their staff needed for activities where they do not apply reliance, for example, such as in local adverse event monitoring, market surveillance and control, national labelling and product information activities and for approval of locally manufactured products.

Equally, authorities being relied upon should possess and maintain competencies and operate within a robust and transparent regulatory system, underpinned by international standards and guidelines as well as good regulatory practices and a well-functioning quality management system (11). Competencies may be benchmarked using transparent processes to develop trust and build confidence in the reference authorities.

7. Considerations

A number of considerations can guide reliance approaches and facilitate their successful implementation. These considerations include general aspects as well as barriers that NRAs need to overcome and enablers that will help in implementing reliance approaches. The non-exhaustive list of considerations presented below will be further elaborated in the case studies, practice guides and the reliance repository.

Reliance is encouraged in any settings, for example, when supported by common legal or regulatory framework in a regional regulatory system, by bilateral agreements, by mutual recognition agreements or on a purely voluntary, networking or ad-hoc basis.

As a principle, reliance should be based on the original assessment and not on a decision that was itself based on reliance from another assessment (i.e. no reliance on a fully relied upon outcome).
7.1 General considerations

7.1.1 Reliance anchored in a national regulatory authority strategy

In addition to having a legal basis supporting, or at least not precluding reliance approaches (see 7. Principles underpinning good reliance practices), the application of reliance should be anchored in the NRA’s strategy, endorsed by senior management and in the respective high-level National Policy in order to provide a mandate, direction and expectations to NRA staff, guiding them in their day-to-day work. The strategy should be further detailed in procedures and integrated in processes to ensure that maximum benefits accrue. It should also include considerations on a sustainable funding model for the NRA when implementing reliance. The strategy should be published in order to make it accessible and understandable to external stakeholders. Additionally, the implementation of reliance should be supported by training and periodic reviews to ensure that standards are being maintained, to assess whether or not objectives are being met, and to make refinements where warranted.

Implementing reliance should not negatively impact the financial sustainability of the NRA.

NRAs that are practising reliance should establish and publish a list of reference regulatory authorities together with the criteria used for identifying them. The NRA should decide and establish the criteria they want to apply for the selection of the reference regulatory authorities (e.g. application of international standards, longstanding recognition in the international community, proximity and commonality of medical products, etc.). In order to qualify reference regulatory authorities or a specific oversight of a regulatory function, an NRA may refer to an assessment performed by an independent organization (e.g. WHO Benchmarking and WLA, ISO accreditation, the Medical Device Single Audit Program (MDSAP), PIC/S, etc.).

WHO encourages NRAs to monitor and evaluate the impact of regulatory reliance in their country and region and to share their experiences with other regulatory authorities. Where possible, specific measurement of the impact of reliance is strongly encouraged and the respective NRA should prospectively establish the metrics they will employ to measure the impact of using reliance in their regulatory decision-making and the timing when such an impact assessment will be undertaken. These metrics may include, for example, cost savings, efficiencies in the number of products reaching markets or time to market, a redirection of scarce resources to areas of higher regulatory risks, and so on.
7.1.2 Cultural change

The implementation of reliance approaches means moving to a more innovative, effective way of working, based on trust and relying on other NRA outputs. It is essential that the benefits of the strategy be understood and supported at the operational level and that staff expected to implement reliance approaches have input into their development.

This will require engagement, willingness, effective preparation, messaging and support from management and peers that articulates the importance of reliance in better addressing workload pressures without minimizing the rigor of regulatory work or causing the loss of scientific and regulatory competence and capacity. In fact, the use of assessments and information from other trusted regulatory authorities can help build capacity and competence (e.g. through exposure to the reviews and decisions of the reference authority, networking, twinning, staff visits/staff exchanges, etc.). Furthermore, the effective use of such information within the local context requires skills, ability and experience. Thus, the skill set and competency framework needed to practise reliance will need to be developed in the NRA’s workforce.

Senior management, reviewers, inspectors and other staff should build confidence and trust in work that has been done by other NRAs or trusted authorities. Building trust in other NRAs’ work requires time and a change in the culture within the relying NRA. Some regulatory authorities and systems already practise reliance and that experience should be leveraged to promote acceptance and avoid pitfalls.

Trust should also be built with the public and healthcare professionals in order to inform and assure them that the use of reliance offers a more efficient regulatory oversight.

7.1.3 Flexibility in approach: “one size doesn’t fit all”

Following the principles listed above, reliance strategies should be tailored to the needs of the national health and regulatory systems. NRAs may choose to rely on others as part of their routine regulatory oversight and/or during special circumstances such as public health emergencies. Reliance is a tool offering flexibility to NRAs. Whatever the approach, the NRA needs to consider its own capacities and to establish clear goals and efficient processes and ensure the standards and criteria are transparent and well established when adopting reliance.
7.1.4 Implementing reliance needs investment of resources and time

As stated above, reliance should increase the efficiency of a regulatory system in a country and/or region. Nevertheless, the implementation of reliance approaches will first require time and investment of resources. This may include but may not be limited to: legislative changes and the development of guidance documents, the development of approaches and elaboration of procedures and processes, confidence-building through parallel or joint reviews and supported by staff exchanges, the training of staff, dialogue with industry and other stakeholders, as well as the establishment of, or access to, information-sharing platforms. To the best extent possible, the use of publicly available information should also be pursued.

7.1.5 “Sameness” of the product in different jurisdictions

One of the most critical aspects when applying reliance is the verification of the “sameness” of the medical product (see 6.1 Definitions) in different jurisdictions. Reliance can only be applied if the NRAs have the assurance that the medical product assessed by the reference regulatory authority is essentially the same as the one submitted to the NRA, intending to use a foreign assessment as the basis for its own assessment and regulatory decision-making. The role of the manufacturer is essential here in order to confirm the sameness of a product and to provide the same documentation to different NRAs to the exception of the additional country specific information submitted for review such as product stability data according to the stability zone. As part of the process, the manufacturer should confirm in the application that the product is the same and that the dossier contains the same information as much as possible, taking into consideration any potential national requirements.

If the dossier is not submitted simultaneously to the agencies, the manufacturer should highlight any new information acquired about the product since the dossier was submitted to the reference agency with the corresponding assessment.

7.1.6 The role of industry

Industry plays a crucial role in the successful application of reliance mechanisms by NRAs. While industry is widely supportive of reliance as a concept and practice that can bring about efficiency gains, industry must also have clear guidance on its application and see meaningful benefits.

Industry’s support and stringent adherence to the factors that give validity to the reliance process is vital for filing applications in multiple countries or regions, ensuring the sameness of products submitted to reference regulatory authorities and relying NRAs, and sharing unredacted and complete information.
Review and discussion of pilot programs to quickly adapt and improve guidance will be key to benefit from key learnings and improve implementation. Collaboration and dialogue between all stakeholders participating in regulatory reliance activities will help to create and build trust, which is the foundation of regulatory reliance.

### 7.1.8 Reliance in case of a public health emergency

In case of a public health emergency, reliance approaches represent an even more essential tool and should be given more importance to accelerate access to medical products needed in the context of the emergency.

### 7.2 Barriers

#### 7.2.1 Lack of political will

The lack of political will and support at government level can make it difficult for NRAs to implement or facilitate reliance in their daily practice, even if a legal basis is established supporting (or not precluding) reliance and NRAs’ support reliance as a strategy and approach.

#### 7.2.2 Lack of accessible information and confidentiality of information

The lack of access to complete assessments of reference regulatory authorities can pose a major barrier to implementing effective reliance strategies. Reference regulatory authorities should strive to make assessments and other regulatory information publicly available.

Non-public regulatory reports might also be obtained directly from the manufacturer when the company is able to access these reports from the reference regulatory authority. If this is not possible, the relying NRA should approach the reference regulatory authority for the non-public regulatory reports. In these cases, having arrangements between NRAs regarding the exchange of confidential information would facilitate the implementation of the reliance process.

Sensitive, non-public information included in unredacted assessment or inspection reports can also be shared between regulatory authorities upon request. This may include confidential, commercial, trade secret or personal information. In some circumstances, the sharing of such information may require the prior consent of the manufacturer. The sharing of personal information may also require prior consent from the individual in order to comply with data protection regulations.
Given the sensitivity of such non-public information, NRAs may require that confidentiality agreements be signed which govern the exchange, management and disclosure of such information in order to ensure that the confidential nature of the information is protected by relying NRA. Such information should always be exchanged using secure channels or information-sharing platforms.

7.2.3 Other considerations

Additional barriers can include issues around language such as lack of common language or translation difficulties/cost, differences in country-specific regulatory requirements and evidentiary standards, the lack of regulatory alignment of product risk-classifications and inconsistent practices regarding product modifications in the area of medical devices including in vitro diagnostics, the lack of acceptance of foreign clinical data and real-world evidence, the level of detail in regulatory reports, different levels of competencies and, as previously noted, internal resistance and insufficient knowledge of the reference regulatory authority and how it operates. All such factors should be considered in developing the appropriate reliance strategies, as will be further elucidated in the companion documents to follow.

7.3 Enablers

7.3.1 Trust

Trust is a critical element since the reliance requires confidence that the regulatory outcome is based on strong regulatory processes and standards and is, thus, trustworthy. Consequently, initiatives that foster trust among regulatory authorities are essential to promoting reliance. Trust is developed through increasing familiarity and understanding in what stands behind regulatory outputs. By sharing information, including the standards applied to regulatory decisions, working together and learning each other’s ways of working, confidence can be built throughout the entire organization, which thereafter leads to the effective use of reliance in regulatory work. Trust can be built in phases, starting with the exchange of assessment reports, and moving to work-sharing or joint assessments in a stepwise approach. Regulatory authorities may also consider using applications of lower risk (see 6.2.4 Risk-based approach) to initiate reliance processes.

7.3.2 Convergence and harmonization

Convergence and the harmonization of requirements and standards are important enablers of regulatory cooperation and reliance. The more requirements and standards are alike, the more opportunity for collaboration and reliance exists. The implementation of the ICH Common Technical Document (CTD) and the electronic CTD (eCTD) as a common format for regulatory submissions around the globe is just one example how harmonization can facilitate and enable reliance.
The differences in standards and practices, however, do not prevent one authority from relying on another, particularly when the relying authority has limited capacity and expertise. The system upon which an NRA relies should be at least equivalent to or superior to the standards it applies. As a matter of good practice, NRAs should preferably rely on assessments or decisions from reference regulatory authorities that apply international standards and guidelines.

### 7.3.3 Information-sharing and dialogue between regulators

Information-sharing is an essential part of reliance and NRAs are encouraged to share information and good practices with other NRAs as much as possible. The increasing dialogue between regulators is seen in the growing number of international initiatives such as the IPRP or the International Conference of Drug Regulatory Authorities (ICDRA), as well as regulatory information- and work-sharing networks such as PANDRH, the South-East Asia Regulatory Network (SEARN), regulatory networks in the Regional Economic Communities (RECs) under the African Medicines Regulatory Harmonisation (AMRH) Initiative or the Association of Southeast Asian Nations (ASEAN) Pharmaceutical Products Working Group (PPWG), International Coalition of Medicines Regulatory Authorities (ICMRA) and so on, which are great facilitators for reliance.

Scientific and technical events, such as ICH and ICDRA conferences, are also platforms that promote the dissemination of regulatory information and support building knowledge and trust among NRAs.

As already mentioned, the sharing of confidential information should always occur through secure channels or via secure platforms. Investment in the respective IT infrastructure is therefore important to enable reliance.

### 7.3.4 Economic or legal integration

In situations where there is economic or legal integration in a region or for a group of countries, reliance is facilitated and strengthened by the existing mutual provisions, such as the Asia-Pacific Economic Cooperation (APEC), ASEAN, the Caribbean Community and Common Market (CARICOM), the EU, the Eurasian Economic Union, Gulf Cooperation Council (GCC), Pacific Alliance (PA), the RECs in Africa, or the Southern Common Market (MERCOSUR).
7.3.5 Engagement of stakeholders

All relevant stakeholders, including industry, healthcare professionals, policy makers and the public, should be engaged and/or informed in order to increase the understanding and acceptance of reliance approaches as they present some clear benefits for all parties involved. Communications and engagement with stakeholders should be tailored to the target audience.

8. Conclusions

Reliance is seen by a growing number of regulatory authorities as an important means of improving the efficiency of regulatory operations in the oversight of medical products. It allows NRAs to make the best use of resources, build expertise and capacity, increase the quality of regulatory decisions, reduce duplication of effort and, ultimately, promote timely access to safe, efficacious and quality-assured medical products. By adopting reliance measures whenever possible within a well-structured framework, underpinned by national or regional policies and strategies, regulators may focus their resources on key activities that cannot be undertaken by others and that contribute to public health.

Reliance represents a “smarter” form of regulatory oversight based on constructive regional and international collaboration, one that will also facilitate and promote convergence and the use of common international guidelines and standards, as well as ensure access to medical products to patients worldwide with more predictable and faster approvals.

Reliance does not represent a less stringent form of regulatory oversight nor an outsourcing of regulatory mandates or a compromise to independence. On the contrary, the decision to “regulate through reliance” is the hallmark of a modern and efficient regulatory authority.

The inclusion of reliance-related provisions by NRAs as part of their flexible regulatory pathways is encouraged and should be considered for all regulatory functions over the medical product life cycle, as appropriate.

The principles and considerations presented in this document should be taken into account when implementing regulatory reliance frameworks or strategies. Effective implementation of reliance will benefit not only NRAs but also patients, healthcare providers and industry.

While reliance may be viewed as a particularly useful strategy for low-resourced regulatory authorities, it is equally relevant for well-resourced NRAs. Reliance is an approach to be used by all NRAs and, as such, should become an integral part of regulatory operations.
9. Annex 1: Examples

Regulatory reliance can take many forms and encompasses a broad array of regulatory approaches and practices that can involve two or more regulatory authorities. In addition, it can be limited to a discrete regulatory process or function or include the full scope of regulatory functions over the entire life cycle of a medical product.

There are many examples around the world that illustrate the current use of reliance and the diverse models in which national regulatory authorities (NRAs) leverage the work done by others.

Examples are given below to illustrate the different points addressed in this document and to show the use of reliance in the different regulatory functions. The list below is not exhaustive but just an illustration of the current practices of reliance taking place globally. It may be replaced in future by a comprehensive repository of reliance approaches to be established as a part of the Good Reliance Practices (GRelP) toolbox.

a) Clinical trials

Work-sharing for clinical trial assessment is happening in some regions, such as the Voluntary Harmonisation Procedure in the European Union (12) and via the African Vaccine Regulatory Forum (AVAREF) (13). By assessing clinical trial applications together, NRAs and, in some cases, ethics committees from different countries, can benefit from the assessments performed by the different participating countries with a view to facilitating and ensuring the robustness of the approval process across countries. The AVAREF platform has been instrumental in building the expertise and capacity of regulators and ethics committees, promoting the use of international standards and expediting clinical trial assessments and decisions for medical products of high public health interest in both emergency and normal circumstances. Towards this end, a guideline and platform for joint assessment of clinical trials applications, as well as Good Clinical Practices (GCP) site inspections, have been developed and implemented in order to facilitate product development, regulatory decision-making and access to promising new medical products (14).
b) Marketing authorization

Abridged regulatory pathways using reliance for initial marketing authorization

Several procedures are available through stringent regulatory authorities (SRAs) (e.g. EMA, Health Canada (HC), the Pharmaceuticals and Medical Devices Agency (PMDA), Swissmedic, U.S. FDA) or the World Health Organization Prequalification (WHO PQ) Programme in order to enable the use of an abridged regulatory pathway by the relying NRAs.

Among those procedures, the EU Article 58, also referred to as European Union Medicines for all (EU-M4 all) (15), the Swissmedic Marketing Authorisation for Global Health Products (MAGHP) (16) procedures and the WHO Collaborative Registration Procedure (CRP) (1) are three examples of abridged regulatory pathways using reliance to facilitate the registration of medicinal products in target countries.

In addition to facilitating in-country registration, the EU Article 58 and the Swissmedic MAGHP procedures provide experts from target NRAs the opportunity to both observe and participate actively in the assessment and scientific advice procedures, with the aim of building their own capacities and to establish confidence in the processes.

The CRP facilitates the assessment and accelerates the national registration of WHO prequalified medical products and medicines approved by an SRA. The CRP operates by providing unredacted assessment, inspection and performance evaluation (in the case of in vitro diagnostics) reports upon request (and with the consent of the manufacturer) to participating NRAs, primarily in low- and middle-income countries. The procedures are detailed in WHO guidelines, which also include guidance on how receiving NRAs can make the most efficient use of the reports in reaching their own decisions. Participating NRAs are expected to reach a decision on authorization within 90 calendar days (regulatory time). The CRP tool has shown to be successful in both accelerating decisions in countries and building the capacity of regulatory authorities.

The WHO Certificate of a pharmaceutical product (CPP) is also being used as a reliance tool, in lieu of full of partial assessment for marketing authorization (18). If a CPP is provided, it is being used in lieu of a full or partial review and assessment is accelerated. Such procedures currently exist in Benin, Bolivia, Bolivia, Cameroon, Congo, Cuba, Curacao, Guinea, Haiti, Hong Kong and Honduras.
Quality information

Many NRAs, as well as the WHO Prequalification Programme (WHO PQ), recognize Certificates of Suitability to the monographs of the European Pharmacopoeia (CEP) (19) for active pharmaceutical ingredients (API) as a validation of the quality of a certain API. Some countries also recognize the Confirmation of API Prequalification (CPQ) issued by the WHO PQ for APIs (20). These two examples not only provide assured mechanisms of reliance, but also reduce the documentation requirements for countries that recognize these certificates. Where a CEP or CPQ is issued, the receiving NRA does not have to duplicate the API assessment but can focus on specific sections not covered under CEP or CPQ.

Work-sharing

The Australia-Canada-Singapore-Switzerland Consortium (ACSS Consortium) (21) is a coalition which was formed in 2007 by “like-minded” medium-sized regulatory authorities in order to promote work-sharing based on greater regulatory collaboration and the alignment of regulatory requirements. The ACSS Consortium explores opportunities for information-and work-sharing initiatives in areas including biosimilar products, complementary medicines, generic medicines, new prescription medicines, medical devices and information technology. The Consortium capitalizes on each country’s area of strength, addresses gaps in science, knowledge and expertise and leverages resources to help expedite risk assessment processes, while maintaining or raising quality and safety standards. The Consortium builds on existing international networks, initiatives and mechanisms in order to advance work- and information-sharing along health product life cycles.

Joint assessments

Joint assessments can provide significant benefits to NRAs by sharing the workload, building capacity by bringing broader experience and expertise together, and helping to build trust in one another’s assessments and decision-making processes. Similarly, industry can benefit from a common review process and set of questions in terms of both resource and time-savings as compared to interacting separately with multiple countries. In recognition of these benefits, a growing number of joint assessment initiatives have been established within the framework of regional regulatory networks, sometimes driven by the higher-level priorities of economic blocks seeking to create common markets. Examples of joint assessments initiatives include those in the Regional Economic Communities in Africa (East African Community (EAC) (22), ZAZIBONA (23) in the SADC, the Economic Community of West African States (ECOWAS)/West African Health Organization (WAHO) (24), the Association of Southeast Asian Nations (ASEAN) Joint Assessment Coordinating Group (25), and so on.
Mutual recognition

The EU system is an example of highly integrated regulatory cooperation and its multiple regulatory pathways depend heavily on work-sharing, recognition and other forms of reliance. The various routes to the approval of medicines in the EU system are based on a single assessment system so that any assessment report from any of the agencies in the EU network can be used as a basis for reliance by other regulators. In this specific case, a strong and common legal framework and harmonized regulatory standards shared among all EU countries enabled and facilitated reliance and recognition (26).

c) Post-approval changes

Following the same principles as for initial marketing authorization, reliance can also be applied broadly for assessing post-approval changes already approved by NRAs considered as reference authorities. In the case of CRP, for example, the participating NRAs for prequalified products are informed by WHO of any variations approved by WHO PQ Team (17).

The Health Sciences Authority (HSA) in Singapore is applying a verification route with shortened timelines for approving post-approval quality and product label changes, which aims to enable greater leveraging of reference agencies’ assessments, minimize duplication of effort and enhance process efficiency as part of HSA’s on-going effort, in particular for effective life cycle management for registered therapeutic medicinal products. To qualify, the proposed changes must be identical to those approved by one of HSA’s five reference agencies, accompanied by the proof of approval of that reference agency as well as the approved product label of that reference agency where applicable (27).

d) Testing and lot release

Network of Official Medicines Control Laboratories

The Network of Official Medicines Control Laboratories (OMCLs) support regulatory authorities in controlling the quality of medicinal products available on the market. Collaboration within the Council of Europe’s General European OMCL Network (GEON) (28) makes the best use of resources via resource pooling and avoids duplication of work or testing. Some of the main goals of the Network are to set mutual recognition, within the members of the networks, of tests carried out by OMCLs at the national level, coordinate activities among the OMCLs, and facilitate knowledge and work-sharing.
Lot release and quality monitoring of vaccines and other biologic products

Launched in 2017, the WHO-National Control Laboratory Network for Biologicals (WHO-NNB) (29) brings together National Control Laboratories (NCLs) and NRAs of vaccine-producing and vaccine-recipient countries, WHO contract laboratories, manufacturer associations, WHO Regional Offices and other stakeholders, including donors. The Network works towards the effective use of globally available resources in providing a platform and infrastructure for the collaboration and exchange of quality and technical information. The main objective of the Network is to facilitate the access to and availability of prequalified vaccines (or other biotherapeutic products) through reliance on the batch release of the respective Network member NRAs/NCLs by recipient countries, thereby reducing redundant testing and contributing to more cost-effective testing and more effective regulatory oversight.

e) Pharmacovigilance

In the field of pharmacovigilance, the exchange and sharing of data is critical. More than 100 Member States contribute by sharing their safety data to the WHO Global database of individual case safety reports (ICSR) - VigiBase - developed and maintained by the Uppsala Monitoring Center (UMC) (30). Member States rely upon this resource (and thereby, on each-others’ data) as a single point of pharmacovigilance information, to confirm and validate signals of adverse events with medicines and vaccines that they may have observed within their own jurisdictions.

The EU introduced the concept of a supervisory authority for pharmacovigilance in 2012 in the Regulation 1235/2010 (31) who shall be responsible for verifying on behalf of the Union that the marketing authorization holder for the medicinal product satisfies the pharmacovigilance requirements as per EU legislation.

f) Inspections

In the field of inspections, governments and NRAs in different regions and parts of the world have worked on mutual recognition agreements in order to rely on each other’s inspection outcomes, avoiding the duplication of inspections and making the best use of resources, e.g. EU Mutual Recognition Agreements (32) with Australia, Canada, Japan, Switzerland and the United States of America (USA); ASEAN Mutual Recognition Agreement (33), etc.
The Pharmaceutical Inspection Co-operation Scheme (PIC/S) is a non-binding, informal co-operative arrangement between regulatory authorities in the field of Good Manufacturing and Good Distribution Practices (GMP and GDP) of medicinal products for human or veterinary use, and more recently also in Good Clinical Practices (GCP) and Good Pharmacovigilance Practices (GVP) (34). It aims at facilitating cooperation and networking between competent authorities, regional and international organizations, thus increasing mutual confidence regarding inspections. PIC/S has also issued a guidance on inspection reliance, which outlines a process for the desk-top assessment of GMP compliance (35).

Reliance is also an important aspect for conducting desktop assessment of compliance with relevant good practice guidelines and requirements, as described in the respective WHO guidance (36).

The OECD operates the Mutual Acceptance of Data system in the assessment of chemicals (including pharmaceuticals) which supports the acceptance of data, generated in any member country in accordance with OECD test guidelines and Principles of Good Laboratory Practices (GLP), in any other member country for assessment purposes relating to the protection of human health and the environment (37).

g) **Examples in the field of medical devices**

The use of reliance is equally prevalent in the regulation of medical devices including in vitro diagnostics. An example of this is the Medical Device Single Audit Program (MDSAP) (38) originally developed through the auspices of the International Medical Device Regulators Forum (IMDRF). Under this program, the regulatory authorities of Australia, Brazil, Canada, Japan and the United States have pooled their resources in order to develop and implement a robust system of oversight of third party auditing organizations that, in turn, conduct audits of the quality management systems of medical device manufacturers. The MDSAP allows an auditing organization recognized by the Program to conduct a single regulatory audit that satisfies the relevant requirements of the regulatory authorities participating in the program. Collective regulatory resources are directed at establishing and maintaining the oversight of auditing organizations, providing a more effective use of limited regulatory resources. Employing a single audit program allows regulatory authorities to efficiently leverage resources and streamline the regulatory process without compromising public health and to promote more aligned and consistent regulatory requirements.
The IMDRF has also set guidance for the exchange of information between NRAs respect to medical device safety (39). The system focuses on incidents that represent a serious public health threat that extend beyond national borders in order to inform other NRAs of such. Additionally, IMDRF outlines consistent adverse event reporting, coding, and terminology in their IMDRF terminologies for categorized Adverse Event Reporting: terms, terminology structure and codes document (40).

The above-mentioned initiative and guidance are just two examples of the work IMDRF does in the field of harmonization, convergence and reliance in the area of medical devices. Other examples are The IMDRF Optimizing Standards for Regulatory Use (41), the Essential Principles of Safety and Performance of Medical Devices and IVD Medical Devices (42) or the Competence, Training, and Conduct Requirements for Regulatory Reviewers (43).

In Singapore, medical devices and in vitro diagnostics with prior authorization through specific market authorization pathways in the United States, Europe, Canada, Australia, or Japan are eligible for abridged evaluation routes. To qualify for this, the proposed intended use must be identical to that approved in the reference country and typically documentation including proof of approval from the reference regulatory authority and summary technical documentation can be used to satisfy many supporting documentation requirements (44). Additionally, Australia will recognize registrations and certifications from Notifies bodies designated by the medical device regulators of European member states, U.S. FDA, HC, the PMDA and MDSAP auditing organizations (45).
10. References


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International Nonproprietary Names for Pharmaceutical Substances (INN)

Notice is hereby given that, in accordance with article 3 of the Procedure for the Selection of Recommended International Nonproprietary Names for Pharmaceutical Substances, the names given in the list on the following pages are under consideration by the World Health Organization as Proposed International Nonproprietary Names. The inclusion of a name in the lists of Proposed International Nonproprietary Names does not imply any recommendation of the use of the substance in medicine or pharmacy.

Lists of Proposed (1–117) and Recommended (1–78) International Nonproprietary Names can be found in Cumulative List No. 17, 2017 (available in CD-ROM only). The statements indicating action and use are based largely on information supplied by the manufacturer. This information is merely meant to provide an indication of the potential use of new substances at the time they are accorded Proposed International Nonproprietary Names. WHO is not in a position either to uphold these statements or to comment on the efficacy of the action claimed. Because of their provisional nature, these descriptors will neither be revised nor included in the Cumulative Lists of INNs.

Dénominations communes internationales des Substances pharmaceutiques (DCI)

Il est notifié que, conformément aux dispositions de l'article 3 de la Procédure à suivre en vue du choix de Dénominations communes internationales recommandées pour les Substances pharmaceutiques les dénominations ci-dessous sont mises à l'étude par l'Organisation mondiale de la Santé en tant que dénominations communes internationales proposées. L'inclusion d'une dénomination dans les listes de DCI proposées n'implique aucune recommandation en vue de l'utilisation de la substance correspondante en médecine ou en pharmacie.

On trouvera d'autres listes de Dénominations communes internationales proposées (1–117) et recommandées (1–78) dans la Liste récapitulative No. 17, 2017 (disponible sur CD-ROM seulement). Les mentions indiquant les propriétés et les indications des substances sont fondées sur les renseignements communiqués par le fabricant. Elles ne visent qu'à donner une idée de l'utilisation potentielle des nouvelles substances au moment où elles sont l'objet de propositions de DCI. L'OMS n'est pas en mesure de confirmer ces déclarations ni de faire de commentaires sur l'efficacité du mode d'action ainsi décrit. En raison de leur caractère provisoire, ces informations ne figureront pas dans les listes récapitulatives de DCI.

Denominaciones Comunes Internacionales para las Sustancias Farmacéuticas (DCI)

De conformidad con lo que dispone el párrafo 3 del “Procedimiento de Selección de Denominaciones Comunes Internacionales Recomendadas para las Sustancias Farmacéuticas”, se comunica por el presente anuncio que las denominaciones detalladas en las páginas siguientes están sometidas a estudio por la Organización Mundial de La Salud como Denominaciones Comunes Internacionales Propuestas. La inclusión de una denominación en las listas de las DCI Propuestas no supone recomendación alguna en favor del empleo de la sustancia respectiva en medicina o en farmacia.

Las listas de Denominaciones Comunes Internacionales Propuestas (1–117) y Recomendadas (1–78) se encuentran reunidas en Cumulative List No. 17, 2017 (disponible sólo en CD-ROM). Las indicaciones sobre acción y uso que aparecen se basan principalmente en la información facilitada por los fabricantes. Esta información tiene por objeto dar una idea únicamente de las posibilidades de aplicación de las nuevas sustancias a las que se asigna una DCI Propuesta. La OMS no está facultada para respaldar esas indicaciones ni para formular comentarios sobre la eficacia de la acción que se atribuye al producto. Debido a su carácter provisional, esos datos descriptivos no deben incluirse en las listas recapitulativas de DCI.

Comments on, or formal objections to, the proposed names may be forwarded by any person to the INN Programme of the World Health Organization within four months of the date of their publication in WHO Drug Information, i.e., for List 124 – COVID-19 (special edition) of Proposed INN not later than 22 February 2021. Publication date: 23/10/2020

Dénominations communes internationales proposées: Liste 124 - COVID-19 (édition spéciale)

Des observations ou des objections formelles à l'égard des dénominations proposées peuvent être adressées par toute personne au Programme des Dénominations communes internationales de l'Organisation mondiale de la Santé dans un délai de quatre mois à compter de la date de leur publication dans WHO Drug Information, c'est à dire pour la Liste 124 - COVID-19 (édition spéciale) de DCI Proposées le 22 février 2021 au plus tard. Date de publication : 23/10/2020

Denominaciones Comunes Internacionales Propuestas: Lista 124 - COVID-19 (edición especial)

Cualquier persona puede dirigir observaciones u objeciones respecto de las denominaciones propuestas, al Programa de Comunes Internacionales de la Organización Mundial de la Salud, en un plazo de cuatro meses, contados desde la fecha de su publicación en WHO Drug Information, es decir, para la Lista 124 - COVID-19 (edición especial) de DCI Propuestas el 22 de febrero de 2021 a más tardar. Fecha de publicación: 23/10/2020

<table>
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<tr>
<th>Proposed INN (Latin, English, French, Spanish)</th>
<th>Chemical name or description: Action and use: Molecular formula, Chemical Abstracts Service (CAS) registry number: Graphic formula</th>
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<tr>
<td>abdavomeranum # abdavomeran abdavomérán</td>
<td>messenger RNA (mRNA), 5'-capped, encoding the codon-optimised receptor binding domain (RBD) of the SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2, GenBank: MN908947.3) spike (S) glycoprotein, expressed as a fusion protein 5' with an extended S glycoprotein signal peptide and connected 3' by a glycine/serine (GS)-rich linker peptide with a T4 fibritin trimORIZATION domain, flanked by 5' and 3' untranslated regions and a 3' poly(A) tail; contains N1-methylpseudouridine instead of uridine (all-U&gt;m1Ψ). immunological agent for active immunization (anti-SARS-CoV-2)</td>
</tr>
</tbody>
</table>

ARD messager (ARNm), protégé en 5', codant pour le domaine de liaison au récepteur (RBD) de la glycoprotéine spike (S) du SARS-CoV-2 (coronavirus 2 du syndrome respiratoire aigu sévère, GenBank: MN908947.3) avec des codons optimisés, exprimé comme une protéine de fusion 5'-avec un peptide signal de la glycoprotéine S allongé et lié en 3' par un peptide de liaison riche en glycine / sérine (GS) avec un domaine de trimérisation de la fibritine de T4, flanqué par des régions 5' et 3' non traduites et une queue poly(A); contient de la N1-méthylpseudouridine au lieu de l'uridine (tut-U>m1Ψ). agent immunologique d'immunisation active (anti-SARS-CoV-2)
abdavomerán

RNA mensajero (mRNA), protegido en 5’, que codifica para el dominio de unión al receptor (RBD) de la glicoproteína de la espícula (S) de SRAS-CoV-2 (coronavirus 2 del síndrome respiratorio agudo severo, GenBank: MN908947.3) con codones optimizados, expresado como una proteina de fusión en 5’ con un péptido señal de glicoproteína S extendido y conectado en 3’ mediante un péptido enlazador (linker) rico en glicina/serina (GS) con un dominio fibríntina de trimerización de T4, flanqueado por regiones 5’ y 3’ no traducidas y una cola poly(A); contiene N1-metilpseudouridina en lugar de uridina (all-U>m1Ψ).

agente inmunológico para inmunización activa (anti-SRAS-CoV-2)

2417899-75-1

alunacedasum alfa #
alunacedase alfa

human angiotensin-converting enzyme 2 extracellular soluble domain (18-740, 1-723 in the current sequence), dimer, glycosylated, produced in Chinese hamster ovary (CHO) cells;
human angiotensin-converting enzyme 2 (ACE2, angiotensin-converting enzyme homolog, ACEH, ACE-related carboxypeptidase, metalloprotease MPROT15, EC:3.4.17.23), soluble extracellular (18-740)-domain of the proprotein, non-covalent dimer, produced in Chinese hamster ovary (CHO) cells, glycoform alfa

angiotensin-converting enzyme (ACE) 2 analogue

alunacédase alfa
domaine extracellulaire soluble de l'enzyme de conversion de l'angiotensine de type 2 humaine (18-740, 1-723 dans la séquence actuelle), dimère, glycosylé, produit dans des cellules ovariennes de hamster chinois (CHO) ;
enzyme de conversion de l'angiotensine de type 2 humaine (ECA2, enzyme de conversion homologue de l'angiotensine, HECA, carboxypeptidase liée à l'ECA, métalloprotéase MPROT15, EC: 3.4.17.23), domaine protéique extracellulaire soluble (18-740), dimère non covalent, produit dans des cellules ovariennes de hamster chinois (CHO), glycoforme alfa

analogue de l’enzyme de conversion de l’angiotensine de type 2

alunacedasa alfa
enzima humana convertidora de la angiotensina 2 dominio extracelular soluble (18-740, 1-723 en la secuencia actual) dúmero, glicosilado, producido en células ováricas de hámster Chino (CHO);
enzima humana convertidora de la angiotensina 2 (ECA2, homólogo enzima convertidora de angiotensina, HECA, ECA-carboxipeptidasa relacionada, metaloproteasa MPROT15, EC:3.4.17.23), soluble extracelular (18-740)-dominio de la proproteína, dúmero no covalente, producido en células ováricas de hámster Chino (CHO), glicoforma alfa

análogo de la enzima conversora de la angiotensina 2
atibuclimabum #

immunoglobulin G4-kappa, anti-[*Homo sapiens* CD14, membrane (mCD14) and soluble (sCD14)], chimeric monoclonal antibody; gamma4 heavy chain chimeric (1-442) [VH *Mus musculus* (Mus mus musculus IGHV3-2*02 (95.9%) -(IGHD) -Mus musmus IGJ3*01 (92.9%) A128-S (115)) CDR-IMGT [9.7.8] (26-34.52-58.97-104) (1-115) -*Homo sapiens* IGH4*01 (100%), CH1 (116-213), hinge 1-12 (214-225), CH2 (226-335), CH3 (336-440), CHS (441-442)] (116-442), (129-218)-disulfide with kappa light chain chimeric (1-218*) -[V-KAPPA *Mus musculus* (Mus mus IGK3-5*01 (97.0%) -IGKJ2*01 (100%) CDR-IMGT [10.3.9] (27-36.54-56.93-101) (1-111*) -*Homo sapiens* IGKC*01 (100%) Km3 A45.1 (157), V101 (195) (112-218*)]; dimer (221-221*-224-224*)-bisdisulfide, produced in a Chinese hamster ovary (CHO)-DG44 cell line, glycoform alfa

*immunomodulator*

atibuclimab

immunoglobuline G4-kappa anti-[*Homo sapiens* CD14, membrane (mCD14) et soluble (sCD14)], anticorps monoclonal chimérique; chaîne lourde gamma4 chimérique (1-442) [VH *Mus musculus* (Mus mus musculus IGHV3-2*02 (95.9%) -(IGHD) -Mus musmus IGJ3*01 (92.9%) A128-S (115)) CDR-IMGT [9.7.8] (26-34.52-58.97-104) (1-115) -*Homo sapiens* IGH4*01 (100%), CH1 (116-213), chaîne 1-12 (214-225), CH2 (226-335), CH3 (336-440), CHS (441-442)] (116-442), (129-218*)-disulfure avec la chaîne légère kappa chimérique (1-218*) -[V-KAPPA *Mus musculus* (Mus mus IGK3-5*01 (97.0%) -IGKJ2*01 (100%) CDR-IMGT [10.3.9] (27-36.54-56.93-101) (1-111*) -*Homo sapiens* IGKC*01 (100%) Km3 A45.1 (157), V101 (195) (112-218*)]; dième (221-221*-224-224*)-bisdisulfure, produit dans des cellules ovariennes de hamster chinois (CHO) lignée cellulaire CHO-DG44, glycoforme alfa

*immunomodulateur*
atibuclimab

inmunoglobulina G4-kappa anti-[Homo sapiens CD14, membrana (mCD14) y soluble (sCD14)], anticuerpo monoclonal químico;
cadena pesada gamma4 químico (1-442) [VH Mus musculus (Mus musculus IGHV3-2*02 (95.9%) -IGHD) - Musmus IGHJ3*01 (92.9%) A128>S (115)] CDR-IMGT [9.7.8] (26-34.52-58.97-104) (1-115) -Homo sapiens IGH4*01 (100%), CH1 (116-213), bisagra 1-12 (214-225), CH2 (226-335), CH3 (336-440), CHS (441-442)) (116-442)], (129-218)-disulfuro con la cadena ligera kappa química (1-218) [V-KAPPA Mus musculus (Mus musculus IGKV3-5*01 (97.0%) -IGKJ2*01 (100%)] CDR-IMGT [10.3.9] (27-36.54-56.93-101) (1-111) -Homo sapiens IGKC*01 (100%) Km3 A45.1 (157), V101 (195) (112-218)]; dímero (221-221':224-224')-bisdisulfuro, producido en las células ováricas de hámster chino (CHO) línea celular CHO-DG44, forma glicosilada alfa inmunomodulador

2417175-94-9

bamlanivimab

immunoglobulin G1-kappa, anti-[Homo sapiens severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike (S) protein], Homo sapiens monoclonal antibody;
gamma1 heavy chain Homo sapiens (1-455) [VH (Homo sapiens IGHV1-69*04 (99.0%) -IGHD) -IGHJ6*01 (90.9%) T123>A (120)] CDR-IMGT [8.8.18] (26-33.51-58.97-114) (1-125) -Homo sapiens
IGHG1*03 (100%) G1m3, nG1m1 (CH1 R120 (222) (126-223), hinge 1-15 (224-238), CH2 (239-348), CH3 E12 (364), M14 (366) (349-453), CHS (454-455) (126-454)), (228-214')-disulfide with kappa light chain *Homo sapiens* (1'-214') [V-KAPPA (Homo sapiens IGKV1-39*01 (97.9%) -IGKJ1*01 (100%)) CDR-IMGT [6.3.9] (27-32.50-52.89-97) (1'-107') -*Homo sapiens* IGKC*01 (100%) Km3 A45.1 (153), V101 (191) (108'-214')); dimer (234-234":237-237")-bisdisulfide, produced in a Chinese hamster ovary (CHO) cell line derived from CHO-K1SV, lacking the glutamine synthetase (GS) gene, glycoform alfa antiviral

bamlanivimab immunoglobuline G1-kappa anti-*Homo sapiens* protéine spike (S) du coronavirus 2 du syndrome respiratoire aigu sévère (SARS-CoV-2), anticorps monoclonal *Homo sapiens*; chaîne lourde gamma1 *Homo sapiens* (1-455) [VH (Homo sapiens IGHV1-69*04 (99%)) -IGHD - IGHJ6*01 (90.9%) T123>A (120)] CDR-IMGT [8.8.18] (26-33.51-58.97-114) (1-125) -*Homo sapiens* IGHG1*03 (100%) G1m3, nG1m1 (CH1 R120 (222) (126-223), charnière 1-15 (224-238), CH2 (239-348), CH3 E12 (364), M14 (366) (349-453), CHS (454-455) (126-454)), (228-214')-disulfure avec la chaîne légère kappa *Homo sapiens* (1'-214') [V-KAPPA (Homo sapiens IGKV1-39*01 (97.9%) -IGKJ1*01 (100%)) CDR-IMGT [6.3.9] (27-32.50-52.89-97) (1'-107') -*Homo sapiens* IGKC*01 (100%) Km3 A45.1 (153), V101 (191) (108'-214')); dimère (234-234":237-237")-bisdisulfure, produit dans des cellules ovariennes de hamster chinois (CHO) dérivant de la lignée cellulaire CHO-K1SV, ne présentant pas le géne de la glutamine synthétase, glycoforme alfa antiviral

bamlanivimab inmunoglobulina G1-kappa anti-*Homo sapiens* proteína espícula (S) del coronavirus 2 del síndrome respiratorio agudo severo (SRAS-CoV-2), anticuerpo monoclonal *Homo sapiens*; cadena pesada gamma1 *Homo sapiens* (1-455) [VH (Homo sapiens IGHV1-69*04 (99%)) -IGHD - IGHJ6*01 (90.9%) T123>A (120)] CDR-IMGT [8.8.18] (26-33.51-58.97-114) (1-125) -*Homo sapiens* IGHG1*03 (100%) G1m3, nG1m1 (CH1 R120 (222) (126-223), bisagra 1-15 (224-238), CH2 (239-348), CH3 E12 (364), M14 (366) (349-453), CHS (454-455) (126-454)), (228-214')-disulfuro con la cadena ligera kappa *Homo sapiens* (1'-214') [V-KAPPA (Homo sapiens IGKV1-39*01 (97.9%) -IGKJ1*01 (100%)) CDR-IMGT [6.3.9] (27-32.50-52.89-97) (1'-107') -*Homo sapiens* IGKC*01 (100%) Km3 A45.1 (153), V101 (191) (108'-214')); dímero (234-234":237-237")-bisdisulfuro, producido en las células ováricas de hámster chino (CHO) derivante de la linaje celular CHO-K1SV, en ausencia del gen glutamina sintetasa (GS), forma glicosilada alfa antiviral
casirivimab

immunoglobulin G1-kappa, anti-[Homo sapiens severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike (S) protein, receptor binding domain (RBD)]. Homo sapiens monoclonal antibody; gamma1 heavy chain Homo sapiens (1-450) [VH (Homo sapiens IGHV3-11*01 (96.9%)-(IGHD)-IGHJ4*01 (100%)] CDR-IMGT [8.8.13] (26-33.51-58.97-109) (1-120)-Homo sapiens IGHG1*01 (100%); dimer (223-229)-disulfide, produced in Chinese hamster ovary (CHO) cells, glycoform alfa antiviral

casirivimab

immunoglobuline G1-kappa anti-[Homo sapiens protéine spike (S) du coronavirus 2 du syndrome respiratoire aigu sévère (SARS-CoV-2), domaine de liaison au récepteur (RBD)] anticorps monoclonal Homo sapiens;
chaîne lourde gamma1 *Homo sapiens* IGVH3-11*1*01 (96.9%) -IGHD -IGHJ4*01* (100%) CDR-IMGT [8.8.13] (26-33.51-58.97-109) (1-120) -*Homo sapiens* IGHG1*01* (100%) G1m17,1 (CH1 K120 (217) (121-218), charnière 1-15 (219-233), CH2 (234-343), CH3 D12 (359), L14 (361) (344-448), CHS (449-450)) ([121-450]), ([223-214]) disulfure avec la chaîne légère kappa *Homo sapiens* (1'-214') [V-KAPPA (*Homo sapiens* IGKV1-33*01* (96.8%) -IGKJ4*01* (100%)) CDR-IMGT [6.3.9] (27-32.50-52.89-97) (1'-107') -*Homo sapiens* IGKC*01* (100%) Km A45.1 (153), V101 (191) (108'-214')); dimère ([229-229]*232-232")-bisdisulfure, produit dans des cellules ovariennes de hamster chinois (CHO), glycoforme alfa *antiviral*

**casirivimab**

imunoglobulina G1-kappa anti-[*Homo sapiens* proteína espícula (S) del coronavirus 2 del síndrome respiratorio agudo severo (SRAS-CoV-2), dominio de unión al receptor (RBD)], anticuerpo monoclonal *Homo sapiens*; cadena pesada gamma1 *Homo sapiens* (1-450) [VH (*Homo sapiens* IGVH3-11*1*01 (96.9%) -IGHD -IGHJ4*01* (100%)) CDR-IMGT [8.8.13] (26-33.51-58.97-109) (1-120) -*Homo sapiens* IGHG1*01* (100%) G1m17,1 (CH1 K120 (217) (121-218), bisagra 1-15 (219-233), CH2 (234-343), CH3 D12 (359), L14 (361) (344-448), CHS (449-450)) ([121-450]), ([223-214]) disulfure con la cadena ligera kappa *Homo sapiens* (1'-214') [V-KAPPA (*Homo sapiens* IGKV1-33*01* (96.8%) -IGKJ4*01* (100%)) CDR-IMGT [6.3.9] (27-32.50-52.89-97) (1'-107') -*Homo sapiens* IGKC*01* (100%) Km A45.1 (153), V101 (191) (108'-214')); dímero ([229-229]*232-232")-bisdisulfure, producido en las células ováricas de hámster chino (CHO), forma glicosilada alfa *antiviral*

2415933-42-3

**Heavy chain / Chaîne lourde / Cadena pesada**

QVQLVISEGGGLVQIVVSLRLSLCAASGTFTPSQYKPGLEMWVSSY50
ITYSGTSYASGFYWTQSRGSKLSNAGSLYVLQMELSGSEDFANGGNY 100
VTIVTSQRTY VQGSTVSELNSGTSPVSNLDSIHEKLEQVLSGVEQK 150
TVFMFFVYQKCQSTLVSSSGVSAGVLKVQVGTFKLLFHLVSNQL 200
CH120K120 (217) (121-218), (223-214')-disulfure avec la chaîne légère kappa *Homo sapiens* (1'-214') [V-KAPPA (*Homo sapiens* IGKV1-33*01* (96.8%) -IGKJ4*01* (100%)) CDR-IMGT [6.3.9] (27-32.50-52.89-97) (1'-107') -*Homo sapiens* IGKC*01* (100%) Km A45.1 (153), V101 (191) (108'-214')); dimère ([229-229]*232-232")-bisdisulfure, producido en las células ováricas de hámster chino (CHO), forma glicosilada alfa *antiviral*

**Light chain / Chaîne légère / Cadenaligera**

DIQMTQSPSSLEASVVNGTSTICQASQDITNYLNWYQQKKPGAKELILY 50
ASNLETQSSSDLVFSQSSTSTPDFTFSLGQVRYDIAPEYQQQGDLYLVT 100
DNALQSGNSQTEQDSKTSSTYGAMTHQGPKRPAWNSGQGPGDNVIII 150
DMALQSGNSQTEQDSKTSSTYGAMTHQGPKRPAWNSGQGPGDNVIII 200

**Post-translational modifications**

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro

Intra-H (C23-C104) 22-96 147-203 264-324 370-428
22''-96'' 147''-203'' 264''-324'' 370''-428''

Intra-L (C23-C104) 23'-88' 134'-194'
23'''-88''' 134'''- 194'''

Inter-H-L (h 5-CL 126) 223-214' 223''-214''

Inter-H-H (h 11, h 14) 229-229'' 232-232''

N-terminal glutamine cyclization to pyroglutamyl (pL, 5-oxoprolyl)

H VH Q1: 1, 1"'

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación

H CH2 N84: 300, 300'

Fucosylated complex bi-antennary CHO-type glycans / glycanes de tipo CHO bi-antennaires complexes fucosilados.

C-terminal lysine clipping / Coupure de la lysine C-terminale / Recorte de lisina C-terminal

H CHS K2 450, 450"
cilgavimabum #

cilgavimab

immunoglobulin G1-kappa anti-[Homo sapiens severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike (S) protein, receptor binding domain (RBD)], Homo sapiens monoclonal antibody; gamma1 heavy chain Homo sapiens (1-461) [VH (Homo sapiens IGHV3-15*01 (96.0%) -IGHD) -IGHJ4*01 (100%)) CDR-IMGT [8.10.22] (26-33.51-60.99-120) (1-131)]-Homo sapiens IGHG1*03 G1m3, nG1m1, G1v21 CH2 Y15.1, T16, E18, G1v39 CH2 F1.3, E1.2, S116 (CH1 R120 (228) (132-229)), hinge 1-15 (230-244), CH2 L1.3=F (248), L1.2=E (249), M15.1>Y (266), S16>T (268), T18=E (270), P116>S (345) (245-354), CH3 E12 (370), M14 (372) (355-459), CHS (460-461)) (132-461), (234-219')-disulfide with kappa light chain Homo sapiens (1'-219') [V-KAPPA (Homo sapiens IGKV4-1*01 (96.0%)- IGKJ4*01 (100%)) CDR-IMGT [12.3.8] (27-38.56-58.95-102) (1'-112')]-Homo sapiens IGKC*01 (100%) Km3 A45.1 (158), V101 (196) (113'-219')]; dimer (240-240'':243-243'')-bisdisulfide, produced in Chinese hamster ovary (CHO) cells, glycoform alfa antiviral

cilgavimab

immunoglobuline G1-kappa anti-[Homo sapiens protéine spike (S) du coronavirus 2 du syndrome respiratoire aigu sévère (SARS-CoV-2), domaine de liaison au récepteur (RBD)], anticorps monoclonal Homo sapiens; chaîne lourde gamma1 Homo sapiens (1-461) [VH (Homo sapiens IGHV3-15*01 (96.0%)-IGHD) -IGHJ4*01 (100%)) CDR-IMGT [8.10.22] (26-33.51-60.99-120) (1-131)]-Homo sapiens IGHG1*03 G1m3, nG1m1, G1v21 CH2 Y15.1, T16, E18, G1v39 CH2 F1.3, E1.2, S116 (CH1 R120 (228) (132-229)), charnière 1-15 (230-244), CH2 L1.3=F (248), L1.2=E (249), M15.1>Y (266), S16>T (268), T18=E (270), P116>S (345) (245-354), CH3 E12 (370), M14 (372) (355-459), CHS (460-461)) (132-461), (234-219')-disulfide avec la chaîne légère kappa Homo sapiens (1'-219') [V-KAPPA (Homo sapiens IGKV4-1*01 (96.0%)- IGKJ4*01 (100%)) CDR-IMGT [12.3.8] (27-38.56-58.95-102) (1'-112')]-Homo sapiens IGKC*01 (100%) Km3 A45.1 (158), V101 (196) (113'-219')]; dimère (240-240'':243-243'')-bisdisulfure, produit dans des cellules ovariennes de hamster chinois (CHO), glycoforme alfa antiviral

cilgavimab

inmunoglobulina G1-kappa anti-[Homo sapiens proteína espícula (S) del coronavirus 2 del síndrome respiratorio agudo severo (SRAS-CoV-2), dominio de unión al receptor (RBD)], anticuerpo monoclonal Homo sapiens;
Proposed INN: List 124 – COVID-19
(special edition)

WHO Drug Information, Vol. 34, No. 3, 2020

650

cadena pesada gamma1 Homo sapiens (1-461) [VH (Homo sapiens IGHV3-15*01 (96.0%) -IGHD) -IGHJ4*01 (100%)) CDR-IMGT [8.10.22] (26-33.51-60.99-120) (1-131) -Homo sapiens IGHGI*03 G1m3, G1m1, G1v21 CH2 Y15.1, T16, E18, G1v39 CH2 F1.3, E1.2, S116 (CH1 R120 (228) (132-229), bisagra 1-15 (230-244), CH2 L1.3-F (248), L1.2-E (249), M15.1-Y (266), S16-T (268), T18-E (270), P116>S (345) (245-354), CH3 E12 (370), M14 (372) (355-459), CHS (460-461)) (132-461)], (234-219’)-disulfuro con la cadena ligera kappa Homo sapiens (1-219’) [V-KAPPA (Homo sapiens IGKV4-1*01 (96.0%) -IGKJ4*01 (100%)) CDR-IMGT [12.3.8] (27-38.56-58.95-102) (1-112) -Homo sapiens IGKC*01 (100%) Km3 (158), V101 (196) (113-219’); dímero (240-240’=243-243’)-bisdisulfuro, producido en las células ováricas de hámster chino (CHO), forma glicosilada alfa antiviral 2420563-99-9

Heavy chain / Chaîne lourde / Cadena pesada
EVQLVESGGG LVKPGGSLRL SCAASGFTFR DVVIMWVRQA PGKGLEWVGR 50
IKSKIDGGTT DYAAPVKGRF TISRDDSKNT LYLQMNSLKT EDTAVYYCTT 100
AGSYYYDTVG PGLPEGFVX TGQTITUVTS SASTERGSVF PLAPSSKSTS 150
GOTAALQLLV EVDVPEGTVV SNMGSALSGV VHPPFVQSGS DGLAELGSV 200
TVESSLCTQ YTVCNFRKKE SKEGVRKPE FEGCGREPGF 250
GFEVLFPPKR KEDLYITYRE PVTCVDCVS SVKLPFVXN VYCOEVEVH 300
ANTKPPQXKKQSTTVVSVL TVLQGWNLG KEVKPGSIKR ALPASIIEKT 350
SAQRQVPQGTVYTVISQEFEMTQVQL VSLGDSQPSL K 400
PENNYTTFPV VLDSGSPFPL YEKLTVVSR WQGQNVFSCS VMHEALNHNH 450
TQKSISSIPG K 461

Light chain / Chaîne légère / Cadena ligera
DIVMTQSPDS LAVSLGERAT INCKSSQSVL YSSNNKNYLA WYQQKPGQFF 50
KLINMWSATR ESGVPDRFSG SGSGAEFTLT ISSLQAEDVA IYYCQQYYST 100
LTFGGGTKYE IHRVTAAPSV FIPPPIDSEQK KSSTASVQCL LNNFYPEEAK 150
VQNYGDNLIT QSNDQEVYRV QSDKSTSYL SSITLWKSAD YERHVKFAC 200
VTQCSLISIPV TSKFGBNC 219

Post-translational modifications
Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro
Intra-H (C23-C104) 22-98 158-214 275-335 381-439
22’-98’ 158’-214’ 275’-335’ 381’-439’
Intra-L (C23-C104) 23’-94’ 139’-199’
23’-94’ 139’-199’
Inter-H-L (h 5-CL126) 234-219 234-219’
Inter-H-H (h 11, h 14) 240-240’ 243-243’

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
H CH2 N84.4: 311, 311’

Fucosylated complex bi-antennary CHO-type glycans / glycanes de type CHO bi-antennaires complejos fucosilados / glicanos de tipo CHO biantenarios complejos fucosilados.

C-terminal lysine clipping / Coupe de la lysine C-terminale / Recorte de lisina C-terminal

H CHS K2: 461, 461’

dazcapistatum
dazcapistat
rac-N-[(2R)-4-amino-3,4-dioxo-1-phenylbutan-2-yl]-4-(2-fluorophenyl)-2-methyl-1,3-oxazole-5-carboxamide
calpain inhibitor
dazcapistat
rac-N-[(2R)-4-amino-3,4-dioxo-1-phenylbutan-2-yl]-4-(2-fluorophenyl)-2-methyl-1,3-oxazole-5-carboxamide
inhibiteur de la calpaine
dazcapistat
rac-N-[(2R)-4-amino-3,4-dioxo-1-phenylbutan-2-yl]-4-(2-fluorofenil)-2-metil-1,3-oxazol-5-carboxamida
inhibidor de la calpaina
**WHO Drug Information, Vol. 34, No. 3, 2020**


**eclitasertibum**

**eclitasertib**

5-benzyl-N-[(3S)-5-methyl-4-oxo-2,3,4,5-tetrahydropyrido[3,2-b][1,4]oxazepin-3-yl]-1H-1,2,4-triazole-3-carboxamide

*receptor-interacting serine/threonine protein (RIP-1) kinase inhibitor*

**éclitasertib**

5-benzyl-N-[(3S)-5-méthyl-4-oxo-2,3,4,5-tétrahydropyrindo[3,2-b][1,4]oxazépin-3-yl]-1H-1,2,4-triazole-3-carboxamide

*inhibiteur de la sérine/thréonine protéine kinase interagissant avec le récepteur (RIPK-1)*

**eclitasertib**

5-bencil-N-[(3S)-5-métil-4-oxo-2,3,4,5-tetrahidropirido[3,2-b][1,4]oxazépin-3-il]-1H-1,2,4-triazol-3-carboxamida

*inhibidor de la proteína kinasa que interactúa con el receptor serina/treonina (RIPK-1)*

**enpatoranum**

**enpatoran**

5-[(3R,5S)-3-amino-5-(trifluoromethyl)piperidin-1-yl]quinoline-8-carbonitrile

*toll-Like receptor antagonist*

**enpatoran**

5-[(3R,5S)-3-amino-5-(trifluorométhyl)pipéridin-1-yl]quinoléine-8-carbonitrile

*antagoniste des récepteurs de type toll*

**enpatorán**

5-[(3R,5S)-3-amino-5-(trifluorometil)piperidin-1-il]quinoleína-8-carbonitrilo

*antagonista del receptor tipo toll*
etesevimabum #
etesevimab

Immunoglobulin G1-kappa, anti-[*Homo sapiens* severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike (S) protein, receptor binding domain (RBD)], *Homo sapiens* monoclonal antibody; gamma1 heavy chain *Homo sapiens* (1-449) [VH (*Homo sapiens* IGHV3-66*01 (96.9%) -IGHD) -IGHJ4*01 (100%)) CDR-IMGT [8.7.13] (26-33.51-57.96-108) (1-119) -*Homo sapiens* IGHG1*03 G1m3, nG1m1, G1v14 A1.3, A1.2 (CH1 R120 (216) (120-217), hinge 1-15 (218-232), CH2 L1.3>A (236), L1.2>A (237), (233-342), CH3 E12 (358), M14 (360) (343-447), CHS (448-449) (120-449)), (222-216")-disulfide with kappa light chain *Homo sapiens* (1"-216") [V-KAPPA (*Homo sapiens* IGKV1-39*01 (97.9%) -IGKJ2*01 (100%)) CDR-IMGT [6.3.11] (27-32.50-52.89-99) (1"-109") -*Homo sapiens* IGKC*01 (100%) Km3 A45.1 (155), V101 (193) (110"-216")]; dimer (228-228"*:231-231")-bisdisulfide, produced in a Chinese hamster ovary (CHO) cell line derived from CHO-K1SV, lacking the glutamine synthetase (GS) gene, glycoforme alfa antiviral

étésévimab

Immunoglobuline G1-kappa anti-[*Homo sapiens* protéine spike (S) du coronavirus 2 du syndrome respiratoire aigu sévère (SARS-CoV-2), domaine de liaison au récepteur (RBD)], anticorps monoclonal *Homo sapiens*; chaîne lourde gamma1 *Homo sapiens* (1-449) [VH (*Homo sapiens* IGHV3-66*01 (96.9%) -IGHD) -IGHJ4*01 (100%)) CDR-IMGT [8.7.13] (26-33.51-57.96-108) (1-119) -*Homo sapiens* IGHG1*03 G1m3, nG1m1, G1v14 A1.3, A1.2 (CH1 R120 (216) (120-217), charnière 1-15 (218-232), CH2 L1.3>A (236), L1.2>A (237), (233-342), CH3 E12 (358), M14 (360) (343-447), CHS (448-449) (120-449)), (222-216")-disulfure avec la chaîne légère kappa *Homo sapiens* (1"-216") [V-KAPPA (*Homo sapiens* IGKV1-39*01 (97.9%) -IGKJ2*01 (100%)) CDR-IMGT [6.3.11] (27-32.50-52.89-99) (1"-109") -*Homo sapiens* IGKC*01 (100%) Km3 A45.1 (155), V101 (193) (110"-216")]; dimère (228-228"*:231-231")-bisdisulfure, produit dans des cellules ovariennes de hamster chinois (CHO) dérivant de la lignée cellulaire CHO-K1SV, ne présentant pas le gène de la glutamine synthétase, glycoforme alfa antiviral
etesevimab inmunoglobulina G1-kappa anti-[Homo sapiens proteína espícula (S) del coronavirus 2 del síndrome respiratorio agudo severo (SRAS-CoV-2), dominio de unión al receptor (RBD)], anticuerpo monoclonal Homo sapiens;

cadena pesada gamma1 Homo sapiens (1-449) [VH (Homo sapiens IGHV3-66*01 (96.9%) -IGHD -IGHJ4*01 (100%)) CDR-IMGT [8.7.13] (26-33.51-57.96-108) (1-119) -Homo sapiens IGHV1*03 G1m3, G1m1, G1v14 A1.3, A1.2 (CH1 R120 (216) (120-217), bisagra 1-15 (218-232), CH2 L1.3-A (236), L1.2-A (237), (233-342), CH3 E12 (358), M14 (360) (343-447), CHS (448-449) (120-449)), (222-216)-disulfuro con la cadena ligera kappa Homo sapiens (1’-216) [V-KAPPA (Homo sapiens IGKV1-39*01 (97.9%) -IGKJ2*01 (100%)) CDR-IMGT [6.3.11] (27-32.50-52.89-99) (1’-109) -Homo sapiens IGKC*01 (100%) Km3 A45.1 (155), V101 (193) (110’-216’)); dímero (228-228”-231-231”)-bisdisulfuro, producido en las células ováricas de hámster chino (CHO) línea celular derivada de CHO-K1SV, en ausencia del gen Glutamina Sintetasa (GS), forma glicosilada alfa antiviral

2423948-94-9

Heavy chain / Chaîne lourde / Cadena pesada
EVQLVESGGG LVQPGGSLRL SCAASGFTVS SLYMNWQKPA PGKLEKNSV Y 50
IYSGGSTFYA DSVKGRFTIS RDNSMNTLFL QMNSLRAEDT AVYYCARVLP 100
MYGDYLDYWG QGTLVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD 150
YFPEPVTVSV NGALTSQSVF YLSELVTVY FSESNLGQTV 200
IENNYFRENS TVAYQERVFV SCQKSTYPCP CFAPEAAQQ SVYLFVRFP 250

Light chain / Chaîne légère / Cadena ligera
DIVMTQSPSS LSASVGDRVT ITCRASQSIS RYLVNYYQKF GAPFKLILY Y 50
ASELQGVQPF RPPGGSGQDT FLITLSSLQF EQATFYQCOQ SYSTPPEFPFT 100
QCQTELEHEK TVAYQERVFV SCQKSTYPCP CFAPEAAQQ SVYLFVRFP 150

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
H CH2 N84.4: 299, 299”
Fucosylated complex bi-antennary CHO-type glycans / glicanos de tipo CHO biantenarios complejos fucosilados.

Post-translational modifications
Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro
Intra-H (C23-C104) 22-95 146-202 263-323 369-427
22”-95” 146”-202” 263”-323” 369”-427”
Intra-L (C23-C104) 23-88 136-196
23”-88” 136”-196”
Inter-H-L (h 5-CL 126) 222-216 222”-216”
Inter-H-H (h 11, h 14) 228-228” 231-231”

immunological agent for active immunization (anti-SARS-CoV-2)

ganulameranum #
ganulameran

message RNA (mRNA), 5’-capped, encoding the codon-optimised receptor binding domain (RBD) of the SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2, GenBank: MN908947.3) spike (S) glycoprotein expressed as a fusion protein, 5’ with an extended S glycoprotein signal peptide, and 3’ with a T4 fibrin trimerization domain and the S glycoprotein transmembrane domain (TM) connected by two glycine/serine-rich (GS) linker peptides, flanked by 5’ and 3’ untranslated regions and a 3’ poly(A) tail; contains N1-methylpseudouridine instead of uridine (all-U>Ψ).

C-terminal lysine clipping / Coupe de la lysine C-terminale / Recorte de lisina C-terminal
H CHO N84.4: 299, 299”

immunological agent for active immunization (anti-SARS-CoV-2)
ganulaméran

ARN messager (ARNm), protégé en 5', codant pour le domaine de liaison au récepteur (RBD) de la glycoprotéine spike (S) du SARS-CoV-2 (coronavirus 2 du syndrome respiratoire aigu sévère, GenBank: MN908947.3) avec des codons optimisés, exprimés sous forme de protéine de fusion, 5' avec un peptide signal de la glycoprotéine S allongé et 3' avec un domaine de trimérisation de la fibrine de T4 et le domaine transmembranaire (TM) de la glycoprotéine S, liés au moyen de deux peptides de liaison (linker) riches en glycine / sérine (GS), flanqués de régions 5' et 3' non traduites et d'une queue poly(A); contient de la N1-méthylpseudouridine au lieu de l'uridine (\( \text{all-U}>\text{m}^1\text{Ψ} \)).

agent immunologique d'immunisation active (anti-SARS-CoV-2)

ganulamerán

RNA mensajero (mRNA), protegido en 5', que codifica para el dominio de unión al receptor (RBD) de la glicoproteína de la espícula (S) de SRAS-CoV-2 (coronavirus 2 del síndrome respiratorio agudo severo, GenBank: MN908947.3) con codones optimizados, expresado como una proteína de fusión, en 5' con un péptido señal de glicoproteína S extendido y en 3' con un dominio fibrínico de trimerización de T4 y el dominio transmembrana (TM) de la glicoproteína S, conectado mediante dos péptidos enlazadores (linker) ricos en glicina/serina (GS), flanqueado por regiones 5' y 3' no traducidas y una cola poly(A); contiene N1- metilpseudouridina en lugar de uridina (\( \text{all-U}>\text{m}^1\text{Ψ} \)).

agente inmunológico para inmunización activa (anti-SRAS-CoV-2)

2433844-55-2
goflikiceptum #
goflikicept

human interleukin-1 receptor accessory protein fragment (21-358, 1-338 in the current sequence) fused via peptidyl linker \( ^{339}\text{GSGGG}^{343} \) to a human immunoglobulin G1 Fc fragment (344-570, C-terminal Lys clipped) variant \((\text{S}>\text{C}^{477}, \text{T}>\text{W}^{489}, \text{K}>\text{A}^{532})\), covalent dimer with human interleukin-1 receptor type 1 fragment (21-333, 1-313 in the current sequence) fused via peptidyl linker \( ^{314}\text{GSGG}^{318} \) to a human immunoglobulin G1 Fc fragment (319-545, C-terminal Lys clipped) variant \((\text{Y}>\text{C}^{447}, \text{T}>\text{S}^{464}, \text{L}>\text{A}^{466}, \text{F}>\text{K}^{503}, \text{Y}>\text{V}^{505})\), glycosylated, produced in Chinese hamster ovary (CHO) cells;

fusion protein comprising the (1-338)-fragment of the human interleukin 1 receptor accessory protein (IL1RAP, IL-1RAcP, interleukin-1 receptor 3, IL1R3), a GSGGG linker (339-343), and the \((\text{S}>\text{C}^{477}, \text{T}>\text{W}^{489}, \text{K}>\text{A}^{532})\) variant of the C-terminal 227-peptide (Fc fragment) of human immunoglobulin G1 (344-570), \((349-324';352-327';477-447')\)-trisdisulfide with a fusion protein comprising the (21-333)-fragment of the precursor of human interleukin 1 receptor type 1 \((\text{IL1R1, IL1R1a, IL1R1 type I, p80, CD121a} \ (1-313))\), a GSGGG linker (314-318), and the \((\text{Y}>\text{C}^{447}, \text{T}>\text{S}^{464}, \text{L}>\text{A}^{466}, \text{F}>\text{K}^{503}, \text{Y}>\text{V}^{505})\) variant of the C-terminal 227-peptide (Fc fragment) of human immunoglobulin G1 (319-545), produced in Chinese hamster ovary (CHO) cells, glycoform alfa immunomodulator
goflikicept

fragment de la protéine accessoire du récepteur de l'interleukine 1 humaine (21-358, 1-338 dans la séquence actuelle) fusionné via un peptide liant GSGGG à l'immunoglobuline humaine G1 (344-570, C-terminal attaché Lys) variant (S>C477, T>W489, K>A532), dimère covalent avec fragment de récepteur de l'interleukine-1 humaine de type 1 (21-333, 1-313 dans la séquence actuelle) fusionné via un peptide liant GSGGG à un fragment Fc d'immunoglobuline humaine G1 (319-545, attaché au variant C-terminal Lys) (Y>C447, T>S464, L>A466, F>K503, Y>V505), glycosylé, produit dans des cellules ovariennes de hamster chinois (CHO);

une protéine de fusion comprenant le fragment (1-338) de la protéine accessoire du récepteur de l'interleukine 1 humaine (IL1RAP, IL-1RAcP, récepteur 3 de l'interleukine-1, IL1R3), un linker GSGGG, et le variant (S>C477, T>W489, K>A532) du peptide C-terminal-227 (fragment Fc) de l'immunoglobuline humaine G1 (344-570), (349-324':352-327':477-447')-trisdisulfure avec une protéine de fusion comprenant le fragment- (21-333) du précurseur du récepteur de l'interleukine humaine de type 1 (IL1R1, IL1Ra, IL1R type I, p80, CD121a) (1-313), une liaison GSGGG et le variant (Y>C447, T>S464, L>A466, F>K503, Y>V505) du peptide C-terminal-227 (fragment Fc) de l'immunoglobuline humaine G1 (319-545), produit dans des cellules ovariennes de hamster chinois (CHO), glycoforme alfa immunomodulante

immunomodulateur

goflikicept

receptor de la interleukina-1 humana fragmento de la proteína complemento (21-358, 1-338 en la secuencia actual) fusionado a través de un enlace peptidil GSGGG a la inmunoglobulina humana G1 Fc fragmento (344-570, fijado al C-terminal Lis) variante (S>C477, T>W489, K>A532) del receptor de interleukina-1 humana fragmento tipo 1 (21-333, 1-313 en la secuencia actual) fusionado a través del enlace peptidil GSGGG a una inmunoglobulina humana G1 Fc fragmento (319-545, fijado al C-terminal Lis) variante (Y>C447, T>S464, L>A466, F>K503, Y>V505), glicosilado, producido en células ováricas de hámster Chino (CHO);

una proteína de fusión que comprende el fragmento-(1-338) del receptor humano de la interleukina 1 proteína accesorio (IL1RAP, IL-1RAcP, interleukina-1 receptor 3, IL1R3), un enlace GSGGG, y la variante (S>C477, T>W489, K>A532) del termina-C péptido-227 (Fc fragmento) de la inmunoglobulina humana G1 (344-570), (349-324':352-327':477-447')-trisdisulfuro con una proteína de fusión que comprende el fragmento-(21-333) del precursor del receptor tipo 1 de la interleukina humana (IL1R1, IL1Ra, IL1R tipo I, p80, CD121a) (1-313), un enlace GSGGG y la (Y>C447, T>S464, L>A466, F>K503, Y>V505) variante del terminal-C péptido-227 (Fc fragmento) de inmunoglobulina humana G1 (319-545), producido en células ováricas de hámster Chino (CHO), glicoforima alfa immunomodulator
imdevimab #
imdevimab

immunoglobulin G1-lambda, anti-[Homo sapiens severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike (S) protein, receptor binding domain (RBD)], Homo sapiens monoclonal antibody; gamma1 heavy chain Homo sapiens (1-450) [VH (Homo sapiens IGHV3-30*01 (96.9%) -IGHD) -IGHJ4*01 (100%)]
CDR-IMGT [8.8.13] (26-33.51-58.97-109) (1-120) -Homo sapiens IGHL1*01 (100%) G1m17,1 (CH1 K120 (217) (121-218), hinge 1-15 (219-233), CH3 D12 (359), L14 (361) (344-448), CHS (449-450)] (121-450), (223-215')-disulfide with lambda light chain Homo sapiens (1-216') [VL (Homo sapiens IGLV2-14*01 (93.9%) -IGLV3*02 (100%)) CDR-IMGT [9.3.10] (26-34.52-54.91-100) (1-110') -Homo sapiens IGLC2*01 (100%) (111'-216')] dimer (229-229':232-232')-bisdisulfide, produced in Chinese hamster ovary (CHO) cells, glycoform alpha antiviral

imdévimab

immunoglobuline G1-lambda anti-[Homo sapiens protéine spike (S) du coronavirus 2 du syndrome respiratoire aigu sévère (SARS-CoV-2), domaine de liaison au récepteur (RBD)], anticorps monoclonal Homo sapiens;
chaîne lourde gamma1 Homo sapiens (1-450) [VH (Homo sapiens IGHV3-30*01 (96.9%) -IGHD -IGHJ4*01 (100%)) CDR-IMGT [8.8.13] (26-33.51-58.97-109) (1-120) -Homo sapiens IGHI*01 (100%) G1m17,1 (CH1 K120 (217) (121-218), charnière 1-15 (219-233), CH2 (234-343), CH3 D13 (359), L14 (361) (344-448), CHS (449-450)) (121-450)), (223-215')-disulfure avec la chaîne légère lambda Homo sapiens (1'-216') [V-LAMBDA (Homo sapiens IGLV2-14*01 (93.9%) -IGLJ3*02 (100%)) CDR-IMGT [9.3.10] (26-34.52-54.91-100) (1'-110') -Homo sapiens IGLC2*01 (100%) (111'-216')]; dimère (229-229''-232-232'')-bisdisulfure, produit dans des cellules ovariennes de hamster chinois (CHO), glycoforme alfa antiviral

imdevimab

immunoglobulina G1-lambda anti-[Homo sapiens proteína espícula (S) del coronavirus 2 del síndrome respiratorio agudo severo (SRAS-CoV-2), dominio de unión al receptor (RBD)], anticuerpo monoclonal Homo sapiens;
cadena pesada gamma1 Homo sapiens (1-450) [VH (Homo sapiens IGHV3-30*01 (96.9%) -IGHD -IGHJ4*01 (100%)) CDR-IMGT [8.8.13] (26-33.51-58.97-109) (1-120) -Homo sapiens IGHI*01 (100%) G1m17,1 (CH1 K120 (217) (121-218), bisagra 1-15 (219-233), CH2 (234-343), CH3 D13 (359), L14 (361) (344-448), CHS (449-450)) (121-450)), (223-215')-disulfuro con la cadena ligera lambda Homo sapiens (1'-216') [V-LAMBDA (Homo sapiens IGLV2-14*01 (93.9%) -IGLJ3*02 (100%)) CDR-IMGT [9.3.10] (26-34.52-54.91-100) (1'-110') -Homo sapiens IGLC2*01 (100%) (111'-216')]; dímero (229-229''-232-232'')-bisdisulfuro, producido en las células ováricas de hamster chino (CHO), forma glicosilada alfa antiviral

2415933-40-1

Heavy chain / Chaîne lourde / Cadena pesada
QVQLVSLGPGVYQPSRGSGT SCAASGFTPS YNY AMYWVRQA PGKLEKAVV 50
ISFGSGSRLGVVRNIGTFTSK GQSGMSFLTS LSQGNSLATE TAVV YCAUGS 100
DYGDYLLVYW QGDTLVTQSS ASTRGKSNSPF LASPPKSTGG TAAALGCCLKVE 150
DYFPEPVTVVE WNSGALTGVS KTFVPVQLGS GLASYLSELT VPSDLQGQT 200
YCVYYNKGEKMTKGVKPSQ KCSDRHGHTCP FCPAPAPLGG PSSVFLIPPPK 250
KCMLM1RSTPV ETVVCVVDVS HEDPEVKFNM YGVDQVENHA KTFREQEYQNN 300
STTVYRSSLVTL QQLQNLGK XRYCVPSNKA LAPIEITKTIS KAKQPVFMQFQ 350
VTTPNPSLGDQ TETNQSVQI7CT LVGQFYSEPQ CAVWEGHQQG ENNVTETFPFQ 400
IDDSGQFLSL SKLTVKSSRM QQQNVFSVCSMVHEALHNYTY QKSLISLSPQK 450

Light chain / Chaîne légère / Cadena ligera
QSALTQPSAV SGEPQSSSTI SCTCTSDSDG HGVHSWSQHPQ GPQAPKLMN 50
TDYSGSQRPSGV SWKFRSGSKEG NTASLTLISGL QSSDAEYCTG HELSISHTMW 100
PGGCTKLTVL GQQPAAPVSRT LFPPSSEEQN ANPATLVCIL SDQYPARSYTV 150
AKWADFSPVX AGVETTTPSQQ QNNKXADDLSLITPSQVMK SHRSHSDQQTQ 200
HEGLSTVERTVAPTECS 216

Post-translational modifications
Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro
Intra-H (E23-C104) 22-96 147-203 264-324 370-428
22''-96'' 147''-203'' 264''-324'' 370''-428''
Intra-L (E23-C104) 22-90 138-197
22''-90'' 138''-197''
Inter-H-L (h 5-CL 126) 223-215' 223'-214''
Inter-H-H (h 11, h 14) 229-229'' 232-232''

N-terminal glutamine cyclization to pyroglutamyl (pE, S-oxoprolyl)
H VH Q1: 1, 1'
L VH Q1: 1, 1'

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
H CH2 N84: 4: 500, 300'
Fucoylated complex bi-antennary CHO-type glycans / glicanos de tipo CHO biantenarios complejos fucosilados.

C-terminal lysine clipping / Coupe de la lysine C-terminale / Recorte de lisina C-terminal
H CHS K2: 450, 450''
molnupiravirum
molnupiravir
\( N^4\)-hydroxycytidine 5\(^\prime\)-(2-methylpropanoate) antiviral

molnupiravir
5\(^\prime\)-(2-méthylpropanoate) de \( N^4\)-hydroxycytidine antiviral

molnupiravir
5\(^\prime\)-(2-metilpropanoato) de \( N^4\)-hidroxicitidina antiviral

\[
C_{13}H_{19}N_3O_7 \quad 2349386-89-4
\]

nezulcitinibum
nezulcitinib
[3-(dimethylamino)azetidin-1-yl][\((6S)-2-[6-(2-ethyl-4-hydroxyphenyl)-1H-indazol-3-yl]-5-(propan-2-yl)-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-6-yl]methanone
Janus kinase inhibitor

nézulcitinib
[3-(diméthylamino)azétidin-1-yl][\((6S)-2-[6-(2-éthyl-4-hydroxyphényl)-1H-indazol-3-yl]-5-(propan-2-yl)-4,5,6,7-tétrahydro-1H-imidazo[4,5-c]pyridin-6-yl]méthanone
inhibiteur de la kinase de Janus

nezulcitinib
[3-(dimetilamino)azetidin-1-il][\((6S)-2-[6-(2-etil-4-hidroxifenil)-1H-indazol-3-il]-5-(propan-2-il)-4,5,6,7-tetrahidro-1H-imidazo[4,5-c]piridin-6-il]metanona
inhibidor de la kinasa de Janus

\[
C_{30}H_{37}N_7O_2 \quad 2412496-23-0
\]

pemziviptadilum #
pemziviptadil
human \( L \)-methionyl vasoactive intestinal peptide (2-29) fused to 121 repeats of different elastin-derived pentapeptides (VPGVG, VPPGG, VPGAG, VPGWP) (30-634), produced in \textit{Escherichia coli};
fused protein comprising L-methionyl (1)-vasoactive intestinal polypeptide (human VIP) (2-29) and an elastin-like artificial polymer (30-629) of 120 alternating pentapeptides of three types VPGVG, VPGGG, and VPGAG, and a C-terminal pentapeptide VPGWP (630-634), produced in *Escherichia coli* vasoactive intestinal peptide (VIP) analogue

**pemziviptadil**

L-méthionyl peptide vasoactif intestinal humain (2-29) fusionné à 121 répétitions de différents pentapeptides dérivés de l’élastine (VPGVG, VPGGG, VPGAG, VPGWP) (30-634), produits dans *Escherichia coli* ; protéine de fusion comprenant le polypeptide intestinal vasoactif L-méthionyl (1) (VIP humain) (2-29) et un polymère artificiel de type élastine (30-629) de 120 pentapeptides alternés de trois types VPGVG, VPGGG et VPGAG, et un pentapeptide C-terminal VPGWP (630-634), produit dans *Escherichia coli* analogue du peptide vasoactif intestinal (PVI)

**pemziviptadil**

péptido humano L-metionil vasoactivo intestinal (2-29) fusionado a 121 repeticiones de pentapéptidos derivados de elastina diferentes (VPGVG, VPGGG, VPGAG, VPGWP) (30-634), producido en *Escherichia coli*; proteína de fusión que comprende polipéptido intestinal vasoactivo L-metionil (1) (humano VIP) (2-29) y un polímero artificial parecido a la elastina (30-629) de 120 pentapéptidos alternos de tres tipos VPGVG, VPGGG y VPGAG, y un pentapéptido C-terminal VPGWP (630-634), producido en *Escherichia coli* análogo del péptido intestinal vasoactivo (PIV)

<table>
<thead>
<tr>
<th>Sequence / Séquence / Secuencia</th>
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<tbody>
<tr>
<td>MHEGAVFTDN YTTLALKQAV KEYLSNLAW PGDVPGVGPGDVPGAGV PGDVPGAGV 50</td>
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<tr>
<td>PAGVPGVPGVPGAGV PGAGVPGAGV PGDVPGAGV PAGVPGVPGVPGAGV 100</td>
</tr>
<tr>
<td>PAGVPGVPGVPGAGV PGAGVPGAGV PGDVPGAGV PAGVPGVPGVPGAGV 150</td>
</tr>
<tr>
<td>PAGVPGVPGVPGAGV PGAGVPGAGV PGDVPGAGV PAGVPGVPGVPGAGV 200</td>
</tr>
<tr>
<td>PAGVPGVPGVPGAGV PGAGVPGAGV PGDVPGAGV PAGVPGVPGVPGAGV 250</td>
</tr>
<tr>
<td>PAGVPGVPGVPGAGV PGAGVPGAGV PGDVPGAGV PAGVPGVPGVPGAGV 300</td>
</tr>
<tr>
<td>PAGVPGVPGVPGAGV PGAGVPGAGV PGDVPGAGV PAGVPGVPGVPGAGV 350</td>
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<tr>
<td>PAGVPGVPGVPGAGV PGAGVPGAGV PGDVPGAGV PAGVPGVPGVPGAGV 400</td>
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</tr>
<tr>
<td>PAGVPGVPGVPGAGV PGAGVPGAGV PGDVPGAGV PAGVPGVPGVPGAGV 600</td>
</tr>
<tr>
<td>PAGVPGVPGVPGAGV PGAGVPGAGV PGDVPGAGV PAGVPGVPGVPGAGV 634</td>
</tr>
</tbody>
</table>

positions 30-634: 12 × pattern AABCAAABCB of 10 pentapeptides of three types

A = VPGVG, B = VPGGG, and C = VPGAG plus a C-terminal pentapeptide VPGWP

**pidacmeranum # pidacmeran**

self-replicating messenger RNA (mRNA), 5'-capped, encoding *Venezuelan equine encephalitis virus* (VEEV) RNA-dependent RNA polymerase (VEEV proteins nsP1, nsP2, nsP3 and nsP4) and a full-length codon-optimised pre-fusion stabilised conformation variant (K986P and V987P) of the SARS-CoV-2 (severe acute respiratory syndrome coronaviruse 2, GenBank: MN908947.3) spike (S) glycoprotein, flanked by 5' and 3' untranslated regions and a 3' poly(A) tail; replication of the RNA is under control of a VEEV subgenomic promoter.

*immunological agent for active immunization (anti-SARS-CoV-2)*
pidacméran

ARN messager (ARNm) auto-répliquant, protégé en 5', codant pour l'ARN polymérase ARN-dépendante du *virus de l'encéphalite équine vénézuélienne* (protéines VEEV nsP1, nsP2, nsP3 et nsP4) et une variante complète de pré-fusion de conformation stabilisée (K986P et V987P) de la glycoprotéine spike (S) du SARS-CoV-2 (coronavirus 2 du syndrome respiratoire aigu sévère, GenBank: MN908947.3) avec des codons optimisés, flanqués de régions 5 ' et 3' non traduites une queue poly(A) 3'; la réplication de l'ARN est sous le contrôle du promotor sous-génomique de VEEV.

agent immunologique d'immunisation active (anti-SARS-CoV-2)

pidacmerán

RNA mensajero auto replicativo (mRNA), protegido en 5', que codifica para la RNA polimerasa dependiente de RNA del *virus de la encefalitis equina venezolana* (proteínas VEEV nsP1, nsP2, nsP3 y nsP4) y una variante pre-fusión completa de conformación estabilizada (K986P and V987P) de la glicoproteína de la espícula (S) del SRAS-CoV-2 (coronavirus 2 del síndrome respiratorio agudo severo, GenBank: MN908947.3) con codones optimizados, flanqueada por regiones 5' y 3' no traducidas y una cola poly(A) en 3'; la replicación del ARN está bajo el control del promotor subgenómico de VEEV.

agente inmunológico para inmunización activa (anti-SRAS-CoV-2)

regdanvimabum #

regdanvimab

immunoglobulin G1-lambda, anti-[*Homo sapiens* severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike (S) protein, receptor binding domain (RBD)], humanized and *Homo sapiens* monoclonal antibody; gamma1 heavy chain humanized (1-458) [VH (*Homo sapiens* IGHV2-70*12 (92.9%) -IGHD - IGHJ6*01 (100%)) CDR-IMGT [10.7.20] (26-35.53-59.98-117) (1-128) -Homo sapiens IGHG1*08p (100%) G1m3,1 (CH1 R120 (225) (129-226), hinge 1-15 (227-241), CH2 (242-351), CH3 D12 (367), L14 (369) (352-456), CHS (457-458)) (129-458)], (231-215')-disulfide with lambda light chain *Homo sapiens* (1'-216') [V- LAMBDA (*Homo sapiens* IGLV1-51*01 (100%) - IGLJ2*01 (90.9%) K123>E (106)) CDR-IMGT [8.3.11] (26-33.51-53.90-100) (1'-110') -Homo sapiens IGLC2*01 (98.1%) S45>G (156), T82>K (167) (111'-216')]; dimer (237-237":240-240")-bisdisulfide, produced in a Chinese hamster ovary (CHO) cell line derived from CHO-K1, glycoform alfa antiviral

regdanvimab

immunoglobuline G1-lambda anti-[*Homo sapiens* protéine spike (S) du coronavirus 2 du syndrome respiratoire aigu sévère (SARS-CoV-2), domaine de liaison au récepteur (RBD)], anticorps monoclonal humanisé et *Homo sapiens*;
WHO Drug Information, Vol. 34, No. 3, 2020


chaîne lourde gamma1 humanisée (1-458) [VH (Homo sapiens IGHV2-70*12 (92.9%) -IGHD) -IGHJ6*01 (100%)] CDR-IMGT [10.7.20] (26-35.53-59.98-117) (1-128) -Homo sapiens IGHG1*08p (100%) G1m3.1 (CH1 R120 (225) (129-226), châssis 1-15 (227-241), CH2 (242-351), CH3 D12 (367), L14 (369) (352-456), CHS (457-458)) (129-458),] (231-215°)-disulfure avec la chaîne légère lambda Homo sapiens IGLV1-51*01 (100%) -IGLJ2*01 (90.9%) K123=E (106) CDR-IMGT [8.3.11] (26-33.51-59.90-100) (1‘-110°) - HOMO sapiens IGLC2*01 (98.1%) S45=G (156), T82→K (167) (111‘-216°)); dimère (237-237°-240-240°)-bisdisulfure, produit dans des cellules ovariennes de hamster chinois (CHO) dérivant de la lignée cellulaire CHO-K1, glycoforme alfa antiviral

regdanvimab immunoglobulina G1-lambda anti-(Homo sapiens proteína espícula (S) del coronavirus 2 del síndrome respiratorio agudo severo (SRAS-CoV-2), dominio de unión al receptor (RBD)), anticuerpo monoclonal humanizado y Homo sapiens;

cadena pesada gamma1 humanizada (1-458) [VH (Homo sapiens IGHV2-70*12 (92.9%) -IGHD) -IGHJ6*01 (100%)] CDR-IMGT [10.7.20] (26-35.53-59.98-117) (1-128) -Homo sapiens IGHG1*08p (100%) G1m3.1 (CH1 R120 (225) (129-226), bisagra 1-15 (227-241), CH2 (242-351), CH3 D12 (367), L14 (369) (352-456), CHS (457-458)) (129-458),] (231-215°)-disulfure con la cadena ligera lambda Homo sapiens IGLV1-51*01 (100%) -IGLJ2*01 (90.9%) K123=E (106) CDR-IMGT [8.3.11] (26-33.51-59.90-100) (1‘-110°) - HOMO sapiens IGLC2*01 (98.1%) S45=G (156), T82→K (167) (111‘-216°)); dímero (237-237°-240-240°)-bisdisulfuro, producido en las células ováricas de hamster chino (CHO) línea celular derivada de CHO-K1, forma glicosilada alfa antiviral

2444308-95-4
reluscovtogenum ralaplasmidum #
reluscovtgène ralaplasmide
reluscoctogén ralaplasmida
sotrovimabum #
sotrovimab

DNA plasmid expressing a consensus sequence* of the full-length SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) spike (S) glycoprotein, with an N-terminal IgE leader sequence, under control of the human CMV promoter (hCMV promoter) and a bovine growth hormone polyadenylation signal (bGH poly(A)). The plasmid also contains a pUC origin of replication and a kanamycin antibiotic resistance gene. *based upon sequences published on GISAID (Global Initiative on Sharing All Influenza Data) in early 2020. immunological agent for active immunization (anti-SARS-CoV-2)

plasmide d’ADN exprimant une séquence consensus* complète de la glycoprotéine spike (S) du SARS-CoV-2 (coronavirus 2 du syndrome respiratoire aigu sévère), avec une séquence leader N-terminale d’IgE, sous contrôle du promoteur du CMV humain (promoteur hCMV) et d’un signal de polyadénylation de l’hormone de croissance bovine (bGH poly(A)). Le plasmide contient également une origine de réplication pUC et un gène de résistance à la kanamycine. *basé sur des séquences publiées dans GISAID (Global Initiative on Sharing All Influenza Data) début 2020. agent immunologique d’immunisation active (anti-SARS-CoV-2)

plásmido de DNA que expresa una secuencia consenso* completa de la glicoproteína de la espícula (S) de SARS-CoV-2 (coronavirus 2 del síndrome respiratorio agudo severo), con una secuencia líder N-terminal de la IgE, bajo el control del promotor de CMV humano (promotor hCMV) y una señal de poliadenilación de la hormona de crecimiento bovina (bGH poly(A)). El plásmido contiene también un origen de replicación pUC y un gen de resistencia al antibiótico kanamicina. *basada en secuencias publicadas en GISAID (Global Initiative on Sharing All Influenza Data) a principios de 2020. agente inmunológico para inmunización activa (anti-SRAS-CoV-2)

immunoglobulin G1-kappa, anti-[Homo sapiens severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike (S) protein, receptor binding domain (RBD)], Homo sapiens monoclonal antibody;
sotrovimab

immunglobuline G1-kappa anti-[*Homo sapiens* protéine spike (S) du coronavirus 2 du syndrome respiratoire aigu sévère (SARS-CoV-2), domaine de liaison au récepteur (RBD)], anticorps monoclonal *Homo sapiens*; chaîne lourde gamma1 *Homo sapiens* (1-457) [VH (*Homo sapiens* IGHV1-18*01 (92.9%) -IGHD -IGHJ5*01 (92.9%)) CDR-IMGT [8.8.20] (26-33.51-58.97-116) (1-127) -*Homo sapiens* IGHG1*01 G1m17,1, G1v24 CH3 L107, S114(CH1 K120 (224) (128-225), hinge 1-15 (226-240), CH2 (241-350), CH3 D12 (366), L14 (368), M107>L (438), N114>S (444) (351-455), CHS (456-457)) (128-457)], (230-214')-disulfure avec la chaîne légère kappa *Homo sapiens* (1'-214') [V-KAPPA (*Homo sapiens* IGKV3-20*01 (96.7%) -IGKJ4*01 (100%)) CDR-IMGT [7.3.8] (27-33.51-53.90-97) (1'-107') -*Homo sapiens* IGKC*01 (100%) Km3 A45.1 (153), V101 (191) (108'-214')]; dème (236-236*-239-239*)-bisdisulfure, produit dans des cellules ovariennes de hamster chinois (CHO) lignée cellulaire CHO-K1, glycoforme alfa antiviral

sotrovimab

inmunoglobulina G1-kappa anti-[*Homo sapiens* proteína espícula (S) del coronavirus 2 del síndrome respiratorio agudo severo (SARS-CoV-2), dominio de unión al receptor (RBD)], anticuerpo monoclonal *Homo sapiens*; cadena pesada gamma1 *Homo sapiens* (1-457) [VH (*Homo sapiens* IGHV1-18*01 (92.9%) -IGHD -IGHJ5*01 (92.9%)) CDR-IMGT [8.8.20] (26-33.51-58.97-116) (1-127) -*Homo sapiens* IGHG1*01 G1m17,1, G1v24 CH3 L107, S114(CH1 K120 (224) (128-225), bisagra 1-15 (226-240), CH2 (241-350), CH3 D12 (366), L14 (368), M107>L (438), N114>S (444) (351-455), CHS (456-457)) (128-457)], (230-214')-disulfuro con la cadena ligera kappa *Homo sapiens* (1'-214') [V-KAPPA (*Homo sapiens* IGKV3-20*01 (96.7%) -IGKJ4*01 (100%)) CDR-IMGT [7.3.8] (27-33.51-53.90-97) (1'-107') -*Homo sapiens* IGKC*01 (100%) Km3 A45.1 (153), V101 (191) (108'-214')]; dimere (236-236*-239-239*)-bisdisulfuro, producido en las células ováricas de hámster chino (CHO) línea celular CHO-K1, forma glicosilada alfa antiviral

antiviral
Protein sequence:

Heavy chain / Chaîne lourde / Cadena pesada

QVQLVQSGAE VKKPGASVKV SCKASQFTSY GISWVRQA PGQGLEWMGW ISTYQGNTNY AQKFQGRVTM TTDTSTTYGM ERLRRLRSDD TAVYYCARDY TRGAWFGESL IGGFDNWGQG TLVTVSSAST KGPSVFPLAP SSKSTSGGTA ALGCLVKDYF PEPVTVSWNS GALTSGVHTF PAVLQSSGLY SLSSVVTVPS SSLGTQTYIC NVNHKPSNTK VDKKVEPKSC DKTHTCPPCP APELLGGPSV FLFPPKPKDT LMISRTPEVT CVVVDVSHED PEVKFNWYVD GVEVHNAKTK PREEQYNSTY RVVSVLTVLH QDWLNGKEYK CKVSNKALPA PIEKTISKAK GQPREPQVYT LPPSRDELTK NQVSLTCLVK GFYPSDIAVE WESNGQPENN YKTTPVILDS DGSFFLYEKL TVDSRWQQQC NVFSCSULHE ALISHTYQKS

Light chain / Chaîne légère / Cadena ligera

EIVLTQSPGT LSISRGERAT LSCRASQTVS STSLAWYQQK PGEPRLLIY GASSRATGIP DRFSGSGSGT DFTLTISRLE PEDFAVYYCQ QHDTSLTFGG GTKVEIKRTV AAPSVFIFPP SDEQLKSGTA SVCLLLNFY PREAXWQKV 150

Post-translational modifications

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro

Intra-H (C23-C104) 22-96 154-210 271-331 377-435

Intra-L (C23-C104) 23'-89' 134'-194'

Inter-H-L (h 5-CL 126) 230-214' 230''-214''

Inter-H-H (h 11, h 14) 236-236'' 239-239''

N-terminal glutamine cyclization to pyroglutamyl (pE, 5-oxoprolyl)

H VH Q1: 1, 1''

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación

H CH2 N84: 307, 307''

Fucosylated complex bi-antennary CHO-type glycans / glycanes de type CHO bi-antennaires complexes fucosilés / glicanos de tipo CHO biantenarios complejos fucosilados.

Deamidation sites / Sites de désamidation / Posiciones de desamidación

H CH2 N98: 325, 325''

H CH3 N44: 394, 394''

C-terminal lysine clipping / Coupure de la lysine C-terminale / Recorte de lisina C-terminal

H CHS K2: 457, 457''
tixagevimab

immunoglobulin G1-kappa, anti-[*Homo sapiens* severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike (S) protein, receptor binding domain (RBD)], *Homo sapiens* monoclonal antibody; gamma1 heavy chain *Homo sapiens* (1-453) [VH (*Homo sapiens* IGHV1-58*°*01 (98.0%) -IGHD -IGHJ3*°*02 (93.8%)) CDR-IMGT [8.8.16] (26-33.51-58.97-112) (1-123) -*Homo sapiens* IGHGI*°*03 GI1m3, nG1m1, G1v21 C2H Y15.1, T16, E18, G1v39 C2H F1.3, E1.2, S116 (CH1 R120 (220) (124-221), hinge 1-15 (222-226), CH2 L1.3-F (240), L1.2-E (241), M15.1-Y (258), S16-T (260), T18-E (262), P116>S (337) (237-346), CH3 E12 (362), M14 (364) (347-451), CHS (452-453)] (124-453)], (226-216°)-disulfide with kappa light chain *Homo sapiens* (1°-216°) [V-KAPPA (*Homo sapiens* IGKV3-20°01 (98.9%) -IGKJ1°01 (100%)) CDR-IMGT [7.3.10] (27-33.51-53.90-99) (1°-109°) -*Homo sapiens* IGKC°01 (100%) Km3 A45.1 (155), V101 (193) (110°-216°); dimer (232-232°:235-235°)-bisdisulfide, produced in Chinese hamster ovary (CHO) cells, glycoform alfa antiviral

tixagévimab

immunoglobuline G1-kappa anti-[*Homo sapiens* protéine spike (S) du coronavirus 2 du syndrome respiratoire aigu sévère (SARS-CoV-2), domaine de liaison au récepteur (RBD)], anticorps monoclonal *Homo sapiens*;
chaîne lourde gamma1 *Homo sapiens* (1-453) [VH (*Homo sapiens* IGHV1-58°01 (98.0%) -IGHD -IGHJ3°02 (93.8%)) CDR-IMGT [8.8.16] (26-33.51-58.97-112) (1-123) -*Homo sapiens* IGHGI°03 GI1m3, nG1m1, G1v21 C2H Y15.1, T16, E18, G1v39 C2H F1.3, E1.2, S116 (CH1 R120 (220) (124-221), charnière 1-15 (222-226), CH2 L1.3-F (240), L1.2-E (241), M15.1-Y (258), S16-T (260), T18-E (262), P116>S (337) (237-346), CH3 E12 (362), M14 (364) (347-451), CHS (452-453)] (124-453)], (226-216°)-disulfure avec la chaîne légère kappa *Homo sapiens* (1°-216°) [V-KAPPA (*Homo sapiens* IGKV3-20°01 (98.9%) -IGKJ1°01 (100%)) CDR-IMGT [7.3.10] (27-33.51-53.90-99) (1°-109°) -*Homo sapiens* IGKC°01 (100%) Km3 A45.1 (155), V101 (193) (110°-216°); dimère (232-232°:235-235°)-bisdisulfure, produit dans des cellules ovariennes de hamster chinois (CHO), glycoforme alfa antiviral

tixagevimab

imunoglobulina G1-kappa anti-[*Homo sapiens* proteína espícula (S) del coronavirus 2 del síndrome respiratorio agudo severo (SRAS-CoV-2), dominio de unión al receptor (RBD)], anticuerpo monoclonal *Homo sapiens*;
cadena pesada gamma1 *Homo sapiens* (1-453) [VH (*Homo sapiens* IGHV1-58°01 (98.0%) -IGHD -IGHJ3°02 (93.8%)) CDR-IMGT [8.8.16] (26-33.51-58.97-112) (1-123) -*Homo sapiens* IGHGI°03 GI1m3, nG1m1, G1v21 C2H Y15.1, T16, E18, G1v39 C2H F1.3, E1.2, S116 (CH1 R120 (220) (124-221), bisagra 1-15 (222-236), CH2 L1.3-F (240), L1.2-E (241), M15.1-Y (258), S16-T (260), T18-E (262), P116>S (337) (237-346), CH3 E12 (362), M14 (364) (347-451), CHS (452-453)] (124-453)], (226-216°)-disulfuro con la cadena ligera kappa *Homo sapiens* (1°-216°) [V-KAPPA (*Homo sapiens* IGKV3-20°01 (98.9%) -IGKJ1°01 (100%)) CDR-IMGT [7.3.10] (27-33.51-53.90-99) (1°-109°) -*Homo sapiens* IGKC°01 (100%) Km3 A45.1 (155), V101 (193) (110°-216°); dimero (232-232°:235-235°)-bisdisulfuro, producido en las células ovariennes de hámster chino (CHO), forma glicosilada alfa antiviral
**Heavy chain / Chaîne lourde / Cadena pesada**

22-96 101-106 150-206 267-327 373-431

**Light chain / Chaîne légère / Cadena ligera**

22'-96' 101'-106'

**Post-translational modifications**

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro

Intra-H (C23-C104) 22-96 101-106 150-206 267-327 373-431

Intra- H (CDR3) 101-106 101'-106'

Intra-L (C23-C104) 23'-89' 136'-196'

Inter-H-L (h 5-CL126) 226-216' 226''-216''

Inter-H-H (h 11, h14) 232-232'' 235-235''

N-terminal glutamine cyclization to pyroglutamyl (pE, all-U>m1Ψ)

**tozinameranum #**

**tozinameran**

messenger RNA (mRNA), 5'-capped, encoding a full-length, codon-optimised pre-fusion stabilised conformation variant (K986P and V987P) of the SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2, GenBank: MN908947.3) spike (S) glycoprotein, flanked by 5' and 3' untranslated regions and a 3' poly(A) tail; contains N1-methylpseduouridine instead of uridine (all-U>m1Ψ).

**immunological agent for active immunization (anti-SARS-CoV-2)**

**tozinaméran**

ARN messager (ARNm), protégé en 5', codant pour un variant de pré-fusion stabilisé en conformation (K986P et V987P) de la glycoprotéine spike (S) du SARS-CoV-2 (coronavirus 2 du syndrome respiratoire aigu sévère, GenBank: MN908947.3) complet, avec des codons optimisés, flanqués de régions 5' et 3' non traduites et d'une queue poly(A) 3'; contient la N1-méthylpseduouridine au lieu de l'uridine (tout-U>m1Ψ).

**agent immunologique d'immunisation active (anti-SARS-CoV-2)**

**tozinamerán**

RNA mensajero (mRNA), protegido en 5', que codifica para una variante pre-fusión de conformación estabilizada (K986P y V987P) de la glicoproteína de la espícula (S) del SRAS-CoV-2 (coronavirus 2 del síndrome respiratorio agudo severo, GenBank: MN908947.3) completa, con codones optimizados, flanqueada por regiones 5' y 3' no traducidas y una cola poly(A) en 3'; contiene N1-metilpseduouridina en lugar de uridina (all-U>m1Ψ).

**agente inmunológico para inmunización activa (anti-SRAS-CoV-2)**
zansecimabum #
zansecimab

immunoglobulin G4-kappa, anti-[*Homo sapiens* ANGPT2 (angiopoietin 2)], humanized monoclonal antibody; gamma4 heavy chain humanized (1-447) [VH (*Homo sapiens* IGHV1-18*01 (86.7%) - (IGHD) - IGHJ4*01 (93.3%)) CDR-IMGT [8.8.14] (26-33.51-58.97-110) (1-121) - *Homo sapiens* IGHG4*01, G4v5 h P10,G4v4 CH2 A1.3, A1.2 (CH1 (122-219), hinge 1-12 S10>P (229) (220-231), CH2 F1.3>A (235), L1.2>A (236) (232-341), CH3 (342-446), CHS K>del (447) (122-447)], (135-214')-disulfide with kappa light chain humanized (1'-214') [V-KAPPA (*Homo sapiens* IGKV1-12*01 (83.2%) - IGKJ4*01 (100%)) CDR-IMGT [6.3.9] (27-32.50-52.89-97) (1'-107') - *Homo sapiens* IGKC*01 (100%) Km3 A45.1 (153), V101 (191) (108'-214')]; dimer (227-227*:230-230*)-bisdisulfide, produced in a Chinese hamster ovary (CHO) cell line derived from CHO-GSKO, glycoform alfa angiogenesis inhibitor, immunomodulator

zansécimab

immunoglobuline G4-kappa anti-[*Homo sapiens* ANGPT2 (angiopoyetina 2)], anticorps monoclonal humanisé; chaîne lourde gamma4 humanisée (1-447) [VH (*Homo sapiens* IGHV1-18*01 (86.7%) - (IGHD) - IGHJ4*01 (93.3%)) CDR-IMGT [8.8.14] (26-33.51-58.97-110) (1-121) - *Homo sapiens* IGHG4*01, G4v5 h P10,G4v4 CH2 A1.3, A1.2 (CH1 (122-219), charnière 1-12 S10>P (229) (220-231), CH2 F1.3>A (235), L1.2>A (236) (232-341), CH3 (342-446), CHS K>del (447) (122-447)], (135-214')-disulfure avec la chaîne légère kappa humanisée (1'–214') [V-KAPPA (*Homo sapiens* IGKV1-12*01 (83.2%) - IGKJ4*01 (100%)) CDR-IMGT [6.3.9] (27-32.50-52.89-97) (1’-107') - *Homo sapiens* IGKC*01 (100%) Km3 A45.1 (153), V101 (191) (108'-214')]; dimère (227-227*:230-230*)-bisdisulfure, produit dans des cellules ovariennes de hamster chinois (CHO) dérivé de la lignée cellulaire CHO-GSKO, glycoforme alfa inhibiteur de l'angiogénèse, immunomodulateur

zansecimab

immunoglobulina G4-kappa anti-[*Homo sapiens* ANGPT2 (angiopoyetina 2)], anticuerpo monoclonal humanizado; cadena pesada gamma4 humanizada (1-447) [VH (*Homo sapiens* IGHV1-18*01 (86.7%) - (IGHD) - IGHJ4*01 (93.3%)) CDR-IMGT [8.8.14] (26-33.51-58.97-110) (1-121) - *Homo sapiens* IGHG4*01, G4v5 h P10,G4v4 CH2 A1.3, A1.2 (CH1 (122-219), bisagra 1-12 S10>P (229) (220-231), CH2 F1.3>A (235), L1.2>A (236) (232-341), CH3 (342-446), CHS K>del (447) (122-447)], (135-214')-disulfuro con la cadena ligera kappa humanizada (1'-214') [V-KAPPA (*Homo sapiens* IGKV1-12*01 (83.2%) - IGKJ4*01 (100%)) CDR-IMGT [6.3.9] (27-32.50-52.89-97) (1'-107') - *Homo sapiens* IGKC*01 (100%) Km3 A45.1 (153), V101 (191) (108'-214')]; dímero (227-227*:230-230*)-bisdisulfuro, producido en las células ováricas de hamster chino (CHO) derivado de la lignée celular CHO-GSKO, forma glicosilada alfa inhibidor de la angiogénesis, immunomodulador
zorecimeranum #

zorecimeran

messenger RNA (mRNA), 5'-capped, encoding a full-length codon-optimised pre-fusion stabilized conformation variant (K986P and V987P) of the SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2; NC_045512.2) spike (S) glycoprotein, flanked by 5' and 3' untranslated regions; the 3' untranslated region comprises a part of the human alpha globin gene 3' UTR sequence element, a synthetic poly(A) tail and a poly(C)-rich sequence followed by a histone stem loop sequence as a 3' tail.

immunological agent for active immunization (anti-SARS-CoV-2)

zoréciméran

ARN messager (ARNm), protégé en 5', codant pour un variant de pré-fusion stabilisé en conformation (K986P et V987P) de la glycoprotéine spike (S) du SARS-CoV-2 (coronavirus 2 du syndrome respiratoire aigu sévère; NC_045512.2) complet, avec des codons optimisés, flanqués de régions 5' et 3' non traduites. La région 3' non traduite comprend une partie de l'élément de séquence 3' UTR du gène de l'alpha globine humaine, une queue poly(A) synthétique et une séquence riche en poly(C) suivie d'une séquence d'histones stem-loop comme extrémité en 3'.

agent immunologique d'immunisation active (anti-SARS-CoV-2)
zorecimerán RNA mensajero (mRNA), protegido en 5’, que codifica para una variante pre-fusión de conformación estabilizada (K986P and V987P) de la glicoproteina de la espícula (S) del SRAS-Cov-2 (coronavirus 2 del síndrome respiratorio agudo severo, NC_045512.2) completa, con codones optimizados, flanqueada por regiones 5’ y 3’ no traducidas. La región 3’ no traducida comprende una parte del elemento secuencia 3’ UTR del gen de la alfa globina humana, una cola poly(A) sintética y una secuencia rica en poly(C) seguida de una secuencia de histona stem-loop cola 3’.

agente inmunológico para inmunización activa (anti-SRAS-CoV-2)

2432957-15-6

# Electronic structure available on Mednet: http://mednet.who.int/
# Structure électronique disponible sur Mednet: http://mednet.who.int/
# Estructura electrónica disponible en Mednet: http://mednet.who.int/
ANNEX 1

PROCEDURE FOR THE SELECTION OF RECOMMENDED INTERNATIONAL NONPROPRIETARY NAMES FOR PHARMACEUTICAL SUBSTANCES

The following procedure shall be followed by the World Health Organization (hereinafter also referred to as “WHO”) in the selection of recommended international nonproprietary names for pharmaceutical substances, in accordance with resolution WHA3.11 of the World Health Assembly, and in the substitution of such names.

Article 1 - Proposals for recommended international nonproprietary names and proposals for substitution of such names shall be submitted to WHO on the form provided therefore. The consideration of such proposals shall be subject to the payment of an administrative fee designed only to cover the corresponding costs of the Secretariat of WHO (“the Secretariat”). The amount of this fee shall be determined by the Secretariat and may, from time to time, be adjusted.

Article 2 - Such proposals shall be submitted by the Secretariat to the members of the Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations designated for this purpose, such designated members hereinafter referred to as “the INN Expert Group”, for consideration in accordance with the “General principles for guidance in devising International Nonproprietary Names for Pharmaceutical Substances”, annexed to this procedure. The name used by the person discovering or first developing and marketing a pharmaceutical substance shall be accepted, unless there are compelling reasons to the contrary.

Article 3 - Subsequent to the examination provided for in article 2, the Secretariat shall give notice that a proposed international nonproprietary name is being considered.

a) Such notice shall be given by publication in WHO Drug Information and by letter to Member States and to national and regional pharmacopoeia commissions or other bodies designated by Member States.

i) Notice shall also be sent to the person who submitted the proposal (“the original applicant”) and other persons known to be concerned with a name under consideration.

b) Such notice shall:

i) set forth the name under consideration;

ii) identify the person who submitted the proposal for naming the substance, if so requested by such person;

iii) identify the substance for which a name is being considered;

iv) set forth the time within which comments and objections will be received and the person and place to whom they should be directed;

v) state the authority under which WHO is acting and refer to these rules of procedure.

c) In forwarding the notice, the Secretariat shall request that Member States take such steps as are necessary to prevent the acquisition of proprietary rights in the proposed name during the period it is under consideration by WHO.

Article 4 - Comments on the proposed name may be forwarded by any person to WHO within four months of the date of publication, under article 3, of the name in WHO Drug Information.

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2 See Annex 2.

3 Before 1987, lists of international nonproprietary names were published in the Chronicle of the World Health Organization.
**Article 5** - A formal objection to a proposed name may be filed by any interested person within four months of the date of publication, under article 3, of the name in *WHO Drug Information*.

Such objection shall:

i) identify the person objecting;

ii) state his or her interest in the name;

iii) set forth the reasons for his or her objection to the name proposed.

**Article 6** - Where there is a formal objection under article 5, WHO may either reconsider the proposed name or use its good offices to attempt to obtain withdrawal of the objection. Without prejudice to the consideration by WHO of a substitute name or names, a name shall not be selected by WHO as a recommended international nonproprietary name while there exists a formal objection thereto filed under article 5 which has not been withdrawn.

**Article 7** - Where no objection has been filed under article 5, or all objections previously filed have been withdrawn, the Secretariat shall give notice in accordance with subsection (a) of article 3 that the name has been selected by WHO as a recommended international nonproprietary name.

**Article 8** - In forwarding a recommended international nonproprietary name to Member States under article 7, the Secretariat shall:

a) request that it be recognized as the nonproprietary name for the substance; and

b) request that Member States take such steps as are necessary to prevent the acquisition of proprietary rights in the name and to prohibit registration of the name as a trademark or trade name.

**Article 9**

a) In the extraordinary circumstance that a previously recommended international nonproprietary name gives rise to errors in medication, prescription or distribution, or a demonstrable risk thereof, because of similarity with another name in pharmaceutical and/or prescription practices, and it appears that such errors or potential errors cannot readily be resolved through other interventions than a possible substitution of a previously recommended international nonproprietary name, or in the event that a previously recommended international nonproprietary name differs substantially from the nonproprietary name approved in a significant number of Member States, or in other such extraordinary circumstances that justify a substitution of a recommended international nonproprietary name, proposals to that effect may be filed by any interested person. Such proposals shall be submitted on the form provided therefore and shall:

i) identify the person making the proposal;

ii) state his or her interest in the proposed substitution; and

iii) set forth the reasons for the proposal; and

iv) describe, and provide documentary evidence regarding the other interventions undertaken in an effort to resolve the situation, and the reasons why these other interventions were inadequate.

Such proposals may include a proposal for a new substitute international nonproprietary name, devised in accordance with the General principles, which takes into account the pharmaceutical substance for which the new substitute international nonproprietary name is being proposed.

The Secretariat shall forward a copy of the proposal, for consideration in accordance with the procedure described in subsection (b) below, to the INN Expert Group and the original applicant or its successor (if different from the person bringing the proposal for substitution and provided that the original applicant or its successor is known or can be found through diligent effort, including contacts with industry associations).
In addition, the Secretariat shall request comments on the proposal from:

i) Member States and national and regional pharmacopoeia commissions or other bodies designated by Member States (by including a notice to that effect in the letter referred to in article 3(a), and

ii) any other persons known to be concerned by the proposed substitution.

The request for comments shall:

i) state the recommended international nonproprietary name that is being proposed for substitution (and the proposed substitute name, if provided);

ii) identify the person who submitted the proposal for substitution (if so requested by such person);

iii) identify the substance to which the proposed substitution relates and reasons put forward for substitution;

iv) set forth the time within which comments will be received and the person and place to whom they should be directed; and

v) state the authority under which WHO is acting and refer to these rules of procedure.

Comments on the proposed substitution may be forwarded by any person to WHO within four months of the date of the request for comments.

b) After the time period for comments referred to above has elapsed, the Secretariat shall forward any comments received to the INN Expert Group, the original applicant or its successor and the person bringing the proposal for substitution. If, after consideration of the proposal for substitution and the comments received, the INN Expert Group, the person bringing the proposal for substitution and the original applicant or its successor all agree that there is a need to substitute the previously recommended international nonproprietary name, the Secretariat shall submit the proposal for substitution to the INN Expert Group for further processing. Notwithstanding the foregoing, the original applicant or its successor shall not be entitled to withhold agreement to a proposal for substitution in the event the original applicant or its successor has no demonstrable continuing interest in the recommended international nonproprietary name proposed for substitution.

In the event that a proposal for substitution shall be submitted to the INN Expert Group for further processing, the INN Expert Group will select a new international nonproprietary name in accordance with the General principles referred to in article 2 and the procedure set forth in articles 3 to 8 inclusive. The notices to be given by the Secretariat under article 3 and article 7, respectively, including to the original applicant or its successor (if not the same as the person proposing the substitution, and provided that the original applicant or its successor is known or can be found through diligent effort, including contacts with industry associations), shall in such event indicate that the new name is a substitute for a previously recommended international nonproprietary name and that Member States may wish to make transitional arrangements in order to accommodate existing products that use the previously recommended international nonproprietary name on their label in accordance with national legislation.

If, after consideration of the proposal for substitution and the comments received in accordance with the procedure described above, the INN Expert Group, the original applicant or its successor and the person bringing the proposal for substitution do not agree that there are compelling reasons for substitution of a previously recommended international nonproprietary name, this name shall be retained (provided always that the original applicant or its successor shall not be entitled to withhold agreement to a proposal for substitution in the event that the original applicant or its successor has no demonstrable continuing interest in the recommended international nonproprietary name proposed to be substituted). In such an event, the Secretariat shall advise the person having proposed the substitution, as well as the original applicant or its
successor (if not the same as the person proposing the substitution, and provided that the original applicant or its successor is known or can be found through diligent effort, including contacts with industry associations), Member States, national and regional pharmacopoeia commissions, other bodies designated by Member States, and any other persons known to be concerned by the proposed substitution that, despite a proposal for substitution, it has been decided to retain the previously recommended international nonproprietary name (with a description of the reason(s) why the proposal for substitution was not considered sufficiently compelling).

ANNEX 2

GENERAL PRINCIPLES FOR GUIDANCE IN DEVISING INTERNATIONAL NONPROPRIETARY NAMES FOR PHARMACEUTICAL SUBSTANCES

1. International Nonproprietary Names (INN) should be distinctive in sound and spelling. They should not be inconveniently long and should not be liable to confusion with names in common use.

2. The INN for a substance belonging to a group of pharmacologically related substances should, where appropriate, show this relationship. Names that are likely to convey to a patient an anatomical, physiological, pathological or therapeutic suggestion should be avoided.

These primary principles are to be implemented by using the following secondary principles:

3. In devising the INN of the first substance in a new pharmacological group, consideration should be given to the possibility of devising suitable INN for related substances, belonging to the new group.

4. In devising INN for acids, one-word names are preferred; their salts should be named without modifying the acid name, e.g. "oxacillin" and "oxacillin sodium", "ibufenac" and "ibufenac sodium".

5. INN for substances which are used as salts should in general apply to the active base or the active acid. Names for different salts or esters of the same active substance should differ only in respect of the name of the inactive acid or the inactive base. For quaternary ammonium substances, the cation and anion should be named appropriately as separate components of a quaternary substance and not in the amine-salt style.

6. The use of an isolated letter or number should be avoided; hyphenated construction is also undesirable.

7. To facilitate the translation and pronunciation of INN, “f” should be used instead of “ph”, “t” instead of “th”, “e” instead of “ae” or “oe”, and “i” instead of “y”; the use of the letters “h” and “k” should be avoided.

8. Provided that the names suggested are in accordance with these principles, names proposed by the person discovering or first developing and marketing a pharmaceutical preparation, or names already officially in use in any country, should receive preferential consideration.

9. Group relationship in INN (see General principle 2) should if possible be shown by using a common stem. The following list contains examples of stems for groups of substances, particularly for new groups. There are many other stems in active use. Where a stem is shown without any hyphens it may be used anywhere in the name.

In its Twentieth report (WHO Technical Report Series, No. 581, 1975), the WHO Expert committee on Nonproprietary Names for Pharmaceutical Substances reviewed the general principles for devising, and the procedures for selecting, INN in the light of developments in pharmaceutical compounds in recent years. The most significant change has been the extension to the naming of synthetic chemical substances of the practice previously used for substances originating in or derived from natural products. This practice involves the use of a characteristic “stem” indicative of a common property of the members of a group. The reason for, and the implications of, the change are fully discussed. The guiding principles were updated during the 13th consultation on nonproprietary names for pharmaceutical substances (Geneva, 27-29 April 1983) (PHARM S/NOM 928 13 May 1983, revised 18 August 1983).

A more extensive listing of stems is contained in the working document WHO/EMP/QSM/2011.3 which is regularly updated and can be requested from the INN Programme, WHO, Geneva.
<table>
<thead>
<tr>
<th>Latin</th>
<th>English</th>
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<tbody>
<tr>
<td>-acum</td>
<td>anti-inflammatory agents, ibufenac derivatives</td>
</tr>
<tr>
<td>-adolum</td>
<td>analgesics</td>
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<tr>
<td>-adol-</td>
<td>antiasthmatic, antiallergic substances not acting primarily as antihistamins</td>
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<tr>
<td>-astum</td>
<td>antihistaminics</td>
</tr>
<tr>
<td>-astinum</td>
<td>diazepam derivatives</td>
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<tr>
<td>bol</td>
<td>steroids, anabolic</td>
</tr>
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<td>-cain-</td>
<td>class I antiarrhythmics, proacainamide and lidocaine derivatives</td>
</tr>
<tr>
<td>-cainum</td>
<td>local anaesthetics</td>
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<td>cef-</td>
<td>antibiotics, cefalosporanic acid derivatives</td>
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<tr>
<td>-cillinum</td>
<td>antibiotics, 6-aminopenicillanic acid derivatives</td>
</tr>
<tr>
<td>-conazolum</td>
<td>systemic antifungal agents, miconazole derivatives</td>
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<td>cort</td>
<td>corticosteroids, except prednisolone derivatives</td>
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<td>selective cyclo-oxygenase inhibitors</td>
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<td>-entanum</td>
<td>endothelin receptor antagonents</td>
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<td>gabamimetic agents</td>
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<td>gado-</td>
<td>diagnostic agents, gadolinium derivatives</td>
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<td>-gatranum</td>
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<td>steroids, progestogens</td>
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<td>gli</td>
<td>antihyperglycaemics</td>
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<td>io-</td>
<td>iodine-containing contrast media</td>
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<td>-metacinum</td>
<td>anti-inflammatory, indometacin derivatives</td>
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<td>-oxacinum</td>
<td>antibacterial agents, nalidixic acid derivatives</td>
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<td>-platinum</td>
<td>antineoplastic agents, platinum derivatives</td>
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<td>-poetinum</td>
<td>erythropoietin type blood factors</td>
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<td>-pril(at)um</td>
<td>angiotensin-converting enzyme inhibitors</td>
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<td>-profenum</td>
<td>anti-inflammatory substances, ibuprofen derivatives</td>
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<td>-relinum</td>
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<td>vasopressin receptor antagonents</td>
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<td>vin-</td>
<td>vinca-type alkaloids</td>
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<td>-vin-</td>
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ANNEXE 1

PROCEDURE A SUIVRE EN VUE DU CHOIX DE DENOMINATIONS COMMUNES INTERNATIONALES RECOMMANDÉES POUR LES SUBSTANCES PHARMACEUTIQUES ¹

L’Organisation mondiale de la Santé (également désignée ci-après sous l’appellation « OMS ») observe la procédure exposée ci-dessous pour l’attribution de dénominations communes internationales recommandées pour les substances pharmaceutiques, conformément à la résolution WHA3.11 de l’Assemblée mondiale de la Santé, et pour le remplacement de telles dénominations.

**Article 1** - Les propositions de dénominations communes internationales recommandées et les propositions de remplacement de telles dénominations sont soumises à l’OMS sur la formule prévue à cet effet. L’examen de telles propositions est soumis au paiement d’une taxe administrative destinée uniquement à couvrir les coûts correspondants assumés par le Secrétariat de l’OMS (« le Secrétariat »). Le montant de cette taxe est déterminé par le Secrétariat et peut être modifié de temps à autre.

**Article 2** - Ces propositions sont soumises par le Secrétariat aux experts désignés à cette fin parmi les personnalités inscrites au Tableau d’experts de la Pharmacopée internationale et des Préparations pharmaceutiques, ci-après désignés sous l’appellation « le Groupe d’experts des DCI » ; elles sont examinées par les experts conformément aux « Directives générales pour la formation de dénominations communes internationales pour les substances pharmaceutiques » reproduites ci-après1. La dénomination acceptée est la dénomination employée par la personne qui découvre ou qui, la première, fabrique et lance sur le marché une substance pharmaceutique, à moins que des raisons majeures n’obligent à s’écarter de cette règle.

**Article 3** - Après l’examen prévu à l’article 2, le Secrétariat notifie qu’un projet de dénomination commune internationale est à l’étude.

a) Cette notification est faite par une insertion dans *WHO Drug Information*2 et par l’envoi d’une lettre aux États Membres et aux commissions nationales et régionales de pharmacopée ou autres organismes désignés par les États Membres.

i) Notification est également faite à la personne qui a soumis la proposition (« le demandeur initial ») et à d’autres personnes portant à la dénomination mise à l’étude un intérêt notoire.

b) Cette notification contient les indications suivantes :

i) dénomination mise à l’étude;

ii) nom de l’auteur de la proposition tendant à attribuer une dénomination à la substance, si cette personne le demande ;

iii) définition de la substance dont la dénomination est mise à l’étude ;

iv) délai pendant lequel seront reçues les observations et les objections à l’égard de cette dénomination ; nom et adresse de la personne habilitée à recevoir ces observations et objections ;

v) mention des pouvoirs en vertu desquels agit l’OMS et référence au présent règlement.

c) En envoyant cette notification, le Secrétariat demande aux États Membres de prendre les mesures nécessaires pour prévenir l’acquisition de droits de propriété sur la dénomination proposée pendant la période au cours de laquelle cette dénomination est mise à l’étude par l’OMS.

**Article 4** - Des observations sur la dénomination proposée peuvent être adressées à l’OMS par toute personne, dans les quatre mois qui suivent la date de publication de la dénomination dans *WHO Drug Information* (voir l’article 3).

**Article 5** - Toute personne intéressée peut formuler une objection formelle contre la dénomination proposée dans les quatre mois qui suivent la date de publication de la dénomination dans *WHO Drug Information* (voir l’article 3).

1 Voir annexe 2.
2 Avant 1987, les listes de dénominations communes internationales étaient publiées dans la *Chronique de l’Organisation mondiale de la Santé*. 
Cette objection doit s’accompagner des indications suivantes :

i) nom de l’auteur de l’objection ;

ii) intérêt qu’il ou elle porte à la dénomination en cause ;

iii) raisons motivant l’objection contre la dénomination proposée.

**Article 6** - Lorsqu’une objection formelle est formulée en vertu de l’article 5, l’OMS peut soit soumettre la dénomination proposée à un nouvel examen, soit intervenir pour tenter d’obtenir le retrait de l’ objection. Sans préjudice de l’examen par l’OMS d’une ou de plusieurs appellations de remplacement, l’OMS n’adopte pas d’appellation comme dénomination commune internationale recommandée tant qu’une objection formelle présentée conformément à l’article 5 n’est pas levée.

**Article 7** - Lorsqu’il n’est formulé aucune objection en vertu de l’article 5, ou que toutes les objections présentées ont été levées, le Secrétariat fait une notification conformément aux dispositions du paragraphe a) de l’article 3, en indiquant que la dénomination a été choisie par l’OMS en tant que dénomination commune internationale recommandée.

**Article 8** - En communiquant aux États Membres, conformément à l’article 7, une dénomination commune internationale recommandée, le Secrétariat :

a) demande que cette dénomination soit reconnue comme dénomination commune de la substance considérée ; et

b) demande aux États Membres de prendre les mesures nécessaires pour prévenir l’acquisition de droits de propriété sur cette dénomination et interdire le dépôt de cette dénomination comme marque ou appellation commerciale.

**Article 9** -

a) Dans le cas exceptionnel où une dénomination commune internationale déjà recommandée donne lieu à des erreurs de médication, de prescription ou de distribution ou en comporte un risque démontrable, en raison d’une similitude avec une autre appellation dans la pratique pharmaceutique et/ou de prescription, et où il apparaît que ces erreurs ou ces risques d’erreur ne peuvent être facilement évités par d’autres interventions que le remplacement éventuel d’une dénomination commune internationale déjà recommandée, ou dans le cas où une dénomination commune internationale déjà recommandée diffère sensiblement de la dénomination commune approuvée dans un nombre important d’États Membres, ou dans d’autres circonstances exceptionnelles qui justifient le remplacement d’une dénomination commune internationale recommandée, toute personne intéressée peut formuler une proposition dans ce sens. Cette proposition est présentée sur la formule prévue à cet effet et doit s’accompagner des indications suivantes :

i) nom de l’auteur de la proposition ;

ii) intérêt qu’il ou elle porte au remplacement proposé ;

iii) raisons motivant la proposition ; et

iv) description, faits à l’appui, des autres interventions entreprises pour tenter de régler le problème et exposé des raisons pour lesquelles ces interventions ont échoué.

Les propositions peuvent comprendre une proposition de nouvelle dénomination commune internationale de remplacement, établie conformément aux Directives générales, compte tenu de la substance pharmaceutique pour laquelle la nouvelle dénomination commune internationale de remplacement est proposée.

Le Secrétariat transmet une copie de la proposition pour examen, conformément à la procédure exposée plus loin au paragraphe b), au Groupe d’experts des DCI et au demandeur initial ou à son successeur (s’il s’agit d’une personne différente de celle qui a formulé la proposition de remplacement et pour autant que le demandeur initial ou son successeur soit connu ou puisse être
De plus, le Secrétariat demande aux entités et personnes ci-après de formuler des observations sur la proposition :

i) les États Membres et les commissions nationales et régionales de pharmacopée ou d'autres organismes désignés par les États Membres (en insérant une note à cet effet dans la lettre mentionnée à l'article 3.a), et

ii) toutes autres personnes portant au remplacement proposé un intérêt notoire.

La demande d'observations contient les indications suivantes :

i) dénomination commune internationale recommandée pour laquelle un remplacement est proposé (et la dénomination de remplacement proposée, si elle est fournie) ;

ii) nom de l'auteur de la proposition de remplacement (si cette personne le demande) ;

iii) définition de la substance faisant l'objet du remplacement proposé et raisons avancées pour le remplacement ;

iv) délai pendant lequel seront reçus les commentaires et nom et adresse de la personne habilitée à recevoir ces commentaires ; et

v) mention des pouvoirs en vertu desquels agit l'OMS et référence au présent règlement.

Des observations sur la proposition de remplacement peuvent être communiquées par toute personne à l'OMS dans les quatre mois qui suivent la date de la demande d'observations.

b) Une fois échu le délai prévu ci-dessus pour la communication d'observations, le Secrétariat transmet les observations reçues au Groupe d'experts des DCI, au demandeur initial ou à son successeur et à l'auteur de la proposition de remplacement. Si, après avoir examiné la proposition de remplacement et les observations reçues, le Groupe d'experts des DCI, l'auteur de la proposition de remplacement et le demandeur initial ou son successeur reconnaissent tous qu'il est nécessaire de remplacer la dénomination commune internationale déjà recommandée, le Secrétariat soumet la proposition de remplacement au Groupe d'experts des DCI pour qu'il y donne suite.

Nonobstant ce qui précède, le demandeur initial ou son successeur n'est pas habilité à refuser son accord à une proposition de remplacement au cas où il ne peut être démontré qu'il porte un intérêt durable à la dénomination commune internationale recommandée qu'il est proposé de remplacer.

Dans le cas où une proposition de remplacement est soumise au Groupe d'experts des DCI pour qu'il y donne suite, le Groupe choisit une nouvelle dénomination commune internationale conformément aux Directives générales mentionnées à l'article 2 et selon la procédure décrite dans les articles 3 à 8 inclus. La notification faite par le Secrétariat en vertu de l'article 3 et de l'article 7, respectivement, y compris au demandeur initial ou à son successeur (si ce n'est pas la même personne que celle qui a proposé le remplacement et pour autant que le demandeur initial ou son successeur soit connu ou puisse être retrouvé moyennant des efforts diligents, notamment des contacts avec les associations industrielles), doit dans un tel cas indiquer que la nouvelle dénomination remplace une dénomination commune internationale déjà recommandée et que les États Membres peuvent souhaiter prendre des mesures transitoires pour les produits existants qui utilisent la dénomination commune internationale déjà recommandée sur leur étiquette conformément à la législation nationale.

Si, après examen de la proposition de remplacement et des observations communiquées conformément à la procédure exposée plus haut, le Groupe d'experts des DCI, le demandeur initial ou son successeur et l'auteur de la proposition de remplacement ne s'accordent pas sur le
fait qu’il y a des raisons impératives de remplacer une dénomination commune internationale déjà recommandée, cette dernière est conservée (étant entendu toujours que le demandeur initial ou son successeur n’est pas habilité à refuser son accord à une proposition de remplacement au cas où il ne peut être démontré qu’il porte un intérêt durable à la dénomination commune internationale recommandée qu’il est proposé de remplacer). Dans un tel cas, le Secrétariat informe l’auteur de la proposition de remplacement, ainsi que le demandeur initial ou son successeur (s’il s’agit d’une personne différente de celle qui a formulé la proposition de remplacement et pour autant que le demandeur initial ou son successeur soit connu ou puisse être retrouvé moyennant des efforts diligents, notamment des contacts avec les associations industrielles), les Etats Membres, les commissions nationales et régionales de pharmacopée, les autres organismes désignés par les Etats Membres et toutes autres personnes portant un intérêt notoire au remplacement proposé que, malgré une proposition de remplacement, il a été décidé de conserver la dénomination commune internationale déjà recommandée (avec une brève description de la ou des raisons pour lesquelles la proposition de remplacement n’a pas été jugée suffisamment impérative).

ANNEXE 2

DIRECTIVES GÉNÉRALES POUR LA FORMATION DES DENOMINATIONS COMMUNES INTERNATIONALES APPLICABLES AUX SUBSTANCES PHARMACEUTIQUES

1. Les dénominations communes internationales (DCI) devront se distinguer les unes des autres par leur consonance et leur orthographe. Elles ne devront pas être d’une longueur excessive, ni prêter à confusion avec des appellations déjà couramment employées.

2. La DCI de chaque substance devra, si possible, indiquer sa parenté pharmacologique. Les dénominations susceptibles d’évoquer pour les malades des considérations anatomiques, physiologiques, pathologiques ou thérapeutiques devront être évitées dans la mesure du possible.

Outre ces deux principes fondamentaux, on respectera les principes secondaires suivants :

3. Lorsqu’on formera la DCI de la première substance d’un nouveau groupe pharmacologique, on tiendra compte de la possibilité de former ultérieurement d’autres DCI appropriées pour les substances apparentées du même groupe.

4. Pour former des DCI des acides, on utilisera de préférence un seul mot. Leurs sels devront être désignés par un terme qui ne modifie pas le nom de l’acide d’origine : par exemple «oxacilline» et «oxacilline sodique», «ibufénac» et «ibufénac sodique».

5. Les DCI pour les substances utilisées sous forme de sels devront en général s’appliquer à la base active (ou à l’acide actif). Les dénominations pour différents sels ou esters d’une même substance active ne différeront que par le nom de l’acide inactif (ou de la base inactive). En ce qui concerne les substances à base d’ammonium quaternaire, la dénomination s’appliquera de façon appropriée au cation et à l’anion en tant qu’éléments distincts d’une substance quaternaire. On évitera de choisir une désignation évoquant un sel aminé.

6. On évitera d’ajouter une lettre ou un chiffre isolé ; en outre, on renoncera de préférence au trait d’union.

7. Pour simplifier la traduction et la prononciation des DCI, la lettre « f » sera utilisée à la place de « ph », « t » à la place de « th », « e » à la place de « ae » ou « oe », et « i » à la place de « y » ; l’usage des lettres « h » et « k » sera aussi évité.

8. On retiendra de préférence, pour autant qu’elles respectent les principes énoncés ici, les dénominations proposées par les personnes qui ont découvert ou qui, les premières, ont fabriqué et lancé sur le marché les préparations pharmaceutiques considérées, ou les dénominations déjà officiellement adoptées par un pays.

9. La parenté entre substances d’un même groupe (voir Directive générale 2) sera si possible indiquée dans les DCI par l’emploi de segments-clés communs. La liste ci-après contient des exemples de segments-clés pour des groupes de substances, surtout pour des groupes récents. Il y a beaucoup d’autres segments-clés en utilisation active. 1 Les segments-clés indiqués sans trait d’union pourront être insérés n’importe où dans une dénomination.

<table>
<thead>
<tr>
<th>Latin</th>
<th>Français</th>
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<tr>
<td>-acum</td>
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<td>-cef</td>
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<td>-cil inum</td>
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<td>-con az um</td>
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<td>cort</td>
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<td>-co xib</td>
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<td>-ent anum</td>
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<td>gab</td>
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<td>gado -</td>
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<td>-gat ranum</td>
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<td>-io</td>
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<td>-metacinum</td>
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<td>-my cinum</td>
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<td>-ni daz o lum</td>
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<td>-ololum</td>
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<td>-ox aci num</td>
<td>-oxacine</td>
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<td>-platinum</td>
<td>-platine</td>
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<td>-po eti num</td>
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<td>-pril (at) um</td>
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<td>-pro fenum</td>
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<td>prost</td>
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1 Une liste plus complète de segments-clés est contenue dans le document de travail WHO/EMP/QSM/2011.3 qui est régulièrement mis à jour et qui peut être demandé auprès du programme des DCI, OMS, Genève.
ANEXO 1

PROCEDIMIENTO DE SELECCIÓN DE DENOMINACIONES COMUNES INTERNACIONALES RECOMENDADAS PARA SUSTANCIAS FARMACÉUTICAS

La Organización Mundial de la Salud (OMS) seguirá el procedimiento que se expone a continuación tanto para seleccionar denominaciones comunes internacionales recomendadas para las sustancias farmacéuticas, de conformidad con lo dispuesto en la resolución WHA3.11, como para sustituir esas denominaciones.

Artículo 1 - Las propuestas de denominaciones comunes internacionales recomendadas y las propuestas de sustitución de esas denominaciones se presentarán a la OMS en los formularios que se proporcionen a estos efectos. El estudio de estas propuestas estará sujeto al pago de una tasa destinada a sufragar los costos de administración que ello suponga para la Secretaría de la OMS («la Secretaría»). La Secretaría establecerá la cuantía de esa tasa y podrá ajustarla periódicamente.

Artículo 2 - Estas propuestas serán sometidas por la Secretaría a los miembros del Cuadro de Expertos en Farmacopea Internacional y Preparaciones Farmacéuticas encargados de su estudio, en adelante designados como «el Grupo de Expertos en DCI», para que las examinen de conformidad con los «Principios generales de orientación para formar denominaciones comunes internacionales para sustancias farmacéuticas», anexos a este procedimiento. A menos que haya poderosas razones en contra, la denominación aceptada será la empleada por la persona que haya descubierto o fabricado y comercializado por primera vez esa sustancia farmacéutica.

Artículo 3 - Tras el examen al que se refiere el artículo 2, la Secretaría notificará que está en estudio un proyecto de denominación internacional.

a) Esa notificación se hará mediante una publicación en Información Farmacéutica OMS3 y el envío de una carta a los Estados Miembros y a las comisiones nacionales y regionales de las farmacopeas u otros organismos designados por los Estados Miembros.

i) La notificación será enviada también a la persona que haya presentado la propuesta («el solicitante inicial») y a otras personas que tengan un interés especial en una denominación objeto de estudio.

b) En esa notificación se incluirán los siguientes datos:

i) la denominación sometida a estudio;
ii) la identidad de la persona que ha presentado la propuesta de denominación de la sustancia, si lo pide esa persona;
iii) la identidad de la sustancia cuya denominación está en estudio;
iv) el plazo fijado para recibir observaciones y objeciones, así como el nombre y la dirección de la persona a quien deban dirigirse; y
v) los poderes conferidos para el caso a la OMS y una referencia al presente procedimiento.

2 Véase el anexo 2.
3 Hasta 1987 las listas de DCI se publicaban en la Crónica de la Organización Mundial de la Salud.
c) Al enviar esa notificación, la Secretaría solicitará de los Estados Miembros la adopción de todas las medidas necesarias para impedir la adquisición de derechos de patente sobre la denominación propuesta, durante el periodo en que la OMS la tenga en estudio.

**Artículo 4** - Toda persona puede formular a la OMS observaciones sobre la denominación propuesta dentro de los cuatro meses siguientes a su publicación en Información Farmacéutica OMS, conforme a lo dispuesto en el artículo 3.

**Artículo 5** - Toda persona interesada puede presentar una objeción formal a una denominación propuesta dentro de los cuatro meses siguientes a su publicación en Información Farmacéutica OMS, conforme a lo dispuesto en el artículo 3. Esa objeción deberá acompañarse de los siguientes datos:

1. La identidad de la persona que formula la objeción;
2. Las causas que motivan su interés por la denominación; y
3. Las causas que motivan su objeción a la denominación propuesta.

**Artículo 6** - Cuando se haya presentado una objeción formal en la forma prevista en el artículo 5, la OMS podrá reconsiderar el nombre propuesto o utilizar sus buenos oficios para intentar lograr que se retire la objeción. La OMS no seleccionará como denominación común internacional una denominación a la que se haya hecho una objeción formal, presentada según lo previsto en el artículo 5, que no haya sido retirada, todo ello sin perjuicio de que la Organización examine otra denominación o denominaciones sustitutivas.

**Artículo 7** - Cuando no se haya formulado ninguna objeción en la forma prevista en el artículo 5, o cuando todas las objeciones presentadas hayan sido retiradas, la Secretaría notificará, conforme a lo dispuesto en el párrafo a) del artículo 3, que la denominación ha sido seleccionada por la OMS como denominación común internacional recomendada.

**Artículo 8** - Al comunicar a los Estados Miembros una denominación común internacional, conforme a lo previsto en el artículo 7, la Secretaría:

a) solicitará que esta denominación sea reconocida como denominación común para la sustancia de que se trate; y

b) solicitará a los Estados Miembros que adopten todas las medidas necesarias para impedir la adquisición de derechos de patente sobre la denominación, y prohíban que sea registrada como marca de fábrica o como nombre comercial.

**Artículo 9**

a) En el caso excepcional de que, debido a su semejanza con otra denominación utilizada en las prácticas farmacéuticas y/o de prescripción, una denominación común internacional recomendada anteriormenites ocasione errores de medicación, prescripción o distribución, o suponga un riesgo manifiesto de que esto ocurra, y parezca que tales errores o potenciales errores no sean fácilmente subsanables con otras medidas que no sean la posible sustitución de esa denominación común internacional recomendada anteriormente; en el caso de que una denominación común internacional recomendada anteriormente difiera considerablemente de la denominación común aprobada en un número importante de Estados Miembros, o en otras circunstancias excepcionales que justifiquen el cambio de una denominación común internacional recomendada, cualquier persona interesada puede presentar propuestas en este sentido. Esas propuestas se presentarán en los formularios que se proporcionen a estos efectos e incluirán los siguientes datos:

1. La identidad de la persona que presenta la propuesta;
2. Las causas que motivan su interés en la sustitución propuesta; y
3. Las causas que motivan la propuesta; y
iv) una descripción, acompañada de pruebas documentales, de las otras medidas que se hayan adoptado con el fin de resolver la situación y de los motivos por los cuales dichas medidas no han sido suficientes.

Entre esas propuestas podrá figurar una relativa a una nueva denominación común internacional sustitutiva, formulada con arreglo a los Principios generales y que tenga en cuenta la sustancia farmacéutica para la que se proponga la nueva denominación común internacional sustitutiva.

La Secretaría enviará al Grupo de Expertos en DCI y al solicitante inicial o a su sucesor (en el caso de que sea una persona diferente de la que ha presentado la propuesta de sustitución y siempre que el solicitante inicial o su sucesor sean conocidos o puedan ser encontrados mediante esfuerzos diligentes, como el contacto con las asociaciones industriales) una copia de la propuesta, para que sea examinada de conformidad con el procedimiento descrito en el párrafo b) infra.
Además, la Secretaría solicitará observaciones sobre la propuesta:

i) a los Estados Miembros y a las comisiones nacionales y regionales de las farmacopeas y otros organismos designados por los Estados Miembros (ello se hará incluyendo una notificación a tal efecto en la carta a la que se refiere el párrafo a) del artículo 3), y

ii) a cualquier persona que tenga un interés especial en la sustitución propuesta.

Al solicitar que se formulen estas observaciones se facilitarán los siguientes datos:

i) la denominación común internacional recomendada que se propone sustituir (y la denominación sustitutiva propuesta, si se ha facilitado);

ii) la identidad de la persona que ha presentado la propuesta de sustitución (si lo pide esa persona);

iii) la identidad de la sustancia a la que se refiere la sustitución propuesta y las razones para presentar la propuesta de sustitución;

iv) el plazo fijado para recibir observaciones, así como el nombre y la dirección de la persona a quien deban dirigirse; y

v) los poderes conferidos para el caso a la OMS y una referencia al presente procedimiento.

Toda persona puede formular a la OMS observaciones sobre la sustitución propuesta dentro de los cuatro meses siguientes a la fecha en que se realizó la solicitud de observaciones.

b) Una vez agotado el mencionado plazo para la formulación de observaciones, la Secretaría enviará todos los comentarios recibidos al Grupo de Expertos en DCI, al solicitante inicial o a su sucesor, y a la persona que haya presentado la propuesta de sustitución. Si después de examinar la propuesta de sustitución y las observaciones recibidas, el Grupo de Expertos en DCI, la persona que haya presentado la propuesta de sustitución y el solicitante inicial, o su sucesor, están de acuerdo en la necesidad de sustituir la denominación común internacional recomendada anteriormente, la Secretaría remitirá la propuesta de sustitución al Grupo de Expertos en DCI para que la tramite.
No obstante lo anterior, el solicitante inicial o su sucesor no tendrán derecho a impedir el acuerdo sobre una propuesta de sustitución en el caso de que hayan dejado de tener un interés demostrable en la denominación común internacional cuya sustitución se propone.

En caso de que la propuesta de sustitución sea presentada al Grupo de Expertos en DCI para que la tramite, este grupo seleccionará una nueva denominación común internacional de conformidad con los Principios generales a los que se refiere el artículo 2 y al procedimiento establecido en los artículos 3 a 8 inclusive. En ese caso, en las notificaciones que la Secretaría ha de enviar con arreglo a los artículos 3 y 7, respectivamente, incluida la notificación al solicitante
inicial o a su sucesor (en el caso de que no sea la misma persona que propuso la sustitución y siempre que el solicitante inicial o su sucesor sean conocidos o puedan ser encontrados mediante esfuerzos diligentes, como el contacto con las asociaciones industriales), se indicará que la nueva denominación sustituye a una denominación común internacional recomendada anteriormente y que los Estados Miembros podrán, si lo estiman oportuno, adoptar disposiciones transitorias aplicables a los productos existentes en cuya etiqueta se utilice, con arreglo a la legislación nacional, la denominación común internacional recomendada anteriormente que se haya sustituido.

En caso de que, después de haber estudiado la propuesta de sustitución y los comentarios recibidos de conformidad con el procedimiento descrito anteriormente, el Grupo de Expertos en DCI, el solicitante inicial o su sucesor y la persona que haya presentado la propuesta de sustitución no lleguen a un acuerdo sobre la existencia de razones poderosas para sustituir una denominación común internacional recomendada anteriormente, esta denominación se mantendrá (siempre en el entendimiento de que el solicitante inicial o su sucesor no tendrán derecho a impedir el acuerdo sobre una propuesta de sustitución en el caso de que hayan dejado de tener un interés demostrable en la denominación común internacional cuya sustitución se propone). En ese caso, la Secretaría comunicará a la persona que haya propuesto la sustitución, así como al solicitante inicial o a su sucesor (en el caso de que no sea la misma persona que propuso la sustitución y siempre que el solicitante inicial o su sucesor sean conocidos o puedan ser encontrados mediante esfuerzos diligentes, como el contacto con las asociaciones industriales), a los Estados Miembros, a las comisiones nacionales y regionales de las farmacopeas o a otros organismos designados por los Estados Miembros y a cualquier otra persona que tenga interés en la sustitución propuesta, que, pese a la presentación de una propuesta de sustitución, se ha decidido mantener la denominación común internacional recomendada anteriormente (con una descripción de la o las razones por las que se ha considerado que la propuesta de sustitución no estaba respaldada por razones suficientemente poderosas).

ANEXO 2

PRINCIPIOS GENERALES DE ORIENTACIÓN PARA FORMAR DENOMINACIONES COMUNES INTERNACIONALES PARA SUSTANCIAS FARMACÉUTICAS

1. Las denominaciones comunes internacionales (DCI) deberán diferenciarse tanto fonéticamente como ortográficamente. No deberán ser incómodamente largas, ni dar lugar a confusión con denominaciones de uso común.

2. La DCI de una sustancia que pertenezca a un grupo de sustancias farmacológicamente emparentadas deberá mostrar apropiadamente este parentesco. Deberán evitarse las denominaciones que puedan tener connotaciones anatómicas, fisiológicas, patológicas o terapéuticas para el paciente.

Estos principios primarios se pondrán en práctica utilizando los siguientes principios secundarios:

3. Al idear la DCI de la primera sustancia de un nuevo grupo farmacológico, deberá tenerse en cuenta la posibilidad de poder formar DCI convenientes para las sustancias emparentadas que se agreguen al nuevo grupo.

4. Al idear DCI para ácidos, se preferirán las de una sola palabra; sus sales deberán denominarse sin modificar el nombre del ácido: p. ej. «oxacilina» y «oxacilina sódica», «ibufenaco» y «ibufenaco sódico».

1 En su 20º informe (OMS, Serie de Informes Técnicos, Nº 581, 1975), el Comité de Expertos de la OMS en Denominaciones Comunes para las Sustancias Farmacéuticas revisó los Principios generales para formar denominaciones comunes internacionales (DCI), y su procedimiento de selección, a la luz de las novedades registradas en los últimos años en materia de compuestos farmacéuticos. El cambio más importante había consistido en hacer extensivo a la denominación de sustancias químicas sintéticas el método utilizado hasta entonces para las sustancias originadas en productos naturales o derivadas de éstos. Dicho método conllevaba la utilización de una «partícula» característica que indica una propiedad común a los miembros de un grupo. En el citado informe se examinan en detalle las razones y consecuencias de este cambio. Los Principios generales de orientación se actualizaron durante la 13ª consulta sobre denominaciones comunes para sustancias farmacéuticas (Ginebra, 27 a 29 de abril de 1983) (PHARM S/NOM 928, 13 de mayo de 1983, revisado el 18 de agosto de 1983).
5. Las DCI para las sustancias que se usan en forma de sal deberán en general aplicarse a la base activa o al ácido activo. Las denominaciones para diferentes sales o esteres de la misma sustancia activa solamente deberán diferir en el nombre del ácido o de la base inactivos. En los compuestos de amonio cuaternario, el catión y el anión deberán denominarse adecuadamente por separado, como componentes independientes de una sustancia cuaternaria y no como sales de una amina.

6. Deberá evitarse el empleo de letras o números aislados; también es indeseable el empleo de guiones.

7. Para facilitar la traducción y la pronunciación, se emplearán de preferencia las letras «f» en lugar de «ph», «t» en lugar de «th», «e» en lugar de «ae» u «oe», e «i» en lugar de «y»; se deberá evitar el empleo de las letras «h» y «k».

8. Siempre que las denominaciones propuestas estén de acuerdo con estos principios, recibirán una consideración preferente las denominaciones propuestas por la persona que haya descubierto las sustancias, o que fabrique y comercialice por primera vez una sustancia farmacéutica, así como las denominaciones ya adoptadas oficialmente en cualquier país.

9. El parentesco entre sustancias del mismo grupo se pondrá de manifiesto en las DCI (véase el Principio 2) utilizando una partícula común. En la lista que figura a continuación se indican ejemplos de partículas para grupos de sustancias, en particular para grupos nuevos. Existen muchas otras partículas que se usan habitualmente. Cuando una partícula aparece sin guión alguno, puede utilizarse en cualquier lugar de la palabra.

<table>
<thead>
<tr>
<th>Latin</th>
<th>Español</th>
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<tr>
<td>-acum</td>
<td>-aco antinflamatorios derivados del ibufenaco</td>
</tr>
<tr>
<td>-adolum</td>
<td>-adol analgésicos</td>
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<tr>
<td>-adol-</td>
<td>-adol-</td>
</tr>
<tr>
<td>-astum</td>
<td>-ast antiasmáticos, sustancias antialérgicas cuya acción principal no es la antihistamínica</td>
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<tr>
<td>-astinum</td>
<td>-astina antihistamínicos</td>
</tr>
<tr>
<td>-azeepamum</td>
<td>-azeepam derivados del diazepam</td>
</tr>
<tr>
<td>bol</td>
<td>bol esteroides anabolizantes</td>
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<tr>
<td>-cain-</td>
<td>-caina- antiarrítmicos de clase I, derivados de procaínamida y lidocaína</td>
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<tr>
<td>-caínun</td>
<td>-caína- anestésicos locales</td>
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<tr>
<td>cef-</td>
<td>cef- antibióticos, derivados del ácido cefalosporánico</td>
</tr>
<tr>
<td>-cilinum</td>
<td>-cilina antibióticos derivados del ácido 6-aminopenicilánico</td>
</tr>
<tr>
<td>-conazolum</td>
<td>-conazol antifúngicos sistémicos derivados del miconazol</td>
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<tr>
<td>cort</td>
<td>cort corticosteroides, excepto derivados de prednisolona</td>
</tr>
<tr>
<td>-coxibum</td>
<td>-coxib inhibidores selectivos de ciclooxigenasa</td>
</tr>
<tr>
<td>-entanum</td>
<td>-entán antagonistas del receptor de endotelinia</td>
</tr>
<tr>
<td>gab</td>
<td>gab gabamiméticos</td>
</tr>
<tr>
<td>gado-</td>
<td>gado- agentes para diagnóstico derivados de gadolinio</td>
</tr>
<tr>
<td>-gartranum</td>
<td>-gatrán inhibidores de la trombina antitrombóticos</td>
</tr>
<tr>
<td>gest</td>
<td>gest esteroides progestágenos</td>
</tr>
<tr>
<td>gli</td>
<td>gli hipoglucemiantes, antihiperglucémicos</td>
</tr>
<tr>
<td>io-</td>
<td>io- medios de contraste iodos</td>
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<tr>
<td>-metacinum</td>
<td>-metacina antiinflamatorios derivados de indometacina</td>
</tr>
<tr>
<td>-mycinum</td>
<td>-micina antibióticos producidos por cepas de Streptomyces</td>
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<tr>
<td>-nidadolum</td>
<td>-nidadol antiprototoariorios derivados de metronidazol</td>
</tr>
<tr>
<td>-ololum</td>
<td>-olol antagonistas de receptores β-adrenérgicos</td>
</tr>
<tr>
<td>-oxacinum</td>
<td>-oxacino antibacterianos derivados del ácido nalidíxico</td>
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1 En el documento de trabajo WHO/EMP/QSM/2011.3, que se actualiza periódicamente y puede solicitarse al Programa sobre Denominaciones Comunes Internacionales, OMS, Ginebra, figura una lista más amplia de partículas.
-platinum -platino antineoplásicos derivados del platino
-poetinum -poetina factores sanguíneos similares a la eritropoyetina
-pril(at)um -pril(at) inhibidores de la enzima conversora de la angiotensina
-profenum -profeno antiinflamatorios derivados del ibuprofeno
-prost prost prostaglandinas
-relinum -relina péptidos estimulantes de la liberación de hormonas hipofisarias
-sartanum -sartán antihipertensivos (no peptídicos) antagonistas del receptor de angiotensina II
-vaptanum -vaptán antagonistas del receptor de vasopresina
-vin- vin- alcaloides de la vinca
-vin- vin- )
International Nonproprietary Names for Pharmaceutical Substances (INN)

RECOMMENDED International Nonproprietary Names: List 84

Notice is hereby given that, in accordance with paragraph 7 of the Procedure for the Selection of Recommended International Nonproprietary Names for Pharmaceutical Substances [Off. Rec. Wld Health Org., 1955, 60, 3 (Resolution EB15.R7); 1969, 173, 10 (Resolution EB43.R9); Resolution EB115.R4 (EB115/2005/REC/1)], the following names are selected as Recommended International Nonproprietary Names. The inclusion of a name in the lists of Recommended International Nonproprietary Names does not imply any recommendation of the use of the substance in medicine or pharmacy.

Lists of Proposed (1–1117) and Recommended (1–78) International Nonproprietary Names can be found in Cumulative List No. 17, 2017 (available in CD-ROM only).

Dénominations communes internationales des Substances pharmaceutiques (DCI)

Dénominations communes internationales RECOMMANDÉES: Liste 84


Denominaciones Comunes Internacionales para las Sustancias Farmacéuticas (DCI)

Denominaciones Comunes Internacionales RECOMENDADAS: Lista 84

De conformidad con lo que dispone el párrafo 7 del Procedimiento de Selección de Denominaciones Comunes Internacionales Recomendadas para las Sustancias Farmacéuticas [Act. Of. Mund. Salud, 1955, 60, 3 (Resolución EB15.R7); 1969, 173, 10 (Resolución EB43.R9); Résolution EB115.R4 (EB115/2005/REC/1) EB115.R4 (EB115/2005/REC/1)], se comunica por el presente anuncio que las denominaciones que a continuación se expresan han sido seleccionadas como Denominaciones Comunes Internacionales Recomendadas. La inclusión de una denominación en las listas de las Denominaciones Comunes Recomendadas no supone recomendación alguna en favor del empleo de la sustancia respectiva en medicina o en farmacia.

**Recommended INN: List 84**

**Latin, English, French, Spanish:**

*Chemical name or description; Molecular formula; Graphic formula*

**DCI Recommandée**

*Nom chimique ou description; Formule brute; Formule développée*

**DCI Recomendada**

*Nombre químico o descripción; Fórmula molecular; Fórmula desarrollada*

---

**acidum aligomanuxicum**

*aligomanuxic acid*

\[
\text{O-[oligo-(1\rightarrow4)-}\beta-D\text{-mannopyranuronan-}\beta\text{-osyl}-(1\rightarrow3)-D\text{-mannaric, -(1\rightarrow2)-d-arabinaric, -(1\rightarrow3)-d-arabinaric, (1\rightarrow2)-d-}\text{érythraric, -(1\rightarrow2)-d-thréaric, and -(1\rightarrow2)-glyceraric acids, produced from alginate of brown seaweeds by acid-catalysed partial hydrolysis, isolation of oligomannuronans and oxidation of the reducing end group}.
\]

**acide aligomanuxique**

*acides O-[oligo-(1\rightarrow4)-\beta-D-mannopyranuronan-\beta-osyl]-(1\rightarrow3)-D-mannarique, -(1\rightarrow2)-d-arabinarique, -(1\rightarrow3)-D-arabinarique, (1\rightarrow2)-D-\text{érythrarique}, -(1\rightarrow2)-D-thréarique, et -(1\rightarrow2)-glycerarique, produits à partir d’algues brunes par hydrolyse partielle par catalyse acide, isolation des oligomannuronanes et oxydation du groupe réducteur terminal.*

**ácido aligomanúxico**

*ácidos O-[oligo-(1\rightarrow4)-\beta-D-mannopiranuranan-\beta-osil]-(1\rightarrow3)-d-mannárico, -(1\rightarrow2)-d-arabinárico, -(1\rightarrow3)-d-arabinárico, (1\rightarrow2)-d-eritrárico, -(1\rightarrow2)-d-treárico, y -(1\rightarrow2)-glicerárico, producido a partir de algas pardas por hidrólisis parcialmente por catálisis acida, aislamiento de los oligomanuronanos y oxidación del grupo reductor terminal.*

\[(C_6H_{10}O_6)_n (CH_2O)_{m+m'} C_3H_4O_6 \]

- \( m = 0,1 \) \( n=1 \) (10-30%)
- \( m = 0,1 \) \( n=2 \) (25-30%)
- \( m = 0,1 \) \( n=3 \) (15-30%)
- \( m = 0,1 \) \( n=4-9 \) (20-40%)

**acidum norucholicum**

*norucholic acid*

3α,7β-dihydroxy-24-nor-5β-cholan-23-oic acid

**acide norucholique**

*acide 3α,7β-dihydroxy-24-nor-5β-cholan-23-oïque*

**ácido norucólico**

*ácido 3α,7β-dihidroxi-24-nor-5β-colan-23-oico*
WHO Drug Information, Vol. 34, No. 3, 2020

Recommended INN: List 84

\[
\text{C}_{23}\text{H}_{38}\text{O}_4
\]

**acoramidisum**

acoramidis 3-[3-(3,5-dimethyl-1H-pyrazol-4-yl)propoxy]-4-fluorobenzoic acid

acoramidis acide 3-[3-(3,5-diméthyl-1H-pyrazol-4-yl)propoxy]-4-fluorobenzoïque

acoramidis ácido 3-[3-(3,5-dimetil-1H-pirazol-4-il)propoxi]-4-fluorobenzoico

\[
\text{C}_{15}\text{H}_{17}\text{FN}_2\text{O}_3
\]

adebrelimabum #

adebrelimab immunoglobulin G4-kappa, anti-[*Homo sapiens* CD274 (programmed death ligand 1, PDL1, PD-L1, B7 homolog 1, B7H1)], monoclonal antibody; gamma4 heavy chain (1-446) [VH (*Homo sapiens* IGHV1-46*01 (89.8%) -IGHD) -IGHJ4*01 (93.3%)) CDR-IMGT [8.8.12] (26-33.51-58.97-108) (1-119) - *Homo sapiens* IGHG4*01, G4v5 h P10, G4v4 CH2 A1.3, A1.2 (CH1 (120-217), hinge 1-12 S10>P (227) (218-229), CH2 F1.3>A (233), L1.2>A (234) (230-339), CH3 (340-444), CHS (445-446)) (120-446), (133-218')-disulfide with kappa light chain (1'-218') [V-KAPPA (*Mus musculus* IGKV3-5*01 (84.8%)) -IGKJ2*03 (90.9%)/*Homo sapiens* IGKV4-1*01 (68.3%)) -IGKJ2*01 (100%)) CDR-IMGT [10.3.9] (27-36.54-56.93-101) (1'-111') -*Homo sapiens* IGKC*01 (100%) Km3 A45.1 (157), V101 (195) (112'-218'); dimer (225-225':228-228')-bisdisulfide, produced in Chinese hamster ovary (CHO) cells, glycoform alfa

adébrélimab

immunoglobuline G4-kappa, anti-*Homo sapiens* CD274 (ligand 1 de mort programmée, PDL1, PD-L1, homologue 1 de B7, B7H1)], anticorps monoclonal;
chaîne lourde gamma4 (1-446) [VH (Homo sapiens IGHV1-46*01 (89.8%)) -IGHD -IGHJ4*01 (93.3%)) CDR-IMGT [8.8.12] (26-33.51-58.97-108) (1-119) -Homo sapiens IGHG4*01, G4v5 h P10, G4v4 CH2 A1.3, A1.2 (CH1 (120-217), charnière 1-12 S10>P (227) (218-229), CH2 F1.3>A (233), L1.2>A (234) (230-339), CH3 (340-444), CHS (445-446)) (120-446)], (133-218")-disulfure avec la chaîne légère kappa (1-12") [V-KAPPA (Mus musculus IGKV3-5*01 (84.8%)) -IGKJ2*03 (90.9%)/Homo sapiens IGKV4-1*01 (68.3%)) -IGKJ2*01 (100%)) CDR-IMGT [10.3.9] (27-36.54-56.93-101) (1-111) -Homo sapiens IGKC*01 (100%) Km3 A45.1 (157), V101 (195) (112-218")];
dimère (225-225":228-228")-bisdisulfure, produit dans des cellules ovaries de hamster chinois (CHO), glycoforme alfa adebrelimab
inmunoglobulina G4-kappa, anti-[Homo sapiens CD274 (ligando 1 de muerte programada, PDL1, PD-L1, homólogo 1 de B7, B7H1]), anticuerpo monoclonal;
cadena pesada gamma4 (1-446) [VH (Homo sapiens IGHV1-46*01 (89.8%)) -IGHD -IGHJ4*01 (93.3%)) CDR-IMGT [8.8.12] (26-33.51-58.97-108) (1-119) -Homo sapiens IGHG4*01, G4v5 h P10, G4v4 CH2 A1.3, A1.2 (CH1 (120-217), bisagra 1-12 S10>P (227) (218-229), CH2 F1.3>A (233), L1.2>A (234) (230-339), CH3 (340-444), CHS (445-446)) (120-446)], (133-218")-disulfuro con la cadena ligera kappa (1-12") [V-KAPPA (Mus musculus IGKV3-5*01 (84.8%)) -IGKJ2*03 (90.9%)/Homo sapiens IGKV4-1*01 (68.3%)) -IGKJ2*01 (100%)) CDR-IMGT [10.3.9] (27-36.54-56.93-101) (1-111) -Homo sapiens IGKC*01 (100%) Km3 A45.1 (157), V101 (195) (112-218")];
dímero (225-225":228-228")-bisdisulfuro, producido por células ováricas de hamster chino (CHO), forma glicosilada alfa

Heavy chain / Chaîne lourde / Cadena pesada
QVQLVQSGAE VKKPGASVKV SCKASGYTFT SYWMHWVRQA PGQGLEWMGR 50
QGPMNSGFTSY NEKFKNRVTM TRDTSTSTVY MEISSLSRED TAVYCVARG 100
SSYDYFDYWG QGTTVTVSSA STKGPSVFPL APCSRSTSES TAALGCLVKD 150
YFPEPVTVQIK QGTVTVSDG GYSLSSVTYY PEFLGCQTYT 200
TCNMDKPSN TKVDKREVES YGFCPCPCPA PAGQPSYSVF LLFPQKPVTL 250
MISRTPEVVC VYCVQSSQEGF VEQVNMYVQG VEVKNXTPKY AEQGNTPAK 300
VYCGVVLGAQQ CNLQCEYKLC KYVNGQDGPS IEBTXRMKGN VPPGQYQYTL 350
PPQSGXTMEN QQSTLCLVKEF FYTFDIAVEN ESQHQPENNY KTPPVVLDD 400
GGSFLLYSLTQ VDRSQQQGQN VFESCSWYHEA LNHBYTQKL1 SLSLGG 446

Light chain / Chaîne légère / Cadena ligera
DIVLTQSPAS LAVSPGQRAT ITCRASESVS IHGTHLMHRY QKQPQPPQPL 50
LIVASHSNL GYTPASQGGF SGQTIFITINPV EVRAEDTQY YQQPSQEQPL 100
TCQGDCXKLE KRTVAAEPSV FPPSQDEQLK STGASVYLL MFNPREDK 150
QKVRMDALGS GSQGQSVTEQ SDKEDSTSLK STLLSRSADK AEKVYTAEV 200
THQGLEDSPVY KSFNRGEC 218

Post-translational modifications
Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro
Intra-H (C23-C104) 22-96 146-202 366-424
22"-96" 146"-202" 366"-424"
Intra-L (C23-C104) 23"-92" 138"-198" 23"-92" 138"-198"

N-terminal glutaminyl cyclization to pyroglutamyl (pE, 5-oxoprolyl)
HV HQ 1

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
H CH2 N84.4: 296, 296"
afamitresgén autoleucel

Autologous CD4+ and CD8+ T cells obtained by leukapheresis, transduced with an HIV-derived self-inactivating (SIN) lentiviral vector, encoding an enhanced-affinity T cell receptor (TCR) specific for the human melanoma antigen A4 (MAGE family member A4, antigen MAGE A4) HLA-A*02 peptide driven by the elongation factor 1 alpha (EF1α) promoter. Cells express lymphonode-homing markers CCR7 and CD62L, CD45 isoforms CD45RA and CD45R0, costimulatory markers CD27 and CD28, IL-7 receptor CD127, and chemokine receptor CXCR3. Cells secrete interleukin 2 (IL-2), tumor necrosis factor α (TNF-alpha, TNFα), interferon gamma (interferon γ, IFN-gamma), granzyme, interleukin 4 (IL-4), interleukin 13 (IL-13) and interleukin 17 (IL-17) upon activation.

afamitresgène autoleucel

Lymphocyes T CD4+ et CD8+ autologues obtenus par leucophérèse, transduits par un vecteur lentiviral auto-inactivant (SIN), dérivé du virus de l'immunodéficience humaine (VIIH), codant pour un récepteur de lymphocytes T (TCR) à affinité augmentée spécifique du peptide HLA-A*02 de l'antigène du mélanome humain A4 (membre A4 de la famille MAGE, antigène MAGE-4), sous le contrôle d'un promoteur du facteur d’elongation alpha 1 (EF1α). Les cellules expriment les marqueurs de migration des ganglions lymphatiques CCR7 et CD62L, les isoformes CD45RA and CD45R0 du CD45, les marqueurs co-stimulateurs CD27 et CD28, le récepteur CD127 de l'interleukine 7 (IL-7) et les récepteurs de chimiokines CXCR3. Les cellules secrètent de l'interleukine 2 (IL-2), facteur de nécrose tumorale α (TNF-alpha, TNFα), interféron gamma (interféron γ, IFN-gamma), granzyme, interleukine 4 (IL-4), interleukine 13 (IL-13) et l’interleukine 17 (IL-17) au moment de leur activation.

afamitresgén autoleucel

Linfocitos T CD4+ y CD8+ autólogos obtenidos por leucoaféresis, transducidos con un vector lentiviral auto inactivante derivado del HIV, que codifica para un receptor de linfocitos T (TCR) con afinidad aumentada, específico para el péptido del antígeno de melanoma humano A4 (MAGE A4) presentado por HLA-A*02, dirigido por un promotor del factor de elongación 1 alfa (EF1α). Las células expresan los marcadores de migración a ganglios linfáticos CCR7 y CD62L, las isoformas CD45RA y CD45R0 de CD45, los marcadores coestimuladores CD27 y CD28, el receptor de IL-7 CD127, y el receptor de quimoquinas CXCR3. Las células secretan interleukina 2 (IL-2), factor de necrosis tumoral (TNF-alfa, TNFα), interferón gamma (interferón γ, IFN-gamma), granzima, interleukina 4 (IL-4), interleukina 13 (IL-13) e interleukina 17 (IL-17) tras su activación.
alsevalimabum #
alsevalimab

immunoglobulin G1-kappa, anti-[*Homo sapiens* VTCN1 (V-set domain containing T cell activation inhibitor 1, B7-H4, B7H4)], *Homo sapiens* monoclonal antibody;
gamma1 heavy chain *Homo sapiens* (1-450) [VH (*Homo sapiens* IGHV4-39*01 (96.0%)-(IGHD) - IGHJ5*02 (93.8%)) CDR-IMGT [10.7.12] (26-35.53-59.98-109) (1-120) -*Homo sapiens* IGHG1*01 (100%) G1m17,1 (CH1 K120 (217) (121-218), hinge 1-15 (219-233), CH2 (234-343), CH3 D12 (359), L14 (361) (344-448), CHS (449-450)) (121-450)], (223-214')-disulfide with kappa light chain *Homo sapiens* (1-214') [V-KAPPA (*Homo sapiens* IGKV3-15*01 (96.8%)) - IGKJ4*01 (91.7%)) CDR-IMGT [6.3.9] (27-32.50-52.89-97) (1'-107') -*Homo sapiens* IGKC*01 (100%), Km3 A45.1 (153), V101 (191) (108'-214')];
dimer (229-229':232-232'')-bisdisulfide, produced in Chinese hamster ovary (CHO-FUT8-/-) cells, glycoform alfa

alsévalimab

immunoglobuline G1-kappa, anti-[*Homo sapiens* VTCN1 (inhibiteur 1 de l'activation des cellules T contenant un V-set domain, B7-H4, B7H4)], anticorps monoclonal *Homo sapiens*;
chaîne lourde gamma1 *Homo sapiens* (1-450) [VH (*Homo sapiens* IGHV4-39*01 (96.0%)-(IGHD) - IGHJ5*02 (93.8%)) CDR-IMGT [10.7.12] (26-35.53-59.98-109) (1-120) -*Homo sapiens* IGHG1*01 (100%) G1m17,1 (CH1 K120 (217) (121-218), charnière 1-15 (219-233), CH2 (234-343), CH3 D12 (359), L14 (361) (344-448), CHS (449-450)) (121-450)], (223-214')-disulfure avec la chaîne légère kappa *Homo sapiens* (1'-214') [V-KAPPA (*Homo sapiens* IGKV3-15*01 (96.8%)) - IGKJ4*01 (91.7%)) CDR-IMGT [6.3.9] (27-32.50-52.89-97) (1'-107') -*Homo sapiens* IGKC*01 (100%), Km3 A45.1 (153), V101 (191) (108'-214')];
dimère (229-229':232-232'')-bisdisulfure, produit dans des cellules ovariennes de hamster chinois (CHO-FUT8-/-), glycoforme alfa

alsevalimab

inmunoglobulina G1-kappa, anti-*Homo sapiens* VTCN1 (inhibidor 1 de la activación de las células T que contiene un dominio V-set, B7-H4, B7H4)], anticuerpo monoclonal *Homo sapiens*;
cadena pesada gamma1 *Homo sapiens* (1-450) [VH (*Homo sapiens* IGHV4-39*01 (96.0%)-(IGHD) - IGHJ5*02 (93.8%)) CDR-IMGT [10.7.12] (26-35.53-59.98-109) (1-120) -*Homo sapiens* IGHG1*01 (100%) G1m17,1 (CH1 K120 (217) (121-218), bisagra 1-15 (219-233), CH2 (234-343), CH3 D12 (359), L14 (361) (344-448), CHS (449-450)) (121-450)], (223-214')-disulfuro con la cadena ligera kappa *Homo sapiens* (1'-214') [V-KAPPA (*Homo sapiens* IGKV3-15*01 (96.8%)) - IGKJ4*01 (91.7%)) CDR-IMGT [6.3.9] (27-32.50-52.89-97) (1'-107') -*Homo sapiens* IGKC*01 (100%), Km3 A45.1 (153), V101 (191) (108'-214')];
dímero (229-229':232-232'')-bisdisulfuro, producido por células ováricas de hamster chino (CHO-FUT8-/-), forma glicosilada alfa
Heavy chain / Chaîne lourde / Cadena pesada

693

amcenestrantum
amcenestrant

8-(2,4-dichlorophenyl)-9-(4-(((3S)-1-(3-fluoropropyl)pyrrolidin-3-yl)oxy)phenyl)-6,7-dihydro-5H-benzo[7]annulene-3-carboxylic acid

amcénestrant
acide 8-(2,4-dichlorophényl)-9-(4-(((3S)-1-(3-fluoropropyl)pyrrolidin-3-yl)oxy)phényl)-6,7-dihydro-5H-benzo[7]annulène-3-carboxylique

amcenestrant
ácido 8-(2,4-diclorofenil)-9-(4-(((3S)-1-(3-fluoropropil)pirrolidin-3-il)oxi)fenil)-6,7-dihidro-5H-benzo[7]anuleno-3-carboxílico

C_{31}H_{30}Cl_{2}FNO_{3}

amdakefalinum #
amdakefalin

[6-((D-phenylalanyl-D-phenylalanyl-D-leucyl-D-lysyl)-3,6-diazabicyclo[3.1.1]heptan-3-yl]acetic acid

amdakéfalone
acide [6-(D-phénylalanyl-D-phénylalanyl-D-leucyl-D-lysyl)-3,6-diazabicyclo[3.1.1]heptan-3-yl]acétique

amdakefalina
ácido [6-(D-fenilalilil-D-fenilalilil-D-leucil-D-isisil)-3,6-diazabicielo[3.1.1]heptan-3-il]acético
aramisulpridum
aramisulpride
aramisulpride
aramisulprida

4-amino-5-(ethanesulfonyl)-N-\{[(2R)-1-ethylpyrrolidin-2-yl]methyl\}-2-methoxybenzamide
4-amino-5-(éthanesulfonyl)-N-\{[(2R)-1-éthylpyrrolidin-2-yl]méthyl\}-2-méthoxybenzamide
4-amino-5-(etanosulfonil)-N-\{[(2R)-1-étipirrolidin-2-il]métil\}-2-metoxibenzamida

autogenum cevumeranum
autogene cevumeran

A 5'-capped single-stranded messenger RNA (mRNA) construct for the expression of patient-specific tumour neoantigens comprising a 5'-cap, a 5'-untranslated region derived from human alpha-globin mRNA, an optimised Kozak sequence, sequences encoding a secretory signal peptide (sec2.0), transmembrane and cytoplasmic domains of a major histocompatibility complex (MHC) Class I molecule (MITD), a 3'-untranslated region (FI) and a poly(A)-tail; sequences encoding patient specific antigens are inserted between the secretory signal peptide and the transmembrane/cytoplasmic encoding domains.

autogène cévuméran

ARN messager (ARNm) de simple brin coiffé en 5’ construit pour l’expression de néoantigènes tumoraux spécifiques du patient comprenant une coiffe en 5’, une région en 5’ non-traduite dérivée de l’ARNm de la globine alpha humaine, une séquence optimisée Kozak, et les séquences codant pour un peptide signal (sec2.0), les domaines transmembranaires et cytoplasmique du complexe majeur d’histocompatibilité de groupe I (CMH1) (MITD), une région non traduite en 3’ (FI) et une queue poly(A) ; Les séquences codant les antigènes spécifiques du patient sont insérées entre celles codant le peptide signal et les domaines transmembranaire et cytoplasmique.
Un constructo de RNA mensajero (mRNA) de cadena sencilla y caperuza en 5', para la expresión de neoantígenos tumorales específicos de cada paciente, que contiene una caperuza 5' (5'-cap), una región 5' no traducida derivada del mRNA de la globina alfa humana, una secuencia optimizada Kozak, y las secciones codificantes para el péptido señal (sec2.0), los dominios transmembrana y citoplásmico de complejo mayor de histocompatibilidad de grupo I (CMHI) (MITD), una región non-traducida en 3' (FI) y una cola poly(A); las secciones que codifican los antígenos específicos del paciente se insertan entre las del péptido señal y de los dominios transmembrana y citoplásmico.

azemiglitazonum

azemiglitazone $rac$-$(5R)$-$5$-$(4\cdot[2\cdot(3\text{-}methoxy phenyl})\cdot2\cdot$oxoethoxy)$[phenyl]methyl)-1,3-thiazolidine-2,4-dione

azémiglitazone $rac$-$(5R)$-$5$-$(4\cdot[2\cdot(3\text{-}méthoxy phényl})\cdot2\cdot$oxoéthoxy)$[phényl]métvl)-1,3-thiazolidine-2,4-dione

azemiglitazona $rac$-$(5R)$-$5$-$(4\cdot[2\cdot(3\text{-}metoxifenil})\cdot2\cdot$oxetoxi)$[fenil]metil)-1,3-tiazolidina-2,4-diona

$C_{19}H_{17}NO_{5}S$
belzupacap sarotalocanum #

belzupacap sarotalocan

a modified human papillomavirus (HPV) type 16-derived empty nanoparticle, 55 nm in diameter conjugated to approximately 200 molecules of a phthalocyanine-based photosensitizer (sarotalocan group). Each nanoparticle is comprised of 72 capsomeres, made of 5 molecules of modified viral capsid protein L1 [P78>R, T176>N, D273>T, N285>P, S288>N, T353>P, T389>S] and one molecule of viral capsid protein L2;

human papilloma virus type 16 (HPV16) capsid, a spherical shell of 72 self-assembling pentagonal (L1)5(L2)1 capsomere units comprising the recombinant viral capsid proteins L1 ([P78>R, T176>N, D273>T, N285>P, S288>N, T353>P, T389>S]-modified) and L2, conjugated to approximately 200 sarotalocan groups (near infrared absorbing dye) at N6 of lysine residues;

produced by human embryonic kidney 293 (HEK293) cells

belzupacap sarotalocan

nanoparticle vide dérivée du virus du papillomavirus humain 16 (HPV16) modifié, 55nm de diamètre, conjuguée à approximativement 200 molécules d'un photosensibilisant à base de phthalocyanine (groupe sarotalocan). Chaque particule est composée de 72 capsomères, faits de 5 molécules de protéine de capsid virale L1 modifiée ([P78>R, T176>N, D273>T, N285>P, S288>N, T353>P, T389>S]-modifiée) et L2, conjuguées à environ 200 groupes sarotalocan (colorant absorbant les proches infra-rouges) en N6 des résidus lysine ; produite par des cellules rénales embryonnaires humaines (HEK293)

belzupacap sarotalocán

 nanopartícula vacía derivada del virus del papilomavirus humano 16 (HPV16) modificado, 55nm de diámetro, conjugado con aproximadamente 200 moléculas de un fotosensibilizante a base de ftalociánina (grupo sarotalocán). Cada partícula se compone de 72 capsómberos, hechos de 5 moléculas de proteína de cápside viral L1 modificada ([P78>R, T176>N, D273>T, N285>P, S288>N, T353>P, T389>S]-modificada) y de una molécula de proteína de cápside viral L2; cápside del virus del papilomavirus humano 16 (HPV16), una cavidad esférica de 72 unidades de capsómero pentagonal (L1)5(L2)1, que se autoensamblan abarcando las proteínas recombinantes de cápside viral L1 ([P78>R, T176>N, D273>T, N285>P, S288>N, T353>P, T389>S]-modificada) y L2, conjugadas aproximadamente a 200 grupos sarotalocán (colorante absorbente infrarrojo cercano) en N6 de los residuos de lisina ; producido por las células renales embrionarias humanas (HEK293)
belzutifanum

3-(((1S,2S,3R)-2,3-difluoro-1-hydroxy-7-(methanesulfonyl))-2,3-dihydro-1H-inden-4-yl)oxy)-5-fluorobenzonitrile

belzutifan

3-(((1S,2S,3R)-2,3-difluoro-1-hydroxy-7-(méthanesulfonyl))-2,3-dihydro-1H-indén-4-yl)oxy)-5-fluorobenzonitrile

belzutifán

3-(((1S,2S,3R)-2,3-difluoro-1-hidroxi-7-(metanosulfonil))-2,3-dihidro-1H-indén-4-il)oxy)-5-fluorobenzonitrilo

C_{17}H_{12}F_{3}NO_{5}S
bepranemabum

Bepranemab is a humanized monoclonal antibody; gamma4 heavy chain humanized (1-445) [VH (Homo sapiens IGHV4-4*08 (83.5%) - (IGHD) - IGHJ3*01 (93.3%)) CDR-IMGT [8.7.12] (26-33.51-57.96-107) (1-118) - Homo sapiens IGHG4*01, G4v5 h P10 (CH1 (119-216), hinge 1-12 S10>P (226) (217-228), CH2 (229-338), CH3 (339-443), CHS (444-445)) (119-445), (132-219)*-disulfide with kappa light chain humanized (1*-219)*-V-KAPPA (Homo sapiens IGKV2-29*02 (90.0%)-IGKJ2*01 (100%)) CDR-IMGT [11.3.9] (27-37.55-57.94-102) (1*-112*)- Homo sapiens IGKC*01 (100%), Km3 A45.1 (158), V101 (196) (113*-219*]); dimer (224-224*:227-227*)-bisdisulfide, produced in Chinese hamster ovary (CHO) cells, glycoform alfa.

béranémab

Bepranémab est une immunoglobuline G4-kappa, anti-[Homo sapiens MAPT (protéine tau associée aux microtubules, tau)], anticorps monoclonal humanisé; chaîne lourde gamma4 humanisée (1-445) [VH (Homo sapiens IGHV4-4*08 (83.5%) - (IGHD) - IGHJ3*01 (93.3%)) CDR-IMGT [8.7.12] (26-33.51-57.96-107) (1-118) - Homo sapiens IGHG4*01, G4v5 h P10 (CH1 (119-216), charnière 1-12 S10>P (226) (217-228), CH2 (229-338), CH3 (339-443), CHS (444-445)) (119-445), (132-219*)-disulfure avec la chaîne légère kappa humanisée (1*-219*)-V-KAPPA (Homo sapiens IGKV2-29*02 (90.0%)-IGKJ2*01 (100%)) CDR-IMGT [11.3.9] (27-37.55-57.94-102) (1*-112*)- Homo sapiens IGKC*01 (100%), Km3 A45.1 (158), V101 (196) (113*-219*)); dimère (224-224*:227-227*)-bisdisulfure, produite dans des cellules ovariennes de hamster chinois (CHO), glycoforme alfa.

bepranemab

Bepranemab is an immunoglobulina G4-kappa, anti-[Homo sapiens MAPT (protein tau associated with microtubules, tau)], monoclonal antibody; gamma4 heavy chain humanized (1-445) [VH (Homo sapiens IGHV4-4*08 (83.5%) - (IGHD) - IGHJ3*01 (93.3%)) CDR-IMGT [8.7.12] (26-33.51-57.96-107) (1-118) - Homo sapiens IGHG4*01, G4v5 h P10 (CH1 (119-216), bisagra 1-12 S10>P (226) (217-228), CH2 (229-338), CH3 (339-443), CHS (444-445)) (119-445), (132-219*)-disulfur with the light chain kappa humanized (1*-219*)-V-KAPPA (Homo sapiens IGKV2-29*02 (90.0%)-IGKJ2*01 (100%)) CDR-IMGT [11.3.9] (27-37.55-57.94-102) (1*-112*)- Homo sapiens IGKC*01 (100%), Km3 A45.1 (158), V101 (196) (113*-219*)); dímero (224-224*:227-227*)-bisdisulfuro, producida por células ováricas de hamster chino (CHO), forma glicosilada alfa.
bersacapavir

\[N-(3\text{-cyano-4-fluorophenyl})-1\text{-methyl-4-}\{[(2S)\text{-1,1,1-}\text{trifluoropropan-2-yl}]\text{-sulfamoyl}]\text{-1H-pyrrole-2-carboxamide}\]

\[\text{C}_{16}\text{H}_{14}\text{F}_{4}\text{N}_{4}\text{O}_{3}\text{S}\]

bexmarilimab

\[\text{immunoglobulin G4-kappa, anti-} [\text{Homo sapiens STAB1 (stabilin 1, STAB-1, CLEVER-1, FEEL-1, FELE-1, FEX1, SCARH2)], humanized monoclonal antibody; gamma4 heavy chain humanized (1-449) [VH (Homo sapiens IGHV2-5*09 (91.8%) -IGHD) -IGHJ4*01 (100%) [10.7.14] (1-122) -Homo sapiens IGHG4*01, G4v5 h P10, G4v3 CH2 E1.2 (CH1 (123-220), hinge 1-12 S10>P (230)(221-232), CH2 L1.2=E (237) (233-342), CH3 (343-447), CHS (448-449) (123-449)], (136-215')-disulfide with kappa light chain humanized (1'-215') [V-KAPPA (Homo sapiens IGKV3-20*01 (80.2%) -IGKJ2*01 (100%) [7.3.9] (1'-108') -Homo sapiens IGKC*01 (100%), Km3 A45.1 (154), V101 (192) (109'-215')]; dimer (228-228':231-231')-bisdisulfide, produced in Chinese hamster ovary (CHO) cells, glycoform alfa}\]
Recommended INN: List 84

**bexmarilimab**

immunoglobulina G4-kappa, anti-[*Homo sapiens* STAB1 (stabilin 1, STAB-1, CLEVER-1, FEEL-1, FELE-1, FEX1, SCARH2)], anticuerpo monoclonal humanizado;

cadena pesada gamma4 humanizada (1-449) [VH (*Homo sapiens* IGHV2-5*09 (91.8%) -IGHD) - IGHJ4*01 (100%)) [10.7.14] (1-122) -*Homo sapiens* IGHG4*01, G4v5 h P10, G4v3 CH2 E1.2 (CH1 (123-220), bisagra 1-12 S10>P (230) (221-232), CH2 L1.2>E (237) (233-342), CH3 (343-447), CHS (448-449)) (123-449)], (136-215')-disulfuro con la cadena ligera kappa humanizada (1-215') [V-KAPPA (*Homo sapiens* IGKV3-20*01 (80.2%) -IGKJ2*01 (100%)) [7.3.9] (1-108') -*Homo sapiens* IGKC*01 (100%), Km3 A45.1 (154), V101 (192) (109'-215')];
dímero (228-228'':231-231'')-bisdisulfuro, producido por células ováricas de hamster chino (CHO), forma glicosilada alfa

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**bexmarilimab**

immunoglobulina G4-kappa, anti-*Homo sapiens* STAB1 (stabilin 1, STAB-1, CLEVER-1, FEEL-1, FELE-1, FEX1, SCARH2), anticorps monoclonal humanisé;

cadence lourde gamma4 humanisée (1-449) [VH (*Homo sapiens* IGHV2-5*09 (91.8%) -IGHD) - IGHJ4*01 (100%)) [10.7.14] (1-122) -*Homo sapiens* IGHG4*01, G4v5 h P10, G4v3 CH2 E1.2 (CH1 (123-220), charnière 1-12 S10>P (230) (221-232), CH2 L1.2>E (237) (233-342), CH3 (343-447), CHS (448-449)) (123-449)], (136-215')-disulfure avec la chaîne légère kappa humanisée (1'-215') [V-KAPPA (*Homo sapiens* IGKV3-20*01 (80.2%) -IGKJ2*01 (100%)) [7.3.9] (1'-108') -*Homo sapiens* IGKC*01 (100%), Km3 A45.1 (154), V101 (192) (109'-215')];
dimère (228-228':231-231'')-bisdisulfure, produit dans des cellules ovariennes de hamster chinois (CHO), glycoforme alfa
bomedemstatum

\[
N\{(2S)-5-\{[1R,2S]-2-(4-fluorophenyl)cyclopropyl]amino\}-1-(4-methylpiperazin-1-yl)-1-oxopentan-2-yl\}-4-(1H,1,2,3-triazol-1-yl)benzamide
\]

\[
C_{28}H_{34}FN_{7}O_{2}
\]

cevostamabum #

immunoglobulin G1-kappa, anti-[\textit{Homo sapiens} FCRL5 (Fc receptor like 5, FCRH5, IRTA2, BXMAS1, CD3O7e)] and anti-[\textit{Homo sapiens} CD3E (CD3 epsilon, Leu-4)], monoclonal antibody, bispecific tetravalent; gamma1 heavy chain anti-FCRL5 (1-450) [\textit{Mus musculus} IGHV2-4*01 (77.1%) -IGHD -IGHJ3*01 (90.9%)/\textit{Homo sapiens} IGHV4-4*08 (72.9%) -IGHD -IGHJ5*01 (85.7%)) CDR-IMGT [8.7.14] (26-33.51-57.96-109) (1-120) -\textit{Homo sapiens} IGHG1*03v,G1m3>G1m17, nG1m1, G1v30 CH2 G84.4, G1v32 CH3 W22 (CH1 R120>K (217) (121-218), hinge 1-15 (219-233), CH2 N84.4>G (300) (234-343), CH3 E12 (359), M14 (361), T22>W (369) (344-448), CHS (449-450)) (121-450), (223-214')-disulfide with kappa light chain anti-FCRL5 (1'-214') [V-KAPPA (\textit{Homo sapiens} IGKV1-16*01 (83.2%))-IGKJ1*01 (91.7%)) CDR-IMGT [6.3.9] (27-32.50-52.89-97) (1'-107') -\textit{Homo sapiens} IGKC*01 (100%), Km3 A45.1 (153), V101 (191) (108'-214')];
gamma1 heavy chain anti-CD3 (1''-449'') [\textit{Homo sapiens} IGHV1-3*01 (82.7%)-IGHD -IGHJ4*01 (100%)) CDR-IMGT [8.8.12] (26-33.51-58.97-108) (1''-119) -\textit{Homo sapiens} IGHG1*03v, G1m3>G1m17, nG1m1, G1v30 CH2 G84.4, G1v33 S22, A24, V86 (CH1 R120>K (216) (120-217), hinge 1-15 (218-232), CH2 N84.4>G (299) (233-342), CH3 E12 (358), M14 (360), T22>S (368), L24>A (370), Y86>V (409) (343-447), CHS (448-449)) (120''-449''), (222'-219'')-disulfide with kappa light chain anti-CD3 (1''-219'') [V-KAPPA (\textit{Homo sapiens} IGKV4-1*01 (88.8%)-IGKJ1*01 (100%)) CDR-IMGT [12.3.8] (27-38.56-58.95-102) (1''-112') -\textit{Homo sapiens} IGKC*01 (100%), Km3 A45.1 (158), V101 (196) (113''-219'');
dimer (229-228'-232-231')-bisdisulfide, produced in Chinese hamster ovary (CHO) cells
cévostamab

immunoglobuline G1-kappa anti-[Homo sapiens FCRL5 (récepteur Fc like 5, FCRH5, IRTA2, BXMAS1, CD307e)] et anti-[Homo sapiens CD3E (CD3 epsilon, Leu-4)], anticorps monoclonal, bispicéifique tétravalent; chaîne lourde gamma1 anti-FCRL5 (1-450) [VH (Mus musculus IGHV2-4*01 (77.1%) -(IGHD) -IGHJ3*01 (90.9%)/Homo sapiens IGHV4-4*08 (72.9%) -(IGHD) -IGHJ5*01 (85.7%)) CDR-IMGT [8.7.14] (26-33.51-57.96-109) (1-120) -Homo sapiens IGHG1*03v,G1m3>G1m17, G1m1, G1v30 CH2 G84.4, G1v32 CH3 W22 (CH1 R120>K (217) (121-218), charnière 1-15 (219-233), CH2 N84.4>G (300) (234-343), CH3 E12 (359), M14 (361), T22>W (369) (344-448), CHS (449-450)) (121-450), (223-214)-disulfure avec la chaîne légère kappa anti-FCRL5 (1'-214') [V-KAPPA (Homo sapiens IGKV1-16*01 (83.2%) -IGKJ1*01 (91.7%)) CDR-IMGT [6.3.9] (27-32.50-52.89-97) (1'-107') -Homo sapiens IGKC*01 (100%), Km3 A45.1 (153), V101 (191) (108'-214')];

chaîne lourde gamma1 anti-CD3 (1''-449'') [VH (Homo sapiens IGHV1-3*01 (82.7%) -(IGHD) -IGHJ4*01 (100%)) CDR-IMGT [8.8.12] (26-33.51-58.97-108) (1''-119'') -Homo sapiens IGHG1*03v, G1m3>G1m17, nG1m1, G1v30 CH2 G84.4, G1v33 S22, A24, V86 (CH1 R120>K (216) (120-217), charnière 1-15 (218-232), CH2 N84.4>G (299) (233-342), CH3 E12 (358), M14 (360), T22>S (368), L24>A (370), Y66>V (409) (343-447), CHS (448-449)) (120'-449''), (222''-219'')-disulfure avec la chaîne légère kappa anti-CD3 (1''-219'') [V-KAPPA (Homo sapiens IGKV4-1*01 (88.8%) -IGKJ1*01 (100%)) CDR-IMGT [12.3.8] (27-38.56-58.95-102) (1''-112'') -Homo sapiens IGKC*01 (100%), Km3 A45.1 (158), V101 (196) (113''-219'')];

dimère (229-228'':232-231'')-bisdisulfure, produit dans des cellules ovariennes de hamster chinois (CHO)

cevostamab

inmunoglobulina G1-kappa anti-[Homo sapiens FCRL5 (receptor Fc like 5, FCRH5, IRTA2, BXMAS1, CD307e)] y anti-[Homo sapiens CD3E (CD3 epsilon, Leu-4)], anticuerpo monoclonal, biespecífico tetravalente; cadena pesada gamma1 anti-FCRL5 (1-450) [VH (Mus musculus IGHV2-4*01 (77.1%) -(IGHD) -IGHJ3*01 (90.9%)/Homo sapiens IGHV4-4*08 (72.9%) -(IGHD) -IGHJ5*01 (85.7%)) CDR-IMGT [8.7.14] (26-33.51-57.96-109) (1-120) -Homo sapiens IGHG1*03v, G1m3>G1m17, nG1m1, G1v30 CH2 G84.4, G1v32 CH3 W22 (CH1 R120>K (217) (121-218), charnière 1-15 (219-233), CH2 N84.4>G (300) (234-343), CH3 E12 (359), M14 (361), T22>W (369) (344-448), CHS (449-450)) (121-450), (223-214)-disulfuro con la cadena ligera kappa anti-FCRL5 (1'-214') [V-KAPPA (Homo sapiens IGKV1-16*01 (83.2%) -IGKJ1*01 (91.7%)) CDR-IMGT [6.3.9] (27-32.50-52.89-97) (1'-107') -Homo sapiens IGKC*01 (100%), Km3 A45.1 (153), V101 (191) (108'-214')];

cadena pesada gamma1 anti-CD3 (1''-449'') [VH (Homo sapiens IGHV1-3*01 (82.7%) -(IGHD) -IGHJ4*01 (100%)) CDR-IMGT [8.8.12] (26-33.51-58.97-108) (1''-119'') -Homo sapiens IGHG1*03v, G1m3>G1m17, nG1m1, G1v30 CH2 G84.4, G1v33 S22, A24, V86 (CH1 R120>K (216) (120-217), charnière 1-15 (218-232), CH2 N84.4>G (299) (233-342), CH3 E12 (358), M14 (360), T22>S (368), L24>A (370), Y66>V (409) (343-447), CHS (448-449)) (120'-449''), (222''-219'')-disulfuro con la cadena ligera kappa anti-CD3 (1''-219'') [V-KAPPA (Homo sapiens IGKV4-1*01 (88.8%) -IGKJ1*01 (100%)) CDR-IMGT [12.3.8] (27-38.56-58.95-102) (1''-112'') -Homo sapiens IGKC*01 (100%), Km3 A45.1 (158), V101 (196) (113''-219'')];

dimero (229-228'':232-231'')-bisdisulfuro, producido por células ováricas de hamster chino (CHO)
ciltacabtagenum autoleucelum # ciltacabtagene autoleucel

autologous peripheral blood mononuclear cell (PBMC)-derived T lymphocytes transduced ex vivo with a non-replicating, self-inactivating (SIN) lentiviral vector encoding a chimeric antigen receptor (CAR) targeting two epitopes of the human B cell maturation antigen (BCMA) under the control of a human elongation factor 1 alpha (EF1α) promoter

The coding sequence comprises a human CD8α signal peptide (CD8αSP), a BCMA targeting domain consisting of two variable heavy chain-only antibodies (VHH1 and VHH2) targeting two distinct BCMA epitopes, a human CD8α hinge and transmembrane domain (CD8αhinge + TM), a human CD137 cytoplasmic domain (4-1BB) and a human CD3ζ cytoplasmic domain.

The vector genome contains a chimeric Rous sarcoma virus (RSV)/truncated 5’LTR and a self-inactivating 3’LTR-SIN (Δ-U3).
ciltacabtagène autoleucel
lymphocytes T autologues dérivés de cellules mononucléées du sang périphérique (PBMC) transduits ex vivo avec un vecteur lentiviral non-répliquant, auto-inactivant (SIN) codant pour un récepteur d’antigène chimérique (CAR) ciblant deux épitopes de l’antigène de maturation des lymphocytes B (BCMA) humains sous le contrôle d’un promoteur du facteur d’élongation 1-alpha humain (EF1α).
La séquence code pour un peptide signal CD8 alpha humain (CD8α SP), un domaine ciblant le BCMA consistant en seulement la partie variable des chaînes lourdes (VHH1 and VHH2) de deux anticorps dirigés contre deux épitopes du BCMA, une charnière et un domaine transmembranaire du CD8 alpha humain, un domaine cytoplasmique du CD 137 humain (4-1BB) et un domaine cytoplasmique du CD3 zéta humain (CD3ζ).
Le génome du vecteur contient en 5’, une séquence LTR (terminale longue répétée) tronquée d’un virus du sarcome de Rous (RSV) chimérique et en 3’, une séquence LTR-SIN (Δ-U3) auto-inactivante.

ciltacabtagén autoleucel
linfocitos T autólogos derivados de células mononucleares de sangre periférica (PBMC) transducidos ex vivo con un vector lentiviral no replicativo, auto inactivante (SIN), que codifica para un receptor de antígenos quimérico (CAR) dirigido a dos epitopos del antígeno de maduración de linfocitos B (BCMA) humano bajo el control de un promotor del factor de elongación 1 alfa humano (promotor EF1α).
La secuencia codificante consta de un péptido señal del CD8 alfa humano, un dominio dirigido a BCMA consistente en sólo la parte variable de las cadenas pesadas (VHH1 y VHH2) de dos anticuerpos dirigidos a dos epitopos del BCMA, una bisagra y un dominio transmembrana del CD8 alfa humano, un dominio citoplasmático del CD137 humano (4-1BB) y un dominio citoplasmático del CD3 zeta humano (CD3ζ).
El genoma del vector contiene un LTR 5’ truncado/RSV (virus del sarcoma de Rous) químérico y un LTR 3’-SIN auto inactivante (Δ-U3).

conendostatinum
L-methionyl-human endostatin [human collagen type XVIII α-1 (COL18A1) C-terminal (1572-1754)-fragment (1-183)], canonical D104, R110, S150 form, produced in Escherichia coli

conendostatine
L-méthionyl-endostatine humaine [fragment C-terminal (1572-1754) du collagène humain de type XVIII α-1 (COL18A1) (1-183)], forme canonique D104, R110, S150, produit dans Escherichia coli

conendostatina
L-metionil-endostatina humana [fragmento C-terminal (1572-1754) del colágeno humano de tipo XVIII α-1 (COL18A1) (1-183)], forma canónica D104, R110, S150, producido en Escherichia coli
cudarolimabum # cudarolimab

immunoglobulin G1-kappa, anti-[Homo sapiens TNFRSF4 (tumor necrosis factor receptor (TNFR) superfamily member 4, ACT35, OX40, CD134)], Homo sapiens monoclonal antibody; gamma1 heavy chain Homo sapiens (1-453) [VH (Homo sapiens IGHV3-30*03 (100%) -IGHD -IGHJ3*02 (100%)) CDR-IMGT [8.8.17] (26-33.51-58.97-113) (1-124) -Homo sapiens IGHGI*01 (100%) G1m17,1 (CH1 K120 (221) (125-222), hinge 1-15 (223-237), CH2 (238-347), CH3 D12 (363), L14 (365) (348-452), CHS K>del (453)) (125-453)], (227-213')-disulfide with kappa light chain Homo sapiens (1-213') [V-KAPPA (Homo sapiens IGKV1-33*01 (96.8%) -IGKJ4*01 (100%)) CDR-IMGT [6.3.8] (27-32.50-52.89-96) (1'-106') -Homo sapiens IGKC*01 (100%), Km3 A45.1 (152), V101 (190) (107'-213')]; dimer (233-233'';236-236'')-bisdisulfide, produced in Chinese hamster ovary (CHO) cells, glycoform alfa

cudarolimab

immunoglobuline G1-kappa, anti-[Homo sapiens TNFRSF4 (membre 4 de la super famille des récepteurs du facteur de nécrose tumorale, ACT35, OX40, CD134)], anticorps monoclonal Homo sapiens; chaîne lourde gamma1 Homo sapiens (1-453) [VH (Homo sapiens IGHV3-30*03 (100%) -IGHD -IGHJ3*02 (100%)) CDR-IMGT [8.8.17] (26-33.51-58.97-113) (1-124) -Homo sapiens IGHGI*01 (100%) G1m17,1 (CH1 K120 (221) (125-222), charnière 1-15 (223-237), CH2 (238-347), CH3 D12 (363), L14 (365) (348-452), CHS K>del (453)) (125-453)], (227-213')-disulfure avec la chaîne légère kappa Homo sapiens (1'-213') [V-KAPPA (Homo sapiens IGKV1-33*01 (96.8%) -IGKJ4*01 (100%)) CDR-IMGT [6.3.8] (27-32.50-52.89-96) (1'-106') -Homo sapiens IGKC*01 (100%), Km3 A45.1 (152), V101 (190) (107'-213')]; dimère (233-233'';236-236'')-bisdisulfure, produite dans des cellules ovuliennes de hamster chinois (CHO), glycoforme alfa

cudarolimab

immunoglobulina G1-kappa, anti-[Homo sapiens TNFRSF4 (miembro 4 de la super familia de los receptores del factor de necrosis tumoral, ACT35, OX40, CD134)], anticuerpo monoclonal Homo sapiens;
cadena pesada gamma1 *Homo sapiens* (1-453) [VH (Homo sapiens IGHV3-30*03 (100%) - (IGHD) - IGHJ3*02 (100%)) CDR-IMGT (8.8.17) (26-33.51-58.97-113) (1-124) - *Homo sapiens* IGHG1*01 (100%) G1m17,1 (CH1 K120 (221) (125-222), bisagra 1-15 (223-237), CH2 (238-347), CH3 D12 (363), L14 (365) (348-452), CHS K>del (453)) (125-213') - disulfuro con la cadena ligera kappa *Homo sapiens* (1'-213') [VKAPPA (Homo sapiens IGKV1-33*01 (96.8%) - IGKJ4*01 (100%)) CDR-IMGT (6.3.8) (27-32.50-52.89-96) (1'-106') - *Homo sapiens* IGKC*01 (100%), Km A45.1 (152), V101 (190) (107'-213')); dímero (233-233':236-236'')-bisdisulfuro, producida por células ováricas de hamster chino (CHO), forma glicosilada alfa

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**Heavy chain / Chaîne lourde / Cadena pesada**

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<thead>
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<td>ISDYGKNYY ADYQKRPT1 SRHDSKNTLY QMNSLRAED TAVYCARGR 100</td>
</tr>
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<tr>
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</tr>
<tr>
<td>G1m17,1 (CH1 K120 (221) (125-222), bisagra 1-15 (223-237), CH2 (238-347), CH3 D12 (363), L14 (365) (348-452), CHS K&gt;del (453)) (125-213') - disulfuro con la cadena ligera kappa <em>Homo sapiens</em> (1'-213') [VKAPPA (Homo sapiens IGKV1-33<em>01 (96.8%) - IGKJ4</em>01 (100%)) CDR-IMGT (6.3.8) (27-32.50-52.89-96) (1'-106') - <em>Homo sapiens</em> IGKC*01 (100%), Km A45.1 (152), V101 (190) (107'-213')); dímero (233-233':236-236'')-bisdisulfuro, producida por células ováricas de hamster chino (CHO), forma glicosilada alfa</td>
</tr>
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**Light chain / Chaîne légère / Cadena ligera**

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<td>ASNLETGVPS RFSGSGGTGD FPTTEISSLP EDIATYCYGQ SDHYTPREGQ 100</td>
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<td>TRVEIKRTVA APSVFIFPS DEQASQGTAS VCVLHNRPF REVKVRKVD 150</td>
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<td>NALQSGNSQE SVTEQDSKDS TYSLSSTLTL SKADYEKHKV YACEVTHQGL 200</td>
</tr>
<tr>
<td>N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación</td>
</tr>
<tr>
<td>H CH2 N84.4: 304, 304''</td>
</tr>
<tr>
<td>Fucosylated complex bi-antennary CHO-type glycans / glycanes de type CHO biantenarios complejos fucosilados</td>
</tr>
</tbody>
</table>

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dapatifagenum navolactibacum #

dapatifagene navolactibac

A recombinant live attenuated *Lactococcus lactis*, subspecies *cremoris* (strain MG1363), expressing a fusion protein comprising lactococcal secretion leader SSusp45 and human trefoil factor protein 1 (hTFF1), driven by the promoter from the homologous *hIIA* gene (*PhlA*); the transduced gene is located in the thymidylate synthase A (*thyA*) locus which has been deleted (930102-930469).

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dapatifagène navolactibac

*Lactococcus lactis*, sous-espèce *cremoris*, recombinante (souche MG1363), vivante atténuée exprimant une protéine de fusion consistant en le leader de sécrétion lactococcien SSusp45 et le facteur en trèfle-1 humain (hTFF1), sous le contrôle du promoteur du gène homologue *hIIA* (*PhlA*); le gène transduit est localisé sur le locus de la thymidylate synthase A (*thyA*) qui a été supprimé (930102-930469).
dapatifagén navolactibac

*Lactococcus lactis*, subespecie *cremoris* (cepà MG1363), recombinante, viva atenuada, que expresa una proteína de fusión consistente en el leader de secreción lactocócica SSusp45 y la proteína 1 del factor trébol humano (hTFF1), dirigida por el promotor del gen homólogo *hIIA* (*PhIIA*); el gen transducido se localiza en el locus de la timidilato sintasa A (thyA), que ha sido delecionado (930102-930469).

datopotamabum #
datopotamab

Immunoglobulin G1-kappa, anti-*Homo sapiens* TACSTD2 (tumor-associated calcium signal transducer 2, membrane component chromosome 1 surface marker 1, M1S1, gastrointestinal tumor-associated antigen GA7331, pancreatic carcinoma marker protein GA733-1, epithelial glycoprotein-1, EGP-1, trophoblast antigen-2, cell surface glycoprotein Trop-2, TROP2), humanized monoclonal antibody;
gamma1 heavy chain humanized (1-451) [VH (*Homo sapiens* IGHV1-3*01 (79.6%) -IGHD -IGHJ4*01 (93.3%)) [8.8.14] (1-121) - *Homo sapiens* IGHG1*03 (100%) G1m3, nG1m1 (CH1 R120 (218) (122-219), hinge 1-15 (220-234), CH2 (235-344), CH3 E12 (360), M14 (362) (345-449), CHS (450-451) (122-451)), (224-214')-disulfide with kappa light chain humanized (1'-214') [V-KAPPA (*Homo sapiens* IGKV1-39*01 (84.2%) -IGKJ2*01 (100%)) [6.3.9] (1'-107') - *Homo sapiens* IGKC*01 (100%), Km3 A45.1 (153), V101 (191) (108'-214')]; dimer (230-230'-233-233'')-bisdisulfide, produced in Chinese hamster ovary (CHO) cells, glycoform alfa

datopotamab

Immunoglobuline G1-kappa, anti-*Homo sapiens* TACSTD2 (tumor-assosiated calcium signal transducer 2, membrane component chromosome 1 surface marker 1, M1S1, antigène GA7331 associé aux tumeurs gastrointestinales, protéine GA733-1 marqueur de carcinomes pancréatiques, glycoprotéine épithéliale 1, EGP-1, antigène 2 du trophoblaste, glycoprotéine Trop-2 à la surface des cellules, TROP2), anticorps monoclonal humanisé;
chaîne lourde gamma1 humanisée (1-451) [VH (*Homo sapiens* IGHV1-3*01 (79.6%) -IGHD -IGHJ4*01 (93.3%)) [8.8.14] (1-121) - *Homo sapiens* IGHG1*03 (100%) G1m3, nG1m1 (CH1 R120 (218) (122-219), charnière 1-15 (220-234), CH2 (235-344), CH3 E12 (360), M14 (362) (345-449), CHS (450-451) (122-451)), (224-214')-disulfur avec la chaîne légère kappa humanisée (1'-214') [V-KAPPA (*Homo sapiens* IGKV1-39*01 (84.2%) -IGKJ2*01 (100%)) [6.3.9] (1'-107') - *Homo sapiens* IGKC*01 (100%), Km3 A45.1 (153), V101 (191) (108'-214')]; dimère (230-230'-233-233'')-bisdisulfure, produit dans des cellules ovariennes de hamster chinois (CHO), glycoforme alfa
datopotamab

immunoglobulina G1-kappa, anti-{*Homo sapiens* TACSTD2 (transductor 2 de señales cálcicas asociado a los tumores, componente membranario del cromosoma 1 marcador de superficie 1, M1S1, antígeno GA7331 asociado a los tumores gastrointestinal, proteína GA733-1 marcador de carcinomas pancreáticos, glicoproteína epitelial 1, EGP-1, antígeno 2 del trofoblasto, glicoproteína Trop-2 en la superficie de las células, TROP2)}, anticuerpo monoclonal humanizado; cadena pesada gamma 1 humanizada (1-451) [VH (*Homo sapiens* IGHV1-3*01 (79.6%) -(IGHD) -IGHJ4*01 (93.3%)) [8.8.14] (1-121) - *Homo sapiens* IGHG1*03 (100%) G1m3, nG1m1 (CH1 R120 (218) (122-219), bisagra 1-15 (220-234), CH2 (235-344), CH3 E12 (360), M14 (362) (345-449), CHS (450-451) (122-24), (224-214))-disulfuro con la cadena ligera kappa humanizada (1'-214') [V-KAPPA (*Homo sapiens* IGKV1-39*01 (84.2%)- IGKJ2*01 (100%)) [6.3.9] (1'-107') - *Homo sapiens* IGKC*01 (100%) Km3 A45.1 (153), V101 (191) (108-214')); dímero (230-230'-233-233')-bisdisulfuro, producido por células ováricas de hamster chino (CHO), forma glicosilada alfa

Heavy chain / Chaîne lourde / Cadena pesada

```
VQQLVQSGAE VKKPGASVKV SCKASGYTFT TAGMQWVRQA PGQGLEWMGW 50
INTHSGVPKY AEDFKGRVTI SADTSTSTAY LQLSLSDLK TAIVYCAARG 100
FGQGNYWYF WQQQLTITSTG SADTKGQFVP LPLREKSTSS GOTAALGCV 150
KDXFYPFVTG SNNSCGALSG VRTFPAFQKV EGSYLSLSSV TYPFSSSGTQ 200
TYICNVHRK SPHTVQSRWE PKEDCQRTNC PPCAPPELGL GSPVFLFPKK 250
PKQIMLSIET PRESVTVVGGN SEDTPFQFEN VQVGEEHEH ARKQKREKQ 300
RETVVLTVYL TVLHQQMLNG KEYCKGKVHK ALAPAIETKI SRAGQQRSEP 350
QVYTLPSYRE EMTHQNQVLT CLEKGYPPED FIAEWEKGQ FENYYRTPPP 400
VLSDGGFSTL YSKLVQDVKR WQQNYTVSCS VMHRAHLHHT TQKLQSLSPG 450
K 451
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Light chain / Chaîne légère / Cadena ligera

```
DIQMTQSPSS LSASVGDRVT ITCKASQDVS TAVANYQKQF GQPKLLYS 50
ASRTYFPVPS RFKSGGSGTR FTLTISLSIQ EDFAYVYQQC HYTPTLQIQ 100
CTKLQKVSYT AASPVYFVPF SNEQGAGSTA SQCILINHPY FPAEVRQKTV 150
DNAGLSGNNQ EKVTRQDEEK STYSLQSTLT LSKADYERHK VYACEVTHQG 200
LSSPVXTKSNF RGE 214
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Post-translational modifications

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro

Intra-H (C23-C104) 22-96 148-204 265-325 371-429
22''-96'' 148''-204'' 265''-325'' 371''-429''
Intra-L (C104-C23) 23'-88' 134'-194'
23'''-88''' 134'''-194'''
Inter-H-L (h 5-CL126) 224-214 224'-214' 224''-214''
230-230'' 230-233' 230-233''

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación

H CH2 N84.4: 301, 301''
Fucosylated complex bi-antennary CHO-type glycans / glycanes de type CHO biantenarios complejos fucosilados

C-terminal lysine clipping:

H CH3 K2: 451, 451''

datopotamabum deruxtecanum #
datopotamab deruxtecan

immunoglobulin G1-kappa, anti-{*Homo sapiens* TACSTD2 (tumor-associated calcium signal transducer 2, membrane component chromosome 1 surface marker 1, M1S1, gastrointestinal tumor-associated antigen GA7331, pancreatic carcinoma marker protein GA733-1, epithelial glycoprotein-1, EGP-1, trophoblast antigen-2, cell surface glycoprotein Trop-2, TROP2)}, humanized monoclonal antibody conjugated to deruxtecan, comprising a linker and a camptothecin derivative;
gamma1 heavy chain humanized (1-451) [VH (Homo sapiens IGH1V3-01*(79.6%)-(IGHD) - IGHJ4*01 (93.3%)) CDR-IMGT [8.8.14] (26-33.51-58.97-110) (1-121) -Homologous sages IGHG1*03 (100%) G1m3, nG1m1 (CH1 R120 (218) (122-219), hinge 1-15 (220-234), CH2 (235-344), CH3 E12 (360), M14 (362) (345-449), CH3 (450-451)) (122-451)], (224-214)-disulfide with kappa light chain humanized (1*-214*) [V-KAPPA (Homo sapiens IGKV139*01 (84.2%)-IGKJ2*01 (100%)) CDR-IMGT [6.3.9] (27-32.50-52.89-97) (1*-107) -Homologous sages IGKC*01 (100%), Km3 A45.1 (153), V101 (191) (108*-214*)];
dimer (230-230**:233-233**)-bisdissulfide; produced in Chinese hamster ovary (CHO) cells, glycoform alfa, conjugated, on an average of 4 cysteinyl, to deruxtecan, comprising a linker and a camptothecin derivative

datopotamab déruxtécan

immunoglobuline G1-kappa, anti-[Homo sapiens TACSTD2 (transducteur 2 de signaux calciques associé aux tumeurs, composant membranaire du chromosome 1 marqueur de surface 1, M1S1, antigène GA7331 associé aux tumeurs gastrointestinales, protéine GA733-1 marqueur de carcinomes pancréatiques, glycoprotéine épithéliale 1, EGP-1, antigène 2 du trophoblaste, glycoprotéine Trop-2 à la surface des cellules, TROP2)], anticorps monoclonal humanisé conjugué au deruxtecan, comprenant un linker et un dérivé de la camptothécine;
chaîne lourde gamma1 humanisée (1-451) [VH (Homo sapiens IGH1V3-01*(79.6%)-(IGHD) - IGHJ4*01 (93.3%)) CDR-IMGT [8.8.14] (26-33.51-58.97-110) (1-121) -Homologous sages IGHG1*03 (100%) G1m3, nG1m1 (CH1 R120 (218) (122-219), charnière 1-15 (220-234), CH2 (235-344), CH3 E12 (360), M14 (362) (345-449), CH3 (450-451)) (122-451)], (224-214)-disulfure avec la chaîne légère kappa humanisée (1*-214*) [V-KAPPA (Homo sapiens IGKV139*01 (84.2%)-IGKJ2*01 (100%)) CDR-IMGT [6.3.9] (27-32.50-52.89-97) (1*-107) -Homologous sages IGKC*01 (100%), Km3 A45.1 (153), V101 (191) (108*-214*)];
dimère (230-230**:233-233**)-bisdissulfure; produit dans des cellules ovariennes de hamster chinois (CHO), glycoforme alfa, conjugué sur une moyenne de 4 cystéines au déruxtécan, comprenant un linker et un dérivé de la camptothécine

datopotamab deruxtecán

immunoglobulina G1-kappa, anti-[Homo sapiens TACSTD2 (transductor 2 de señales cálcicas asociado a los tumores, componente membrana del cromosoma 1 marcador de superficie 1, M1S1, antígeno GA7331 asociado a los tumores gastrointestinales, proteína GA733-1 marcador de carcinomas pancreáticos, glicoproteína epitelial 1, EGP-1, antígeno 2 del trofoblasto, glicoproteína Trop-2 a la superficie de las células, TROP2)], anticuerpo monoclonal humanizado conjugado con deruxtecán, que comprende un enlace y un derivado de la camptotecina;
cadena pesada gamma1 humanizada (1-451) [VH (Homo sapiens IGHV1-3*01 (79.6%) -IGHD) -IGHJ4*01 (93.3%)) CDR-IMGT [8.8.14] (26-33.51-58.97-110) (1-121) -Homo sapiens IGHG1*03 (100%) G1m3, nG1m1 (Ch1 R120 (218) (122-219), bisagra 1-15 (220-234), CH2 (235-344), CH3 E12 (360), M14 (362) (345-449), CHS (450-451)) (122-451), (224-214)-disulfuro con la cadena ligera kappa humanizada (1'-'214') [V-KAPPA (Homo sapiens IGKV1-39*01 (84.2%) -IGKJ2*01 (100%)) CDR-IMGT [6.3.9] (27-32.50-52.89-97) (1'-'107') -Homo sapiens IGC*01 (100%), Km3 A45.1 (153), V101 (191) (108'-214')); dímero (230-230'':233-233'')-bisdisulfuro; producido por células ováricas de hamster chino (CHO), forma glicosilada al deruxtecan, que comprende un enlace y un derivado de la camptotecina.

![Recommended INN: List 84](WHO Drug Information, Vol. 34, No. 3, 2020)
demupitamab

immunoglobulin G1-kappa, anti-[Homo sapiens EGFR (epidermal growth factor receptor, receptor tyrosine-protein kinase erbB-1, ERBB1, HER1, HER-1, ERBB)], Homo sapiens monoclonal antibody; gamma1 heavy chain Homo sapiens (1-449) [VH (Homo sapiens IGHV4-61*01 (89.9%)-(IGHD) - IGHJ3*02 (100%)) CDR-IMGT [10.7.11] (26-35.53-59.98-108) (1-119) -Homo sapiens IGHG1*01 (100%) G1m17,1 (CH1 K120 (216) (120-217), hinge 1-15 (218-232), CH2 (233-342), CH3 D12 (358), L14 (360) (343-447), CHS K (448-449)) (120-449)], (222-214')-disulfide with kappa light chain Homo sapiens (1'-214') [V-KAPPA (Homo sapiens IGKV1-33*01 (94.7%) - IGKJ4*01 (91.7%)) CDR-IMGT [6.3.9] (27-32.50-52.89-97) (1'-107') -Homo sapiens IGKC*01 (100%), Km3 A45.1 (153), V101 (191) (108'-214')]; dimer (228-228''-231-231'')-bisdisulfide, produced in Chinese hamster ovary (CHO) cells, glycoform alfa

démupitamab

immunoglobuline G1-kappa, anti-[Homo sapiens EGFR (récepteur du facteur de croissance épidermique, récepteur tyrosine-protéine kinase erb-1, ERBB1, HER1, HER-1, ERBB)], anticorps monoclonal humanisé; chaîne lourde gamma1 Homo sapiens (1-449) [VH (Homo sapiens IGHV4-61*01 (89.9%)-(IGHD) - IGHJ3*02 (100%)) CDR-IMGT [10.7.11] (26-35.53-59.98-108) (1-119) -Homo sapiens IGHG1*01 (100%) G1m17,1 (CH1 K120 (216) (120-217), charnière 1-15 (218-232), CH2 (233-342), CH3 D12 (358), L14 (360) (343-447), CHS K (448-449)) (120-449)], (222-214')-disulfure avec la chaîne légère kappa Homo sapiens (1'-214') [V-KAPPA (Homo sapiens IGKV1-33*01 (94.7%) - IGKJ4*01 (91.7%)) CDR-IMGT [6.3.9] (27-32.50-52.89-97) (1'-107') -Homo sapiens IGKC*01 (100%), Km3 A45.1 (153), V101 (191) (108'-214')]; dimère (228-228''-231-231'')-bisdisulfure, produite dans des cellules ovariennes de hamster chinois (CHO), glycoforme alfa

demupitamab

inmunoglobulina G1-kappa, anti-[Homo sapiens EGFR (receptor del factor de crecimiento epidérmico, receptor tirosina-proteína kinasa erb-1, ERBB1, HER1, HER-1, ERBB)], anticuerpo monoclonal humanizado; cadena pesada gamma1 Homo sapiens (1-449) [VH (Homo sapiens IGHV4-61*01 (89.9%)-(IGHD) - IGHJ3*02 (100%)) CDR-IMGT [10.7.11] (26-35.53-59.98-108) (1-119) -Homo sapiens IGHG1*01 (100%) G1m17,1 (CH1 K120 (216) (120-217), bisagra 1-15 (218-232), CH2 (233-342), CH3 D12 (358), L14 (360) (343-447), CHS K (448-449)) (120-449)], (222-214')-disulfuro con la cadena ligera kappa Homo sapiens (1'-214') [V-KAPPA (Homo sapiens IGKV1-33*01 (94.7%) -IGKJ4*01 (91.7%)) CDR-IMGT [6.3.9] (27-32.50-52.89-97) (1'-107') -Homo sapiens IGKC*01 (100%), Km3 A45.1 (153), V101 (191) (108'-214')]; dimero (228-228''-231-231'')-bisdisulfuro, producida por células ováricas de hamster chino (CHO), forma glicosilada alfa
docaravimab

**Recommended INN:** List 84

**WHO Drug Information, Vol. 34, No. 3, 2020**

**docaravimab #**

**docaravimab**

immunoglobulin G2b-kappa, anti-[rabies virus strain ERA (Evelyn-Rockitniki-Abelseth)] glycoprotein ectodomain epitope G-III, *Mus musculus* monoclonal antibody;

gamma2b heavy chain *Mus musculus* (1-455) [VH (*Mus musculus* IGHV2-6-7*01 (92.8%) -(IGHD) - IGHJ2*01 (100%)) CDR-IMGT [8.7.13] (26-33.51-57.96-108) (1-119) - *Mus musculus* IGHG2B*02 (CH1 (120-216), hinge 1-22 (217-238), CH2 (239-348), CH3 (349-453), CHS (454-455)) (120-455), (134-214')-disulfide with kappa light chain *Mus musculus* (1'-214') - V-KAPPA (*Mus musculus* IKGV10-96*01 (93.7%) - IGKJ1*02 (100%)) CDR-IMGT [6.3.9] (27-32.50-52.99-107) (1'-106') - *Mus musculus* IGKC*01 (100%) (108'-214');
dimer (228-228":231-231":234-234":237-237")-tetrakisdisulfide, produced in mouse myeloma cell line SP2/0-Ag14, glycoform alfa
docaravimab

inmunoglobulina G2B-kappa, anti-[ectodominio epítopo G-III glicoproteína del virus de la rabia cepa ERA (Evelyn-Rockitniki-Abelseth)], anticuerpo monoclonal Mus musculus; cadena pesada gamma2b Mus musculus (1-455) [VH (Mus musculus IGHV2-6-7*01 (92.8%)-(IGHD) -IGHJ2*01 (100%))

CDR-IMGT [8.7.13] (26-33.51-57.96-108) (1-119) -Mus musculus IGH2B*02 (CH1 (120-216), bisagra 1-22 (217-238), CH2 (239-348), CH3 (349-453), CHS (454-455)) (120-455)], (134-214")

disulfuro con la cadena ligera kappa Mus musculus (1-214") [V-KAPPA (Mus musculus IGKV10-96*01 (93.7%)-(IGKJ1*02 (100%)) CDR-IMGT [6.3.9] (27-32.50-52.99-107) (1'-106") -Mus musculus IGKC*01 (100%) (108'-214")];
dímero (228-228":231-231":234-234":237-237")-tetrasulfidosulfuro, producida en la línea celular de mieloma murino SP2/0-Ag14, glicofoma alfa

Heavy chain / Chaîne lourde / Cadena pesada

QVQLKEEGG LLLAPQQLSLI TCTVSGFELT CHGWNNYVQDP PQGKLEHGLG 50

IQAGDDTNYN SALKRLGSLIS KEDQSKQYVL RPMFQGQDT SGYGLARKBD 100

NNDDYFQGW QGDTQTVLVEA KITPYPYGVPY APGQELTQDGV YTVLGUG13V 150

YPFQESTVYN NSGQERSHVR TFPALLQRCGL YMIMESSTYPV SSTWPSQTYT 200

CSVANRASSIT TVDEKLEERPG P31STMPCPN CQKICRRFAP NLWKQGGFPY 250

FPNRTXQVUL LSLTPRTYCV VVQOYSGYDNV YVQDQMQYNYKV NITAQTYRTN 300

REDNVSTIRV VSLTIQPGQD NMSGKEFKCK VNIKDELSPK ERTQKINGL 350

VPDTPQVYYL PPQRLQKTED VTLCLVVGFQ NGDVSIVWMT SQHCKNHYK 400

CTAPLPLSDG SYFYIYKKAM KTIKRKIDTS FSCWIEJKGK KNYLKTGA 450

RSPCK 455

Light chain / Chaîne légère / Cadena ligera

DVQMTQTTSS LEALGLQVTI TCRSPQQDIN HYLSDWQYKP DTVQELYYY 50

TSRLHSGVPS RFQGGSGGTD YELTNLREQ ESPAFYEQDD QMTLPTFEGG 100

CQKEKIFRQD AAPTYYIFPP SRRQELQEGA SYSCPQMYK PSDKVYMKI 150

DQGERQQGYVL NMLTDQKEDK STYMSMSTLT LTKDREYRIN SYCBEATHRT 200

STSIYVSRKIP NNHE 214

Post-translational modifications

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfato

Intra-H (C23-C104) 22-95 146-201 269-329 375-433

22°-95° 146°-201° 269°-329° 375°-433°

Intra-L (C23-C104) 23-88' 134-194'

23°-88° 134°-194°

Inter-H-L (CH1 11-CL 126) 134-214' 231-234' 234-237'

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación

H CH2 N84.4: 305, 305'

Fucosylated complex bis-antennary Sp2/0-type glycans / glycanes de type Sp2/0 bi-antennaires complexes fucosilados / glicanos de tipo Sp2/0 biantenarios complejos fucosilados

ebopiprantum

ebopiprant

(3S)-3-[(2S)-3-[(1,1'-biphenyl]-4-sulfonyl)-1,3-thiazolidine-2-carboxamido]-3-(4-fluorophenyl)propyl L-valinate

ébopiprant

L-valinate de (3S)-3-[(2S)-3-[(1,1'-biphenyl]-4-sulfonyl]-1,3-thiazolidine-2-carboxamido]-3-(4-fluorophényl)propyle

ebopiprant

L-valinate de (3S)-3-[(2S)-3-[(1,1'-bifenil]-4-sulfonil]-1,3-thiazolidina-2-carboxamido]-3-(4-fluorofenil)propilo

C_{30}H_{34}FN_{3}O_{5}S_{2}
efanesoctocog alfa #

human coagulation factor VIII (FVIII, antihemophilic factor, AHF, procoagulant component) with replaced B-domain (746-1648)-sequence [FVIII domains A1-a1-A2-a2 (1-740) and N-terminal B-domain fragment (741-745), fused via a synthetic 291-peptide linker of 24 repeating 12-peptides (4 types) (746-1033) plus tripeptide ASS (1034-1036) to the FVIII C-terminal (1649-2332)-domains a3-A3-C1-C2 (1037-1720)], fused to a human immunoglobulin G1 C-terminal K>del Fc fragment (1721-1946), (1726-663':1729-666')-bisdisulfide with the TIL3-D3-TIL4 domain-containing fragment 742-1218 of the human von Willebrand factor (1'-477') [(C1077>A336',C1120>A379')-mutant] fused via a synthetic 148-peptide linker of 12 repeating 12-peptides (4 types) plus tetrapeptide GASS (478'-625') to a thrombin cleavable FVIII fragment 712-743 (626'-657') [thrombin-cleavable acidic region 2 plus B3 domain (1-3)-peptide] fused to a human immunoglobulin G1 C-terminal K>del Fc fragment (658'-883'), produced in human embryonic kidney 293 (HEK293) cells, glycoform alfa

efanesoctocog alfa

facteur de coagulation VIII humain (FVIII, facteur antihémophilique, AHF, composant procoagulant) dont le domaine B a été remplacé (746-1648) [domaines A1-a1-A2-a2 du FVIII (1-740) et fragment N-terminal du domaine B (741-745), fusionné via un peptide synthétique de 291 acides aminés, fait de 24 peptides de 12 acides aminés chacun, se répétant (4 types) (746-1033), et d’un tripeptide ASS (1034-1036), à la partie C-terminale des domaines a3-A3-C1-C2 1649-2332 du FVIII (1037-1720)], fusionné au fragment Fc C-terminal K>del de l’immunoglobuline G1 humaine (1721-1946), (1726-663':1729-666') lié par des ponts disulfure au fragment contenant le domaine TIL3-D3-TIL4 du facteur de von Willebrand humain 742-1218 (’1-477’) [(C1077>A336’,C1120>A379’)-mutant] fusionné via un peptide synthétique de 148 acides aminés, fait de 12 peptides de 12 acides aminés chacun, se répétant (4 types), plus un tétrapeptide GASS (478’-625’), à un fragment du FVIII clivable par la thrombine 712-743 (626’-657’) [région 2 acide clivable par la thrombine plus le (1-3)-peptide du domaine B3] fusionné au fragment Fc C-terminal K>del de l’immunoglobuline G1 humaine (658’-883’), produit dans des cellules rénales embryonnaires humaines 293 (HEK293), glycoforme alfa

efanesoctocog alfa

factor de coagulación VIII humano (FVIII, factor antihemofilico, AHF, componente procoagulante) en el dominio B reemplazado (746-1648) [dominios A1-a1-A2-a2 del FVIII (1-740) y fragmento N-terminal del dominio B (741-745), fusionado a través de un péptido sintético de 291 aminoácidos, hecho de 24 péptidos de 12 aminoácidos cada uno, que se repiten (4 tipos) (746-1033), y de un tripeptido ASS (1034-1036), con la parte C-terminal de los dominios a3-A3-C1-C2 1649-2332 del FVIII (1037-1720)], fusionado con el fragmento Fc C-terminal K>del de la inmunoglobulina G1 humana (1721-1946), (1726-663’:1729-666’) unido por puentes disulfuro con el fragmento que contiene el dominio TIL3-D3-TIL4 del factor de von Willebrand humano 742-1218 (’1-477’) [(C1077>A336’,C1120>A379’)-mutante] fusionado a través de un péptido sintético de 148 aminoácidos, hecho de 12 péptidos de 12 aminoácidos cada uno, que se repiten (4 tipos), además un tetrapeptido GASS (478’-625’), con un fragmento del FVIII escindible por la trombina 712-743 (626’-657’) [región 2 ácido escindible por la trombina además el (1-3)-péptido del dominio B3] fusionado con el fragmento Fc C-terminal K>del de la inmunoglobulina G1 humana (658’-883’), producido en las células renales embrionarias humanas 293 (HEK293), glycoforma alfa
Sequence / Séquence / Secuencia

(a) BddFVIII-Fc chain:

ATRYLYGAV LSGLVQGMGL LQELPVQDAP PPRVPSFQPPF NTSVXYKTELF VPEFDTHLFPN IAIFPRPMPM LLLGPTQAEV 80

VDVTIYKIAE LGSALGECQL TKLEGATLQP ELFQEGKSWDS ETEISMQLDJR DAASAKRMHF MHTNVGYNR 240

SLPGILGCHR KSVYHYGTM GTTPFVHISIF LGHFTTLPVRN HRQASLIEF N1TLAQELFL MDLQGFLYLC HISSHHQDMG 320

EAYTIVKVSDF EEQLGMKMNNE AEVDDOCDM TVDSDDMFRV DDPSFQFIS Q1SRVAKHFKP TVWYIAAEAA EMDWYAFRLV 400

APDERSYKQS YLNGPQFQIG RKYKTVFPPA YTDTETFTFRE AQHESGQLGG FLPGVEQUVLT DL1FFPNQAS RPRTNYPHQG 480

TDSVLFLSR LPFGVKHLEKD FFILQEGISYP YTVFQVTEGTV THVFGYKSVET LLIYCCQEVDF 560

SQGCQGMSKDL KVTLIVFVPSF ENMDYETQEN MRPQQFSTTV YGQLEPSFGPA SQHNNISING VFSGLSDVLC LWEAYAVVL 640

SIGAQLFDLS YVSTFTYKMH KYMETDTLT FPFSSGQVPM SMENPLWIL GCHSDSFNHM GTMALLAISIS CDMNGQYDYE 720

DESYESAL YKSNIPKCEQ SFQGNYTQSG ASFTPEGSGQ PAGSSTQETS PEGSSATQEG SSPGSSATPS GPSTEGSGS PEGSSATQETP 800

PESQPSGQTE PESGAGPSSP AGGSTPSEEG TSSAPETSGS PSAPEGPSTPS STPSQGTEEG PSPSTPSQEG SSTPSQGTEPS QSTSGSTPSQ 880

GAGSTPSTEEE TSSAPESTQG SPSSTQEGPS STPSGSTQPS PSTPSQGTEPS QSTPSGTQPS PSTPSGTQPS PSTPSQGTEPS QSTPGTPS1 960

TMTFNVQVQH MDPATFDEFDC KAMSWFSDVQ LEFKVHGLSL PLLCVITMT LNFAPKQYTV QVEFALFTPT FDTEKKWYFT 1040

ENRMBNAPCR CN1QHPEQFT KENYRHAIN NYGMDTPEFB YLMDMSQNGH IHSFSGYFV TTVKKEYKQ 1120

MALYNLYFVG FETVEMLPSLK AGIWMVCELI GHLHAGMSLY LFLYSNKQTC TPLLGMASHI RDQITASQGV YQQGKFLARK 1200

LHYSIGNASN STKPEFMSLN VCAEMLPMIIH GZQSKQGQKO FSSLYSIFQP IMYVLSDKQTV TQYVGQSTGT LMFFQVONDS 1280

SQIENHIFNPF IIAYITSLVM PTSSIGOTL MLKGEQCDMN CMMLQPMKYM KAISSISDQTA SYYTSMQFMT WSPSKARLHL 1360

VVCPSEQSGS FTCPQRYLGER NELHGLGQPS IREAPDMNMQ TPFQMNQASRP YTFYGLSSLY QEXQDGQAGK KMFRKVPHNET 1440

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro


(Cys-SH: 310, 692, 1388);

(b) 4'-45', 13'-41', 25'-36', 29'-64', 47'-58', 66'-88', 83'-100', 86'-95', 104'-233', 126'-268', 135'-230',

151'-158', 283'-326', 297'-321', 308'-348', 328'-334', 338'-363', 367'-410', 386'-406', 390'-402',

394'-433', 414'-427', 436'-464', 459'-474', 462'-471', 698'-758', 804'-862'

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación

N41, N239, N1198, N1506, N1797 and N94', N384', N734'

O-glycosylation sites / Sites de O-glycosylation / Posiciones de O-glicosilación

potentially each Ser and Thr in the linker peptides

746-1036 and 478'-625'

Tyr-sulfation sites / Sites de Tyr-sulfation / Posiciones de Tyr-sulfación

346, 718, 719, 723, 729, 1052, 1068 and 632', 633', 637', 643'

eflepedocokinum alfa #

eflepedocokin alfa

human interleukin 22 (IL22, cytokine Zcyto18, IL10-related T-cell-derived inducible factor, IL-TIF) (1-146),

fused via a GSG3S(G4S)2 peptide linker (147-162) to a

human immunoglobulin G2 C-terminal Fc fragment (163-385), E269>S-mutant S316>A-variant, dimer (163'-385),

E269>S-mutant S316>A-variant, dimer (163'-385), E269>S-mutant S316>A-variant, dimer (163'-385), E269>S-mutant S316>A-variant, dimer (163'-385),
**Recommended INN: List 84**  

**WHO Drug Information, Vol. 34, No. 3, 2020**

**eflépédocokine alfa**  
interleukine 22 humaine (IL22, cytokine Zcyto18, facteur inductible dérivé des lymphocytes T lié à IL10, IL-TIF) (1-146), fusionnée via un peptide liant GSGG3S(G4S)2 (147-162) au fragment Fc C-terminal de l'immunoglobuline G2 humaine (163-385), P269>S-mutant S366>A-variante, bisdisulfure, produit dans des cellules ovariennes de hamster chinois (CHO), glycoforme alfa

**eflepedocokina alfa**  
interleukina 22 humana (IL22, citoquina Zcyto18, factor inductible derivado de los linfocitos T relacionado con IL10, IL-TIF) (1-146), fusionada a través de un péptido que se une a GSGG3S(G4S)2 (147-162) con el fragmento Fc C-terminal de la inmunoglobulina G2 humana (163-385), P269>S-mutante S366>A-variante, bisdisulfuro, producido en las células ováricas de hamster chino (CHO), glicoforma alfa

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**efmarodocokinum alfa # efmarodocokin alfa**  
human interleukin 22 (IL22, cytokine Zcyto18, IL10-related T-cell-derived inducible factor, IL-TIF) (1-146), fused to a human immunoglobulin G4 C-terminal Fc fragment (147-377), S158>P, N227>G-mutant; dimer (156-156':159-159')-bisdisulfide, produced in Chinese hamster ovary (CHO) cells, glycoform alfa

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**efmarodocokine alfa**  
interleukine 22 humaine (IL22, cytokine Zcyto18, facteur inductible dérivé des lymphocytes lié à l'IL10, IL-TIF) (1-146), fusionnée au fragment Fc C-terminal de l'immunoglobuline G4 humaine (147-377), mutant S158>P, N227>G, dimère (156-156':159-159')-bisdisulfure, produit dans des cellules ovariennes de hamster chinois (CHO), glycoforme alfa

---

**efmarodocokina alfa**  
interleukina 22 humana (IL22, citoquina Zcyto18, IL10-relacionada factor inductible derivado de células T, IL-TIF) (1-146), fusionada con el fragmento Fc C-terminal de la inmunoglobulina G4 humana (147-377), mutante S158>P, N227>G, dimero (156-156':159-159')-bisdisulfuro, producido en las células ováricas de hamster chino (CHO), glicoforma alfa

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**Sequence / Séquence / Secuencia**

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<th>Sequence</th>
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<td>SMEREOYLM QVLNPITKTV LPPQISDHPF VQKVQVFFIA KLSRHLSTCH 100</td>
<td>IEZGUDLJN QRNQVQKTVK KLSRZGELPA YGEKLLHYNG LSAATGSGGGG 150</td>
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<td>SMSERQCVKV YSLNPITKTV LPPQISDHPF VQKVQVFFIA KLSRHLSTCH</td>
<td>GSGGGGGG GSGVECPPCP PAVPVPVSXL FPPKPVLTIM ISRTPKTVSV 200</td>
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<td>VQVNYHDPVQ YVLPQTSVYQV ENMDKTVRFQP KQLPVQVYQVQV STPLTVSQQR</td>
<td>TKQQPVPQWQ SFSVSMKHL HNHPQK 250</td>
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<td>N21, N35, N64, N235</td>
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<td>Fucosylated complex bi-antennary CHO-type glycans</td>
<td>Glicanos de tipo CHO bi-antennares complejos fucosilados</td>
<td>Glicanos de tipo CHO bi-antennares complejos fucosilados</td>
</tr>
</tbody>
</table>

**C-terminal lysine clipping / Coupe de la lysine C-terminale / supressión de lisina C-terminal**

| H CHS K2 | 385, 385' | H CHS K2 | 385, 385' | H CHS K2 | 385, 385' | H CHS K2 | 385, 385' |

**Post-translational modifications / Modifications post-traductionnelles / Modificaciones posttrasducionales**

- Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro intramolecular: 7-99 56-145 199-259 305-363
- intermolecular: 165-165' 186-168'

- Glycosylation sites / Sites de glycosylation / Posiciones de glicosilación N21, N35, N64, N235
**eliapixantum**

eliapixant

3-(5-methyl-1,3-thiazol-2-yl)-5-{{(3R)-oxolan-3-yl}oxy}-N-{{1(R)}-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

**elinzanetantum**

elinzanetant

2-[3,5-bis(trifluoromethyl)phenyl]-N-{4-(4-fluoro-2-methylphenyle)-6-[[7(S),9aS]-7-(hydroxymethyl)hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl]pyridin-3-yl}-N,2-dimethylpropanamide
enflicoxib
enflicoxib
enflicoxib

$	ext{C}_{33}	ext{H}_{35}	ext{F}_{7}	ext{N}_{4}	ext{O}_{3}$

\[
\text{enflicoxib rac-4-[(5R)-5-(2,4-difluorophenyl)-3-(trifluoromethyl)-4,5-dihydro-1\text{-H}-pyrazol-1-yl]benzene-1-sulfonamide}
\]

$\text{C}_{33}\text{H}_{35}\text{F}_{7}\text{N}_{4}\text{O}_{3}$

esamisulpridum
esamisulpride
esamisulpride
esamisulprida

$\text{C}_{17}\text{H}_{27}\text{N}_{3}\text{O}_{4}\text{S}$

exalurenum
exaluren
exalurène

$\text{C}_{18}\text{H}_{12}\text{F}_{5}\text{N}_{3}\text{O}_{2}\text{S}$

\[
\text{exalurenum 4-O-[(2-amino-2,7-dideoxy-d-glycero-\text{-d-glucopyranosyl})-5-O-(5-amino-5,6-dideoxy-\text{-L-talofuranosyl})-2-deoxy-d-streptamine}}
\]

$\text{exalurène 4-O-[(2-amino-2,7-didésoxy-d-glucéro-\text{-d-glucopyranosyl})-5-O-(5-amino-5,6-didésoxy-\text{-L-talofuranosyl})-2-désoxy-d-streptamine}}$
exalureno

4-O-(2-amino-2,7-didesoxi-D-glicero-α-D-glucohexitopiranosil)-5-O-(5-amino-5,6-didesoxi-α-L-talofuranosil)-2-desoxi-D-estreptamina

C₁₉H₃₈N₄O₁₀

ezabenlimabum

immunoglobulin G4-kappa, anti-[Homo sapiens PDCD1 (programmed cell death 1, PD-1, PD1, CD279)], humanized monoclonal antibody; gamma4 heavy chain humanized (1-446) [VH (Homo sapiens IGHV3-23*04 (86.7%)-(IGHD)-(IGHJ4*01 (100%)) [8.8.13] (1-120)-Homo sapiens IGHG4*01, G4v5 h P10 (CH1 (121-218), hinge 1-12 S10>P (228) (219-230), CH2 (231-340), CH3 (341-445), CHS K2>del (446)) (121-446)], (134-218)-disulfide with kappa light chain humanized (1'-218') [V-KAPPA (Homo sapiens IGKV3D-11*01 (79.8%) -IGKJ2*02 (100%)) [10.3.9] (1'-111') -Homo sapiens IGKC*01 (100%), Km3 A45.1 (157), V101 (195) (112'-218'); dimer (226-226':229-229')-bisdisulfide, produced in Chinese hamster ovary (CHO) cells, glycoform alfa

ezabenlimab

immunoglobuline G4-kappa, anti-[Homo sapiens PDCD1 (protéine 1 de mort cellulaire programmée, PD-1, PD1, CD279)], anticorps monoclonal humanisé; chaîne lourde gamma4 humanisée (1-446) [VH (Homo sapiens IGHV3-23*04 (86.7%)-(IGHD)-(IGHJ4*01 (100%)) [8.8.13] (1-120)-Homo sapiens IGHG4*01, G4v5 h P10 (CH1 (121-218), chaîne 1-12 S10>P (228) (219-230), CH2 (231-340), CH3 (341-445), CHS K2>del (446)) (121-446)], (134-218)-disulfure avec la chaîne légère kappa humanisée (1'-218') [V-KAPPA (Homo sapiens IGKV3D-11*01 (79.8%) -IGKJ2*02 (100%)) [10.3.9] (1'-111') -Homo sapiens IGKC*01 (100%), Km3 A45.1 (157), V101 (195) (112'-218'); dimère (226-226':229-229')-bisdisulfure, produit dans des cellules ovariennes de hamster chinois (CHO), glycoforme alfa

ezabenlimab

immunoglobulina G4-kappa, anti-[Homo sapiens PDCD1 (proteína 1 de muerte celular programada, PD-1, PD1, CD279)], anticuerpo monoclonal humanizado;
cadena pesada gamma4 humanizada (1-446) [VH (Homo sapiens IGHV3-23*04 (86.7%) - IGHD - IGHJ4*01 (100%) [8.8.13] (1-120) - Homo sapiens IGHG4*01, G4v5 h P10 (CH1 (121-218), bisagra 1-12 S10>P (228) (219-230), CH2 (231-340), CH3 (341-445), CHS K2>del (446)) (121-446)], (134-218)-disulfuro con la cadena ligera kappa humanizada (1'-218') [V-KAPPA (Homo sapiens IGKV3D-11*01 (79.8%) - IGKJ2*02 (100%) [10.3.9] (1-111)' - Homo sapiens IGKC*01 (100%), Km3 A45.1 (157), V101 (195) (112-218)'); dímero (226-226':229-229')-bisdisulfuro, producido por células ováricas de hamster chino (CHO), forma glicosilada alfa

Heavy chain/Chaine lourde/Cadena pesada

EHLYSSLYG PQGPLRIAL HSDAVAPIG KPSVAPYV 5G
ISGSSGDTI SSQVGIITIT SSGNNLSLQ NGILPELAD VTVSCEAMN 100
HIVNLYNND DGSCTVYDS ATEASQYQF LACPGTDE K 110
HEQEFYTVWPHSALQK IGFFFYQGKTVTSLGNYYTVASQTVT 200
UYCHNSNH FHTNHEVDS IEPFSGQK TVEPEEFGT 250
LSKLSTDTP ITTVVQGQOS KGQVRWYQVTVQWamide PFS 300
RYSVPTQYGMKPL QRQQPSQG QPSQPSQG 350
LEQKQGDTH NQVQKLV QGGRGTVLQ YVSGGEERQ IEFYQGKTVTSLGNYYTVASQTVT 400
OSPLEXGRA TVDPSGQK QPSQPSQG KPSVAPYV 5G

Light chain/Chaine légère/Cadena ligera

ELVTQSFAT DSSIEQGET DSSIEQGET OQEEPOQFEL 5G
LYTIAADYIQPQGDS SIEQGET DSSIEQGET OQEEPOQFEL 100
TSGQJQOQD OQEEPOQFEL QPSQPSQG 150
QNSYQGDTH NQVQKLV QGGRGTVLQ YVSGGEERQ IEFYQGKTVTSLGNYYTVASQTVT 200

Post-translational modifications
Disulfide bridges locations/Positions des ponts disulfures/Puntos de disulfuro

N-glycosylation sites/Sites de N-glycosylation/Sitios de N-glicosilación

N-[3-(4-[3-[bis(2-methylpropyl)amino]propyl]piperazin-1-yl)propyl]piperazin-1-yl]benzimidazol-2-amine

ezeprogind
ezeprogind
ezeprogind

N-[3-(4-[3-[bis(2-methylpropyl)amino]propyl]piperazin-1-yl)propyl]piperazin-1-yl]benzimidazol-2-amine

N-[3-(4-[3-[bis(2-methylpropyl)amino]propyl]piperazin-1-yl)propyl]piperazin-1-yl]benzimidazol-2-amine

N-[3-(4-[3-[bis(2-methylpropyl)amino]propyl]piperazin-1-yl)propyl]piperazin-1-yl]benzimidazol-2-amine

C25H44N6

N
N
N
C
H3
H3
C
H3
N
C
H3
N
C
H3
feladilimabum #
feladilimab

immunoglobulin G4-kappa, anti-[Homo sapiens ICOS (inducible T-cell costimulator, activation-inducible lymphocyte immunomediatory molecule, AILIM, CD278)]; humanized monoclonal antibody; gamma4 heavy chain humanized (1-448) [VH (Homo sapiens IGHV1-69*04 (84.7%)-(IGHD)-IGHJ6*01 (100%)) [8.8.14] (1-121) -Homo sapiens IGHG4*01, G4v5 h P10, G4v3 CH2 E1.2 (CH1 (122-219), hinge 1-12 S10>P (229)(220-231), CH2 L1.2>E (236) (232-341), CH3 (342-446), CHS (447-448) (122-448)], (135-213')-disulfide with kappa light chain humanized (1'-213') [V-KAPPA (Homo sapiens IGKV3-11*01 (85.3%) -IGKJ2*01 (100%)) [5.3.9] (1'-106') -Homo sapiens IGKC*01 (100%), Km3 A45.1 (152), V101 (190) (107'-213')]; dimer (227-227'':230-230'')-bisdisulfide, produced in Chinese hamster ovary (CHO) cells, glycoform alpha

féladilimab

immunoglobuline G4-kappa, anti-[Homo sapiens ICOS (costimulateur inducible du lymphocyte T, molécule immunomédiateur lymphocytaire inducible par activation, AILIM, CD278)]; anticorps monoclonal humanisé; chaîne lourde gamma4 humanisée (1-448) [VH (Homo sapiens IGHV1-69*04 (84.7%)-(IGHD)-IGHJ6*01 (100%)) [8.8.14] (1-121) -Homo sapiens IGHG4*01, G4v5 h P10, G4v3 CH2 E1.2 (CH1 (122-219), charnière 1-12 S10>P (229) (220-231), CH2 L1.2>E (236) (232-341), CH3 (342-446), CHS (447-448) (122-448)], (135-213')-disulfure avec la chaîne légère kappa humanisée (1'-213') [V-KAPPA (Homo sapiens IGKV3-11*01 (85.3%) -IGKJ2*01 (100%)) [5.3.9] (1'-106') -Homo sapiens IGKC*01 (100%), Km3 A45.1 (152), V101 (190) (107'-213')]; dimère (227-227'':230-230'')-bisdisulfure, produit dans des cellules ovariennes de hamster chinois (CHO), glycoforme alfa

feladilimab

imunoglobulina G4-kappa, anti-[Homo sapiens ICOS (coestimulador inducible del linfocito T, molécula immunomediadora linfocitaria inducible para activación, AILIM, CD278)]; anticuerpo monoclonal humanizado; cadena pesada gamma4 humanizada (1-448) [VH (Homo sapiens IGHV1-69*04 (84.7%)-(IGHD)-IGHJ6*01 (100%)) [8.8.14] (1-121) -Homo sapiens IGHG4*01, G4v5 h P10, G4v3 CH2 E1.2 (CH1 (122-219), bisagra 1-12 S10>P (229) (220-231), CH2 L1.2>E (236) (232-341), CH3 (342-446), CHS (447-448) (122-448)], (135-213')-disulfuro con la cadena ligera kappa humanizada (1'-213') [V-KAPPA (Homo sapiens IGKV3-11*01 (85.3%) -IGKJ2*01 (100%)) [5.3.9] (1'-106') -Homo sapiens IGKC*01 (100%), Km3 A45.1 (152), V101 (190) (107'-213')]; dímero (227-227'':230-230'')-bisdisulfuro, producido por células ováricas de hamster chino (CHO), forma glicosilada alfa
**Recommended INN: List 84**

**WHO Drug Information, Vol. 34, No. 3, 2020**

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**felzartamab**

immunoglobulin G1-lambda, anti-[*Homo sapiens* CD38 (ADP-ribosyl cyclase 1, cyclic ADP-ribose hydrolase 1, cADPr hydrolase 1, T10)], humanized monoclonal antibody;

gamma1 heavy chain (1-450) [VH (*Homo sapiens* IGVH3-30*01 (90.8%) -IGHD -IGHJ4*01 (92.9%))]

CDR-IMGT [8.8.13] (26-33.51-58.97-109) (1-120) - *Homo sapiens* IGGH1*03 (100%) G1m3, nG1m1 (CH1 R120 (217) (121-218), hinge 1-15 (219-233), CH2 (234-343), CH3 E12 (359), M14 (361) (344-448), CHS (449-450)) (121-450), (223-212')-disulfide with lambda light chain (1-213', 1-213") [V-LAMBDa (*Homo sapiens* IGLV3-1*01 (84.1%) -IGLJ3*02 (100%))]

CDR-IMGT [6.3.10] (26-31.49-51.88-97) (1-107") - *Homo sapiens* IGLC2*01 (100%) (108'-213’)

dimer (229-229":232-232")-bisdisulfide, produced in human cell line PER.C6, glycoform alfa

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**felzartamab**

immunoglobuline G1-lambda, anti-[*Homo sapiens* CD38 (ADP-ribosyl cyclase 1, cyclic ADP-ribose hydrolase 1, cADPr hydrolase 1, T10)], anticorps monoclonal humanisé;

chaîne lourde gamma1 (1-450) [VH (*Homo sapiens* IGVH3-30*01 (90.8%) -IGHD -IGHJ4*01 (92.9%))]

CDR-IMGT [8.8.13] (26-33.51-58.97-109) (1-120) - *Homo sapiens* IGGH1*03 (100%) G1m3, nG1m1 (CH1 R120 (217) (121-218), charnière 1-15 (219-233), CH2 (234-343), CH3 E12 (359), M14 (361) (344-448), CHS (449-450)) (121-450), (223-212")-disulfide avec la chaîne légère lambda (1-213") [V-LAMBDa (*Homo sapiens* IGLV3-1*01 (84.1%) -IGLJ3*02 (100%))]

CDR-IMGT [6.3.10] (26-31.49-51.88-97) (1-107") - *Homo sapiens* IGLC2*01 (100%) (108'-213’)

dimère (229-229":232-232")-bisdisulfure, produite dans des cellules humaines PER.C6, glycoforme alfa
felzartamab

inmunoglobulina G1-lambda, anti-[*Homo sapiens* CD38 (ADP-ribosil ciclasa 1, ADP-riboza cíclica hidrolasa 1, cADPr hidrolasa 1, T10)], anticuerpo monoclonal humanizado; cadena pesada gamma1 (1-450) [VH (*Homo sapiens* IGHV3-30*01 (90.8%) -IGHD) - IGHJ4*01 (92.9%)) CDR-IMGT [8.8.13] (26-33.51-58.97-109) (1-120) -*Homo sapiens* IGHG1*03 (100%) G1m3, nG1m1 (CH1 R120 (217) (121-218), disulfuro con la cadena ligera lambda (1-121)*] [V-LAMBDA (*Homo sapiens* IGLV3-1*01 (84.1%) -IGLJ3*02 (100%)) CDR-IMGT [6.3.10] (26-31.49-51.88-97) (1-107) -*Homo sapiens* IGLC2*01 (100%) (108'-213')] dimero (229-229*:232-232*)-bisdisulfuro, producida por células humanas PER.C6, glicofora alfa

**Heavy chain / Chaîne lourde / Cadena pesada**

QVQLVESGGG LVQPGGSLRL SCAASGFTFS SYYMNWVRQA PGKGLENVSG 50
ISGDPSNTYY ASSVKRQFTI SRQSKNTLY LMQLSLRAED TAVYCCAROL 100
PLVTGCGYW QCGGLVTYES ASTSQPSFFP LAPSEQKSTG CTAALGCLVK 150
DVYPFVPVPS RWSIQALTSG HFHVVQGLRS GLXELSSVTV VPSSELGQTD 200
YICGWKNPXS NTRIVNKKVEP KSCMTTHCPP PCAPRKLPLL PGVFLPPFKP 250
KEIHNISSTPV ETVCCGVIVDS HEDQVFKPNH YVQCQFIMANH KTPKREGQYN 300
STRYYVLVT VLIQNHNGGX SYCRRKVNKA LARFMPRTS KAMSQHPFEO 350
VTLPDRSSRE MTRKOQLTCL LGCVFQPSDI AVEKHEMSSQP ENRYKTPFFPV 400
LSSDGGFLY SKLTVKRSWM QQQVVFICSCV MHEAILNHYT QXSLSLSPGK 450

**Light chain / Chaîne légère / Cadena ligera**

DIELTQPPSV SVAPQGTARI ECSCGNHRRY YYVYWQQKFG QAPVLLYIYG 50
SKRPSGIPER FSGSNSGNTA TLTISGTQAE DEADYYCQTY TGGASLVFGG 100
GTKLTVLQGF KAAPVLYLFP FSEELQANK ATLVCLISDF YPGAVTVAWK 150
STVEKTVAPT ECS 213

**Post-translational modifications**

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro

*Intra-H (C23-C104) 22-96 147-203 264-324 370-428* 22''-96'' 147''-203'' 264''-324'' 370''-428''

*Intra-L (C23-C104) 22'-87' 135'-194' 22'''-87''' 135'''-194'''

*Inter-H-L (h 5-CL 126) 223-212' 223''-212''

*Inter-H-H (h 11, h14) 229-229' 232-232''

**N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación**

H CH2 N84.4: 300, 300''

Fucosylated complex bi-antennary PER.C6-type glycans / glycanes de type PER.C6 bi-antennaires complexes fucosylés / glicanos de tipo PER.C6 bi-antenariaos complejos fucosilados

**filapixantum**

**filapixant**

3-(((2R)-4-methylmorpholin-2-yl)methoxy)-5-(5-methyl-1,3-thiazol-2-yl)-N-(((1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl)benzamide

**filapixant**

3-(((2R)-4-méthylmorpholin-2-yl)méthoxy)-5-(5-méthyl-1,3-thiazol-2-yl)-N-(((1R)-1-[2-(trifluorométhyl)pyrimidin-5-yl]éthyl)benzamide

**filapixant**

3-(((2R)-4-metilmorfolin-2-il)matioxi)-5-(5-metil-1,3-tiazol-2-ii)-N-((1R)-1-[2-(trifluorometil)pirimidin-5-il]etil)benzamida

C_{26}H_{26}F_{3}N_{5}O_{3}S
**fosciclopiroxum**

fosciclopirox  
[(6-cyclohexyl-4-methyl-2-oxopyridin-1(2\(H\))-yl)oxy]methyl dihydrogen phosphate

fosciclopirox  
dihydrogénophosphate de [(6-cyclohexyl-4-méthyl-2-oxopyridin-1(2\(H\))-yl)oxy]méthyle

fosciclopirox  
dihidrogenofosfato de [(6-ciclohexil-4-metil-2-oxopiridin-1(2\(H\))-il)oxi]metilo

\[C_{13}H_{20}NO_6P\]

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**fosifidancitinibum**

fosifidancitinib  
(5-[[2-(4-fluoro-3-methoxy-5-methylanilino)-5-methylpyrimidin-4-yl]amino]-2-oxo-1,3-benzoxazol-3(2\(H\))-yl)methyl dihydrogen phosphate

fosifidancitinib  
dihydrogénophosphate de (5-[[2-(4-fluoro-3-methoxy-5-methylanilino)-5-methylpyrimidin-4-yl]amino]-2-oxo-1,3-benzoxazol-3(2\(H\))-yl)méthyle

fosifidancitinib  
dihidrogenofosfato de (5-[[2-(4-fluoro-5-metilanilino-3-metoxi)-5-metilpirimidin-4-il]amino]-2-oxo-1,3-benzoxazol-3(2\(H\))-il)metilo

\[C_{21}H_{21}FN_5O_7P\]

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**genisteinum**

genistein  
5,7-dihydroxy-3-(4-hydroxyphenyl)-4\(H\)-chromen-4-one

génistéine  
5,7-dihydroxy-3-(4-hydroxyphényl)-4\(H\)-chromén-4-one

genisteína  
5,7-dihidroxi-3-(4-hidroxifenil)-4\(H\)-cromen-4-ona

\[C_{15}H_{10}O_5\]
giloralimabum

Giloralimab immunoglobulin G1-kappa, anti-[*Homo sapiens* CD40 (tumor necrosis factor receptor superfamily member 5, TNFRSF5)], monoclonal antibody;
gamma1 heavy chain (1-442) [VF (*Homo sapiens* IGHV4-59*01 (88.8%) -IGHD -IGHJ4*01 (85.7%))]
CDR-IMGT [9.7.5] (26-34.52-58.97-101) (1-112) -
*Homo sapiens* IGHH1*03v, G1m3>G1m17, nG1m1
(CH1 R120>K (209) (113-210), hinge 1-15 (211-225),
CH2 V37>E (268) (226-335), CH3 E12 (351), M14
(353) (336-440), CHS (441-442)) (113-442), (215-
219')-disulfide with kappa light chain (1'-219') [V-
KAPPA (*Mus musculus* IGKV1-122*01 (89.0%) -
IGKJ4*01 (91.7%)/*Homo sapiens* IGKV2-29*02
(86.0%)-IGKJ2*02 (100%)) CDR-IMGT [11.3.9] (27-
37.55-57.94-102) (1'-112) -*Homo sapiens* IGKC*01
(100%) Km3 A45.1 (158), V101 (196) (113'-219');
dimer (221-221*:224-224*)-bisdisulfide

giloralimab

Giloralimab immunoglobulin G1-kappa, anti-[*Homo sapiens* CD40 (membre 5 de la superfamille des récepteurs du TNF, TNFRSF5)], anticorps monoclonal;
chaîne lourde gamma1 (1-442) [VF (*Homo sapiens* 
IGHV4-59*01 (88.8%) -IGHD -IGHJ4*01 (85.7%))]
CDR-IMGT [9.7.5] (26-34.52-58.97-101) (1-112) -
*Homo sapiens* IGHH1*03v, G1m3>G1m17, nG1m1
(CH1 R120>K (209) (113-210), charnière 1-15 (211-
225), CH2 V37>E (268) (226-335), CH3 E12 (351),
M14 (353) (336-440), CHS (441-442)) (113-442),
(215-219')-disulfure avec la chaîne légère kappa (1'-
219') [V-KAPPA (*Mus musculus* IGKV1-122*01 (89.0%)
-IGKJ4*01 (91.7%)/*Homo sapiens* IGKV2-29*02
(86.0%)-IGKJ2*02 (100%)) CDR-IMGT [11.3.9] (27-
37.55-57.94-102) (1'-112) -*Homo sapiens* IGKC*01
(100%) Km3 A45.1 (158), V101 (196) (113'-219');
dimère (221-221*:224-224*)-bisdisulfure

giloralimab

Giloralimab inmunoglobulina G1-kappa, anti-[*Homo sapiens* CD40 (miembro 5 de la superfamilia de los receptores del TNF, TNFRSF5)], anticuerpo monoclonal;
cadena pesada gamma1 (1-442) [VF (*Homo sapiens* 
IGHV4-59*01 (88.8%) -IGHD -IGHJ4*01 (85.7%))]
CDR-IMGT [9.7.5] (26-34.52-58.97-101) (1-112) -
*Homo sapiens* IGHH1*03v, G1m3>G1m17, nG1m1
(CH1 R120>K (209) (113-210), bisagra 1-15 (211-
225), CH2 V37>E (268) (226-335), CH3 E12 (351),
M14 (353) (336-440), CHS (441-442)) (113-442),
(215-219')-disulfuro con la cadena ligera kappa (1'-
219') [V-KAPPA (*Mus musculus* IGKV1-122*01 (89.0%)
-IGKJ4*01 (91.7%)/*Homo sapiens* IGKV2-29*02
(86.0%)-IGKJ2*02 (100%)) CDR-IMGT [11.3.9] (27-
37.55-57.94-102) (1'-112) -*Homo sapiens* IGKC*01
(100%) Km3 A45.1 (158), V101 (196) (113'-219');
dímero (221-221*:224-224*)-bisdisulfuro
giredestrantum

giredestrant

3-[(1R,3R)-1-(2,6-difluoro-4-[(1-(3-fluoropropyl)azetidin-3-yl]amino)phenyl)-3-methyl-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indol-2-yl]-2,2-difluoropropan-1-ol

girédestrant

3-[(1R,3R)-1-(2,6-difluoro-4-[(1-(3-fluoropropyl)azetidin-3-yl]amino)phenyl)-3-méthyl-1,3,4,9-tétrahydro-2H-pyrido[3,4-b]indol-2-yl]-2,2-difluoropropan-1-ol

giredestrant

3-[(1R,3R)-1-(2,6-difluoro-4-[(1-(3-fluoropropyl)azetidin-3-yl]amino)fenil)-3-méthyl-1,3,4,9-tétrahidro-2H-pirido[3,4-b]indol-2-il]-2,2-difluoropropan-1-ol

C_{27}H_{31}F_{5}N_{4}O
icenticaftorum
icenticaftor 3-amino-6-methoxy-N-[(2S)-3,3,3-trifluoro-2-hydroxy-2-methylpropyl]-5-(trifluoromethyl)pyridine-2-carboxamide

icenticaftor 3-amino-6-méthoxy-N-[(2S)-3,3,3-trifluoro-2-hydroxy-2-méthylpropyl]-5-(trifluorométhyl)pyridine-2-carboxamide

icenticaftor 3-amino-6-métoxi-N-[(2S)-3,3,3-trifluoro-2-hidroxi-2-métilpropil]-5-(trifluorometil)píridina-2-carboxamida

icerguastatum
icerguastat (2E)-2-[(2-chlorophenyl)methylidene]hydrazine-1-carboximidamide

icerguastat (2E)-2-[(2-chlorophényl)méthylidène]hydrazine-1-carboximidamide

icerguastat (2E)-2-[(2-clorofenil)metilideno]hidrazina-1-carboximidamida

idetrexedum
idetrexed N-(4-[(6S)-2-(hydroxymethyl)-4-oxo-4,6,7,8-tetrahydro-1H-cyclopenta[g]quinazolin-6-yl]prop-2-yn-1-yl)amino)benzoyl)-L-γ-glutamyl-D-glutamic acid

idétrexed acide N-(4-[[6S]-2-(hydroxyméthyl)-4-oxo-4,6,7,8-tétrahydro-1H-cyclopenta[g]quinazolin-6-yl]prop-2-yn-1-yl)amino)benzoïl)-L-γ-glutamyl-D-glutamic acid

idetrexed ácido N-(4-[[6S]-2-(hidroximetil)-4-oxo-4,6,7,8-tetrahidro-1H-ciclopenta[g]quinazolin-6-il]prop-2-in-1-il)amino)benzoil)-L-γ-glutamili-D-glutámico

idetrexed ácido N-(4-[[6S]-2-(hidroximetil)-4-oxo-4,6,7,8-tetrahidro-1H-ciclopenta[g]quinazolin-6-il]prop-2-2-in-1-il)amino)benzoil)-L-γ-glutamili-D-glutámico
**ifidancitinibum**

ifidancitinib

5-{{2-(4-fluoro-3-methoxy-5-methylanilino)-5-methylpyrimidin-4-yl}amino}-1,3-benzoaxazol-2(3H)-one

\[C_{20}H_{18}FN_{5}O_{3}\]

**imaradentantum**

imaradentant

6-(2-chloro-6-methylpyridin-4-yl)-5-(4-fluorophenyl)-1,2,4-triazin-3-amine

\[C_{15}H_{11}ClFN_{5}\]

**inavolisibum**

inavolisib

(2S)-2-{{2-[4(S)-4-(difluoromethyl)-2-oxo-1,3-oxazolidin-3-yl]-5,6-dihydroimidazo[1,2-d][1,4]benzoxazepin-9-yl}amino}propanamide

\[(2S)-2-{{2-[4(S)-4-(difluoromethyl)-2-oxo-1,3-oxazolidin-3-yl]-5,6-dihydroimidazo[1,2-d][1,4]benzoxazépin-9-yl}amino}propanamida\]
insulinum efsitorum alfa #
insulin efsitora alfa

human insulin B-chain (1-30) variant (Y16>E, F25>H, T27>G, P29>G, K30>G) fused via a G2SG4 peptide linker (31-37) to human insulin A-chain (38-58) variant (I10>T47, Y14>D51, N21>G58) and via a (G4Q)3G5 peptide linker (59-78) to a human immunoglobulin G2 C-terminal K>del Fc fragment (79-299), dimer (80-80’:83-83’)-bisdisulfide, produced in Chinese hamster ovary (CHO) cells, glycoform alfa

insuline efsitora alfa

cadena B de la insulina humana (1-30) variante (Y16>E, F25>H, T27>G, P29>G, K30>G) fusionada a través de un péptido que se une G2SG4 (31-37) a la cadena A de la insulina humana (38-58) variante (I10>T47, Y14>D51, N21>G58) y a través de un péptido que se une (G4Q)3G5 (59-78) al fragmento Fc C-terminal K>del de la inmunoglobulina G2 humana (IgG2) (79-299), dimérim (80-80’:83-83’)-bisdisulfuro, producido por las células ováricas de hamster chino (CHO), glicoforma alfa

insulina efsitora alfa

cadena B de la insulina humana (1-30) variante (Y16>E, F25>H, T27>G, P29>G, K30>G) fusionada a través de un péptido que se une G2SG4 (31-37) a la cadena A de la insulina humana (38-58) variante (I10>T47, Y14>D51, N21>G58) y a través de un péptido que se une (G4Q)3G5 (59-78) al fragmento Fc C-terminal K>del de la inmunoglobulina G2 humana (IgG2) (79-299), dímero (80-80’:83-83’)-bisdisulfuro, producido por las células ováricas de hamster chino (CHO), glicoforma alfa

iptacopanum
iptacopan

4-((2S,4S)-4-ethoxy-1-{(5-methoxy-7-methyl-1H-indol-4-yl)methyl}piperidin-2-yl)benzoic acid
iptacopan

iptacopán

iptacopán ácido 4-{(2S,4S)-4-éthoxy-1-{(7-metil-5-metoxi-1H-indol-4-il)méthyl|piperidin-2-il}benzoico

C₂₅H₃₀N₂O₄

isecarosmabum # isecarosmab

isecarosmab

isécarosmab

isecarosmab

immunoglobulin single chain VH-VH', anti-[Homo sapiens ADAMTSL5 (ADAMTS like 5, THSD6, thrombospondin type I domain 6)] and anti-[Homo sapiens ALB (albumin, human serum albumin, HSA)], Lama glama and humanized monoclonal antibody, bispecific bivalent; sc VH-VH’ (1-275) [Lama glama VH anti-ADAMTSL5 (Lama glama IGHV3S1*01 (81.4%) -IGHD) -IGHJ2*01 (100%)/Homo sapiens IGHV3-23*04 (80.2%) -(IGHD) -IGHJ1*01 (100%)] [8.8.17] (1-124) -35-mer (GGGGS)₇ linker (125-159)-humanized VH anti-ALB (Homo sapiens IGH3V-23*04 (87.5%) -(IGHD) -IGHJ1*01 (100%)) [8.8.8] (160-275), produced in Pichia pastoris yeast, non-glycosylated

immunoglobuline single chaîne VH-VH’, anti-[Homo sapiens ADAMTSL5 (ADAMTS like 5, thrombospondine type I domaine 6)] et anti-[Homo sapiens ALB (albumine, sérum albumine humaine, SAH)], anticorps monoclonal Lama glama et humanisé, bispécifique bivalent; sc VH-VH’ (1-275) [Lama glama VH anti-ADAMTSL5 (Lama glama IGHV3S1*01 (81.4%) -IGHD) -IGHJ2*01 (100%)/Homo sapiens IGHV3-23*04 (80.2%) -(IGHD) -IGHJ1*01 (100%)] [8.8.17] (1-124) -35-mer (GGGGS)₇ linker (125-159)-VH humanisé anti-ALB (Homo sapiens IGH3V-23*04 (87.5%) -(IGHD) -IGHJ1*01 (100%)) [8.8.8] (160-275), produit dans la levure Pichia pastoris, non-glycosylé

immunoglobulina cadena simple VH-VH’, anti-[Homo sapiens ADAMTSL5 (ADAMTS like 5, trombospondina tipo I dominio 6)] y anti-[Homo sapiens ALB (álbume, sero albúmina humana, SAH)], anticuerpo monoclonal Lama glama y humanizado, biespecífico bivalente; sc VH-VH’ (1-275) [Lama glama VH anti-ADAMTSL5 (Lama glama IGHV3S1*01 (81.4%) -IGHD) -IGHJ2*01 (100%)/Homo sapiens IGH3V-23*04 (80.2%) -(IGHD) -IGHJ1*01 (100%)] [8.8.17] (1-124) -linker 35-mer (GGGGS)₇ (125-159)-VH humanizado anti-ALB (Homo sapiens IGH3V-23*04 (87.5%) -(IGHD) -IGHJ1*01 (100%)) [8.8.8] (160-275), producido en la levadura Pichia pastoris, no glicosilado
itacnosertib

N^4-[(2,2'-bipyridin)-3-yl]-N^2-[3-methoxy-4-(4-methylpiperazin-1-yl)phenyl]pyrimidine-2,4-diamine

C_{26}H_{28}N_{8}O

itacnosertib

N^4-[(2,2'-bipyridin)-3-yl]-N^2-[3-méthoxy-4-(4-méthylpipérazin-1-yl)phényl]pyrimidine-2,4-diamine

itepekimab

immunoglobulin G4-kappa, anti-[Homo sapiens IL33 (interleukin 33, interleukin-1 family member 11, IL1F11, nuclear factor for high endothelial venules, NF-HEV)], monoclonal antibody; gamma4 heavy chain (1-449) [VH (Homo sapiens IGHV3-23*04 (88.8%)-IGHD -IGHJ6*03 (91.0%)) [8.8.15] (1-122) -Homo sapiens IGHG4*01, G4v5 h P10 (CH1 (123-220), hinge 1-12 S10=P (230)(221-232), CH2 (233-342), CH3 (343-447), CHS (448-449)) (123-449)], (136-214')-disulfide with kappa light chain Homo sapiens (1'-214') [V-KAPPA (Homo sapiens IGKV1-12*01 (96.8%)-IGKJ5*01 (100%)) [6.3.9] (1'-107') -Homo sapiens IGKC*01 (100%), Km3 A45.1 (153), V101 (191) (108'-214')]; dimer (228-228'':231-231'')-bisdisulfide, produced in Chinese hamster ovary (CHO) cells, glycoform alfa

itpékimab

immunoglobuline G4-kappa, anti-[Homo sapiens IL33 (interleukine 33, membre 11 de la famille 1 d’interleukines, IL1F11, facteur nucléaire des veines à haut endothélium, NF-HEV)], anticorps monoclonal; chaîne lourde gamma4 (1-449) [VH (Homo sapiens IGHV3-23*04 (88.8%)-IGHD -IGHJ6*03 (91.0%)) [8.8.15] (1-122) -Homo sapiens IGHG4*01, G4v5 h P10 (CH1 (123-220), charnière 1-12 S10=P (230)(221-232), CH2 (233-342), CH3 (343-447), CHS (448-449)) (123-449)], (136-214')-disulfure avec la chaîne légère kappa (1'-214') [V-KAPPA (Homo sapiens IGKV1-12*01 (96.8%)-IGKJ5*01 (100%)) [6.3.9] (1'-107') -Homo sapiens IGKC*01 (100%), Km3 A45.1 (153), V101 (191) (108'-214')]; dimère (228-228'':231-231'')-bisdisulfure, produit dans des cellules ovariennes de hamster chinois (CHO), glycoforme alfa
itepekimab

inmunoglobulina G4-kappa, anti-{Homo sapiens} IL33 ( interleukina 33, miembro 11 de la familia 1 de interleukinas, IL1F11, factor nuclear de las vénulas del endotelio alto, NF-HEV), anticuerpo monoclonal; cadena pesada gamma4 (1-449) [Homo sapiens] IGHV3-23*04 (88.8%) - (IGHD) - IGHJ6*03 (91.0%) [8.8.15] (1-122) - {Homo sapiens} IGHG4*01, G4v5 h P10 (CH1 (123-220), bisagra 1-12 S10>P (230)(221-232), CH2 (233-342), CH3 (343-447), CHS (448-449)) (123-449), (136-214")-disulfuro con la cadena ligera kappa (1-214") [V-KAPPA (Homo sapiens IGKV1-12*01 (96.8%)) - IGKV5*01 (100%)][6.3.9] (1-107) - {Homo sapiens} IGKC*01 (100%), Km3 A45.1 (153), V101 (191) (108-214")];

dímero (228-228" : 231-231")-bisdisulfuro, producido por células óvicas de hamster chino (CHO), forma glicosilada alfa

Heavy chain / Cadenas pesadas / Cadenas gamma4
EVQDLREGN LEQPGLLQL SIACSTPAFTY RENPNSRAW FENGSGS 5G
ISGSGQRTY TDYQFRRTI SPSGNGLYLD LQGLSLQEDT PTVYSAG 100
TVDCYTGQK VQMDTTRG WSGHIKIV SGHLGQGTV VTVSGGT 200
KTVHLCRTK KTVHLCRTK KTVHLCRTK KTVHLCRTK KTVHLCRTK 250
TVDCYTGQK VQMDTTRG WSGHIKIV SGHLGQGTV VTVSGGT 300
TVDCYTGQK VQMDTTRG WSGHIKIV SGHLGQGTV VTVSGGT 350
KTVHLCRTK KTVHLCRTK KTVHLCRTK KTVHLCRTK KTVHLCRTK 400
EVQDLREGN LEQPGLLQL SIACSTPAFTY RENPNSRAW FENGSGS 449

Light chain / Cadenas ligeras / Cadenas kappa
EVQDLREGN LEQPGLLQL SIACSTPAFTY RENPNSRAW FENGSGS 5C
ISGSGQRTY TDYQFRRTI SPSGNGLYLD LQGLSLQEDT PTVYSAG 100
TVDCYTGQK VQMDTTRG WSGHIKIV SGHLGQGTV VTVSGGT 200
KTVHLCRTK KTVHLCRTK KTVHLCRTK KTVHLCRTK KTVHLCRTK 250
TVDCYTGQK VQMDTTRG WSGHIKIV SGHLGQGTV VTVSGGT 300
TVDCYTGQK VQMDTTRG WSGHIKIV SGHLGQGTV VTVSGGT 350
KTVHLCRTK KTVHLCRTK KTVHLCRTK KTVHLCRTK KTVHLCRTK 400
EVQDLREGN LEQPGLLQL SIACSTPAFTY RENPNSRAW FENGSGS 449

Post-translational modifications
Disulfide bridge location / Posiciones de los puentes disulfuro
Intra-(C23-C104) 22.96 149-205 263-323 369-427
22.96 149-205 263-323 369-427
Intra-(C23-C104) 23.88 134-194
23.88 134-194
Intra-(C19-C12b) 136-214
136-214
Intra-(b8,b11) 278-288
278-288
231-231

N-glycosylation sites / Sitios de N-glicosilación / Posiciones de N-glicosilación
HCH2N84.4: 299,299

Facetylated complex bio-antígeno CHO: pepsína / glicáceas / glicoproteínas / CHO/antígenos complejos facetylados / glicáceas / glicoproteínas / CHO/antígenos complejos facetylados
C-terminal lysine clipping / C-terminal clipping
HCHSK2: 449,449
izokibepum #

izokibep  fusion protein composed of 3 binding domains consisting of three-alpha-helix motifs, each derived from the immunoglobulin (Ig)-binding Z-domain of staphylococcal protein A (SpA), engineered for binding to two homodimer subunits of human interleukin 17A (IL17A) with the two identical N- and C-terminal domains (1-58, 116-173) and to the domain II of human serum albumin (HSA) with the central domain (59-110), connected via a G₄S peptide linker (111-115);

[IL17A-binding engineered SpA peptide (1-58)]-[HSA-binding engineered SpA peptide (59-110)]-[G₄S linker (111-115)]-[IL17A-binding engineered SpA peptide (116-173)] fusion protein; produced in Escherichia coli

izokibep  protéine de fusion composée de 3 domaines liants, chacun consistant en un motif à 3 hélices alpha dérivé du domaine Z de la protéine staphylocoque A (SpA) se liant à l'immunoglobuline (Ig), mis au point pour se lier aux deux homodimères des sous-unités de l'interleukine 17A humaine (IL17A) avec les deux domaines N- et C-terminaux identiques (1-58, 116-173), et au domaine II de l'albumine sérique humaine (ASH, HSA) avec le domaine central (59-110), connecté via un peptide liant G₄S (111-115);

protéine de fusion [peptide SpA mis au point pour se lier à l'IL17A (1-58)]-[peptide SpA mis au point pour se lier au HSA (59-110)]-[peptide liant G₄S (111-115)]-[peptide SpA mis au point pour se lier à l'IL17A (116-173)]; produite par Escherichia coli

izokibep  proteína de fusión compuesta de 3 dominios de unión, cada uno consistente en un motivo con 3 hélices alfa derivado del dominio Z de la proteína estafilocócica A (SpA) que se une a la inmunoglobulina (Ig), diseñado para unirse a los dos homodímeros de las sub- unidades de la interleukina 17A humana (IL17A) con los dos dominios N- y C-terminal idénticos (1-58, 116-173), y con el dominio II de la albúmina sérica humana (ASH, HSA) con el dominio central (59-110), conectado a través de un péptido que se une a G₄S (111-115);

proteína de fusión [péptido SpA diseñado para unirse a la IL17A (1-58)]-[péptido SpA diseñado para unirse al HSA (59-110)]-[G₄S linker (111-115)]-[péptido SpA diseñado para unirse a la IL17A (116-173)]; producida por Escherichia coli
lazuvapagon

(4S)-N-[(2S)-1-hydroxypropan-2-yl]-methyl-1-[2-methyl-4-(3-methyl-1H-pyrazol-1-yl)benzoyl]-2,3,4,5-tetrahydro-1H-1-benzazepine-4-carboxamide

lecanemab

immunoglobulin G1-kappa, anti-[Homo sapiens APP (amyloid beta A4 precursor protein)] soluble beta-amyloid protofibril, monoclonal antibody;

gamma1 heavy chain (1-454) [VH (Homo sapiens IGHV3-48*01 (89.8%) -IGHD -IGHJ4*01 (92.3%)) CDR-IMGT [8.8.17] (26-33.51-58.97-113) (1-124) -Homo sapiens IGHG1*03 (100%) G1m3, nG1m1 (CH1 R120 (221) (125-222), hinge 1-15 (223-237), CH2 (238-347), CH3 E12 (363), M14 (365) (348-452), CHS (453-454)) (125-454)], (227-219')-disulfide with kappa light chain (1'-219') [V-KAPPA (Mus musculus IGKV1-117*01 (91%) -IGKJ1*02 (90.9%)/Homo sapiens IGKV2-30*02 (84.0%) -IGKJ2*01 (90.9%)) CDR-IMGT [11.3.9] (27-37.55-57.94-102) (1'-112') -Homo sapiens IGKC*01 (100%), Km3 A45.1 (158), V101 (196) (227-219')]; dimer (233-233'':236-236'')-bisdisulfide, produced in Chinese hamster ovary (CHO) cells, glycoform alfa
ilecanemab

inmunoglobulina G1-kappa, anti-[Homo sapiens APP (proteína precursuro amiloide beta A4)] protobifila beta amiloide soluble, anticuerpo monoclonal;
cadena pesada gamma1 (1-454) [VH (Homo sapiens IGHV3-48*01 (89.8%)-(IGHD) -IGHJ4*01 (92.3%)) CDR-IMGT [8.8.2] (26-33.53-57.94-102) (1-112)] -Homo sapiens IGHG1*03 (100%) G1m3, nG1m1 (CH1 R120 (221) (125-222), bisagra 1-15 (223-237), CH2 (238-347), CH3 E12 (363), M14 (365) (348-452), CHS (453-454)], (227-219)-disulfuro con la cadena ligera kappa (1-219) [V-KAPPA (Mus musculus IGKV1-117*01 (91%)-IGKJ1*02 (90.9%)/Homo sapiens IGKV2-30*02 (84.0%)-IGKJ2*01 (90.9%)) CDR-IMGT [11.3.9] (27-37.55-57.94-102) (1-112)] -Homo sapiens IGKC*01 (100%), Km3 A45.1 (158), V101 (196) (227-219);
dímero (233-233";236-236")-bisdisulfure, produite dans des cellules ovarienes de hamster chinois (CHO), glycoforme alfa

lorpucitinib

lorpucitinib

2-{[trans-4-(cyanomethyl)cyclohexyl]-1,6-dihydroimidazol[4,5-d]pyrrolo[2,3-b]pyridin-2-yl}-N-(2-hydroxy-2-methylpropyl)acetamide

lorpucitinib

2-{[trans-4-(cyanomethyl)cyclohexyl]-1,6-dihydroimidazol[4,5-d]pyrrolo[2,3-b]pyridin-2-yl}-N-(2-hydroxy-2-methylpropyl)acetamide

lorpucitinib

2-{[trans-4-(cyanomethyl)cyclohexyl]-1,6-dihydroimidazol[4,5-d]pyrrolo[2,3-b]pyridin-2-yl}-N-(2-hydroxy-2-methylpropyl)acetamide
luvadaxistatum
4-hydroxy-6-{2-[4-(trifluoromethyl)phenyl]ethyl}pyridazin-3(2H)-one

miptenalimab
immunoglobulin G4-kappa, anti-[Homo sapiens LAG3 (lymphocyte activating 3, lymphocyte-activation 3, CD223)], monoclonal antibody; gamma4 heavy chain (1-448) [VH (Homo sapiens IGHV3-33*01 (77.0%) -IGHD -IGHJ4*01 (93.3%)) [10.7.14] (1-122) - Homo sapiens IGHG4*01, G4v5 h P10 (CH1 (123-220), hinge 1-12 S10>P (230) (221-232), CH2 (233-342), CH3 (343-447), CHS K2>del (448)) (123-448)], (136-214')-disulfide with kappa light chain (1'-214') [V-KAPPA (Mus musculus IGGV6-17 (85.3%) -IGKJ2*03 (90.9%) Homo sapiens IGGV1-39*01 (82.1%) -IGKJ2*01 (100%)) [6.3.9] (1*-107') - Homo sapiens IGKC*01 (100%), Km3 A45.1 (153), V101 (191) (108'-214')]; dimer (228-228"-231-231")-bisdisulfide, produced in Chinese hamster ovary (CHO) cells, glycoform alfa

mipténalimab
immunoglobuline G4-kappa, anti-[Homo sapiens LAG3 (activateur 3 des lymphocytes, lymphocyte-activation 3, CD223)], anticorps monoclonal; chaîne lourde gamma4 (1-448) [VH (Homo sapiens IGHV3-33*01 (77.0%) -IGHD -IGHJ4*01 (93.3%)) [10.7.14] (1-122) - Homo sapiens IGHG4*01, G4v5 h P10 (CH1 (123-220), charnière 1-12 S10>P (230) (221-232), CH2 (233-342), CH3 (343-447), CHS K2>del (448)) (123-448)], (136-214')-disulfure avec la chaîne légère kappa (1'-214') [V-KAPPA (Mus musculus IGGV6-17 (85.3%) -IGKJ2*03 (90.9%) Homo sapiens IGGV1-39*01 (82.1%) -IGKJ2*01 (100%)) [6.3.9] (1*-107') - Homo sapiens IGKC*01 (100%), Km3 A45.1 (153), V101 (191) (108'-214')]; dimère (228-228"-231-231")-bisdisulfure, produit dans des cellules ovariennes de hamster chinois (CHO), glycoforme alfa
miptenalimab

inmunoglobulina G4-kappa, anti-[Homo sapiens LAG3 (activador 3 de los linfocitos, linfocito-activación 3, CD223)], anticuerpo monoclonal;
cadena pesada gamma4 (1-448) [IGH (Homo sapiens IGHV3-33*01 (77.0%) -IGHJ4*01 (93.3%))] [IGH4*01 (1-122) -Homo sapiens IGHG4*01, G4v5 h P10 (CH1 (123-220), bisagra 1-12 S10-P (230) (221-232), CH2 (233-342), CH3 (343-447), CHS K2>del (448))] (136-244) -disulfuro con la cadena ligera kappa (1'-214') [V-KAPPA (Mus musculus IGKV6-17 (85.3%) -IGKJ2*03 (90.9%)/Homo sapiens IGKV1-39*01 (82.1%) -IGKJ2*01 (100%)) [6.3.9] (1'-107') -Homo sapiens IGKC*01 (100%), Km3 A45.1 (153), V101 (191) (108'-214')]
dímero (228-228";231-231")-disulfuro, producido por células ováricas de hamster chino (CHO), forma glicosilada alfa

mirdametinib

N-{(2R)-2,3-dihydroxypropoxy}-3,4-difluoro-2-(2-fluoro-4-iodoanilino)benzamide
miromavimabum

miromavimab

immunoglobulin G1-kappa, anti-[rabies virus strain ERA (Evelyn-Rockitniki-Abelseth) glycoprotein ectodomain epitope G-II], *Mus musculus* monoclonal antibody;
gamma1 heavy chain *Mus musculus* (1-445) [VH (*Mus musculus* IGHV1S130*01 (93.9%) -IGHD -IGHJ1*01 (88.2%)) CDR-IMGT [8.8.14] (26-33.51-58.97-110) (1-121) -*Mus musculus* IGHG1*02 (CH1 Q100>E (199) (122-218), hinge 1-13 (219-231), CH2 K81>Q (288), I84.3>F (294) (232-338), CH3 N27>D (369) (339-443), CHS (444-445) ((122-245), (223-214))-disulfide with kappa light chain *Mus musculus* (1'-214') [V-KAPPA (*Mus musculus* IGKV6-17*01 (98.9%) -IGKJ1*02 (100%)) CDR-IMGT [6.3.9] (27-32.50-52.89-97) (1'-107') -*Mus musculus* IGKC*01 (100%) (108'-214')]; dimer (225-225':228-228':230-230')-trisdisulfide, produced in mouse myeloma cell line SP2/0-Ag14, glycoform alfa

miromavimab

immunoglobuline G1-kappa, anti-[épitope G-II de l'ectodomaine de la glycoprotéine de la souche ERA (Evelyn-Rockitniki-Abelseth) du virus de la rage], anticorps monoclonal *Mus musculus*;
chaîne lourde gamma1 *Mus musculus* (1-445) [VH (*Mus musculus* IGHV1S130*01 (93.9%) -IGHD -IGHJ1*01 (88.2%)) CDR-IMGT [8.8.14] (26-33.51-58.97-110) (1-121) -*Mus musculus* IGHG1*02 (CH1 Q100>E (199) (122-218), charnière 1-13 (219-231), CH2 K81>Q (288), I84.3>F (294) (232-338), CH3 N27>D (369) (339-443), CHS (444-445)) (122-245), (223-214')-disulfure avec la chaîne légère kappa *Mus musculus* (1'-214') [V-KAPPA (*Mus musculus* IGKV6-17*01 (98.9%) -IGKJ1*02 (100%)) CDR-IMGT [6.3.9] (27-32.50-52.89-97) (1'-107') -*Mus musculus* IGKC*01 (100%) (108'-214')]; dimère (225-225':228-228':230-230')-trisdisulfure, produite dans la lignée cellulaire de myéome murin SP2/0-Ag14, glycoforme alfa

miromavimab

inmunoglobulina G1-kappa, anti-[-epítopo G-II del ectodominio de la glicoproteína de la cepa ERA (Evelyn-Rockitniki-Abelseth) del virus de la rabia], anticuerpo monoclonal *Mus musculus*;
cadena pesada gamma1 *Mus musculus* (1-445) [VH (*Mus musculus* IGHV1S130*01 (93.9%) -IGHD -IGHJ1*01 (88.2%)) CDR-IMGT [8.8.14] (26-33.51-58.97-110) (1-121) -*Mus musculus* IGHG1*02 (CH1 Q100>E (199) (122-218), bisagra 1-13 (219-231), CH2 K81>Q (288), I84.3>F (294) (232-338), CH3 N27>D (369) (339-443), CHS (444-445)) (122-245), (223-214')-disulfuro con la cadena ligera kappa *Mus musculus* (1'-214') [V-KAPPA (*Mus musculus* IGKV6-17*01 (98.9%) -IGKJ1*02 (100%)) CDR-IMGT [6.3.9] (27-32.50-52.89-97) (1'-107') -*Mus musculus* IGKC*01 (100%) (108'-214')]; dimero (225-225':228-228':230-230')-trisdisulfuro, producida en la línea celular de mieloma murino SP2/0-Ag14, glicoforma alfa
modakafusp alfa #

**modakafusp alfa**

immunoglobulin G4-kappa, anti-[human ADP-ribosyl cyclase/cyclic ADP-ribose hydrolase 1 (EC:3.2.2.6) (ADPRC 1/cADRp hydrolase 1, cell surface antigen CD38)], humanized monoclonal antibody, fused at each C-terminus of the heavy chains (1-447, 1''-447'') to attenuated human interferon α-2b (IFNα2b) variant (K23>R470, T106>A553, A145>D592) (448-612, 448''-612'').

gamma4 heavy chain humanized fused to IFNα2b (1-612) [VH (Homo sapiens IGHV1-69-2*01 (90.7%) -(IGHD)- IGHJ4*01 (85.7%)) CDR-IMGT [8.8.13] (26-33.51-58.97-109) (1-120)-Homo sapiens IGHG4*01, G4v5 hP10 (CH1 (121-218), hinge 1-12 S10>P (228) (219-230), CH2 (231-340), CH3 (341-445), CHS (446-447))(121-447), fused to IFNα2b K23>R (470), T106>A (553), A145>D (592) (448-612),(134-214')-disulfide with kappa light chain humanized (1'-214') [V-KAPPA (Homo sapiens IGKV1-33*01 (83.2%) -IGKJ4*01 (100%)) CDR-IMGT [6.3.9] (27-32.50-52.89-97) (1'-107') -Homo sapiens IGKC*01 (100%), Km3 A45.1 (153), V101 (191) (108'-214')]; dimer (226-226'-229-229')-bisdisulfide; produced in Chinese hamster ovary (CHO) K1SV cells, glycoform alfa

modakafusp alfa

immunoglobuline G4-kappa, anti-[ADP-ribosyl cyclase/ ADP cyclique -ribose hydrolase 1 humaine (EC:3.2.2.6) (ADPRC 1/cADRp hydrolase 1, antigène de surface cellulaire CD38)], anticorps monoclonal humain fusionné à chaque partie C-terminale des chaînes lourdes (1-447, 1''-447'') à un variant (K23>R470, T106>A553, A145>D592) de l’interféron α-2b humain (IFNα2b) atténué, (448-612, 448"-612"__); chaîne lourde gamma4 humanisée fusionnée à IFNα2b (1-612) [VH (Homo sapiens IGKV1-69-2*01 (90.7%) -(IGHD)- IGHJ4*01 (85.7%)) CDR-IMGT [8.8.13] (26-33.51-58.97-109) (1-120)-Homo sapiens IGHG4*01, G4v5 hP10 (CH1 (121-218), chârnière 1-12 S10>P (228) (219-230), CH2 (231-340), CH3 (341-445), CHS (446-447))(121-447), fusionné à IFNα2b K23>R (470), T106>A (553), A145>D (592) (448-612),(134-214')-disulfide avec kappa light chain humanisée (1'-214') [V-KAPPA (Homo sapiens IGKV1-33*01 (83.2%) -IGKJ4*01 (100%)) CDR-IMGT [6.3.9] (27-32.50-52.89-97) (1'-107') -Homo sapiens IGKC*01 (100%), Km3 A45.1 (153), V101 (191) (108'-214')]; dimère (226-226"-229-229")-bisdisulfure ; produit dans des cellules ovariennes de hamster chinois (CHO) K1SV, glycoforme alfa
modakafusp alfa

inmunoglobulina G4-kappa, anti-[ADP-ribois cíclicas/ADP cíclicas -ribois hidrolasa 1 humana (EC:3.2.2.6) (ADPRC 1/cADRP hidrolasa 1, antígono de superficie celular CD38)], anticuerpo monoclonal humano fusionado a cada parte C-terminal de las cadenas pesadas (1-447, 1''-447'') a una variante (K23>R470, T106>A553, A145>D592) del interferón α-2b humano (IFNa2b) atenuado, (448-612, 448''-612''); cadena pesada gamma4 humanizada fusionada al IFNa2b (1-612) [VH (Homo sapiens IGHV1-69-2*01 (90.7%) -(IGHD) IGKJ4*01 (85.7%)) CDR-IMGT [8.6.13] (26-33.51-58.97-109) (1-20)-Homo sapiens IGHC4*01, G4v5 h P10 (Ch1 (121-218), bisagra 1-12 S10-P (228) (219-230), Ch2 (231-340), Ch3 (341-445), CHS (446-447)](121-447), fusionado con IFNa2b K23>R (470), T106>A (553), A145>D (592) (448-612).] (134-214'')-disulfuro con la cadena ligera kappa humanizada (1'-214'') [V-KAPPA (Homo sapiens IGKV1-33*01 (83.2%)-IGKJ4*01 (100%)) CDR-IMGT [6.3.9] (27-32.50-52.89-97) (1'-107') -Homo sapiens IGKC*01 (100%), Km9 A45.1 (191) (108-214)]; dímero (226-226''.229-229'')-bisdisulfuro; producido en células ováricas de hamster chino (CHO) K1SV, glicoforma α

Sequence / Séquence / Secuencia

Heavy chain / Chaîne lourde / Cadena pesada (anti-CD38 4-IFNα2b)
EVQLVQSGAE VKKPGATVKI SCKVSGYTFT DSVMNWVQQA PGKGLEWMGW 50
IDPEYGRTDV AEKFQGRVTI TADTSTDTAY MELSSLRSED TAVYYCARTK 100
YNSGYGFPYW GQGTTVTVSS ASTKGPSVFP LAPCSRSTSE STAALGCLVK 150
DYFPEPVTVS WNSALTIGSV HFFPAVLQSS GLYSLHSMVT VPPFQVPQGT 200
RYTVDKKEFS HYTKGKVYSE KYPFQCPFPC APEFLCPGSP FLFPPKPKGT 250
LMHDRFSSYT CYGGVIGOFQ PEDQFMVNYV GYKHARMTK PKEFGNQGTY 300
RVSQIGSLVR QGWNCHRFRY CFPVMKGFLS SIETSATKSA QGKFRQOVT 350
LPQGQHMKMT NVQLTCLVLR GFYPSDIAVE WESNGQPENN YKTTPPVQLG 400
DGGFYYSLYTL TDQRSRAGDES NVPSFSVMHE LALHHTQKSH LLSLGKQCDL 450
PQTSKLGRK SIEMLAVSKRM HOSPEGQERS HGRKQKARTI 500
PVHLNHQIQI FNLSTFRDSS NAAKETTLDK FYTETLYQLIN DELACVIQVQ 550
GVAEFLMKKE DISALVRKFYQ QRTLYLKEK RYFSCAMEVY RDEIMRSFSIL 600
STNQELLAS NE 612

Light chain / chaîne légère / cadena ligera
DIQMTQSPSS LSASVGDRVT ITCKASQNVD SDVDWYQQKP GKAPKLLIYK 50
ASNDYTGVPS RFSGSSGSTD FEFPFLSLQD EIDATTYQCM SWTRPRFGG 100
CTYKVQRTV TVAPSFLYFIQP SDEQKLSGTQ SVCLLIINPY PREAVQMKV 150
DQALQGNSQQ SVNTQSQKSD STYSLSTLTL LSADAHFHKR TVACEQTHQG 200
LSSQTTFSN RGEO 214

Post-translational modifications
Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro
Intra-H 22-96 147-203 261-321 367-425
22''-96'' 147''-203'' 261''-321'' 367''-425''
Intra-IFN 448-545 476-585 448''-545'' 476''-585''
Intra-L 23-88 134-194 23''-88'' 134''-194''
Intr-H-L 134-214' 134'-214''
Intr-H-H 226-226'' 229-229''

Glycosylation sites / Sites de glycosylation / Posiciones de glicosilación
H CH2 N84:4: N297, N297''
Fucosylated complex bi-antennary CHO-type glycans / Glycanes de type CHO bi-antennes complexes fucosilés / Glicanos de tipo CHO biantenarios complejos fucosilados

murizatoclaxum
murizatoclax

(13S,3R,3''R,4R,5E,8,8,9R)-6'-choloro-4-methoxy-8,9-dimethyl-4-((9aR)-octahydro-2H-pyrido[1,2-ajpyrazin-2-yl)methyl)-3',4'-dihydro-1'H,2'H-spiro[10A6-thia-11-aza-1(5,7)-[1,5]benzoazepina-3(1,2)-cyclobutanacyclodecaphan-5-ene-1',1'-naphthalene]-10,10,12-trione
murizatoclax

\[(1^3S,3^1R,3^2R,4^R,5E,8S,9R)-6’-cloro-4-méthoxy-8,9-
diméthyl-4-\{(9aR)-octahydro-2H-pyrido[1,2-a]pyrazin-
2-y[R]-méthyl]-3,4’-dihydro-1’H,1’H,2’H-spiro[10\’\’-thia-
11-aza-1(5,7)-1,5benzoazépina-3(1,2)-
cyclobutanacyclodécaphan-5-ène-1’\,1’-naphtalène]-
10,10,12-trione\]

nadunolimabum #

nadunolimab

Immunoglobulin G1-kappa, anti-[Homo sapiens
IL1RAP (interleukin-1 receptor accessory protein)],
humanized monoclonal antibody;
gamma1 heavy chain humanized (1-446) [VH (Homo
sapiens IGHV1-69*02 (85.4%) -IGHD -IGHJ4*01
(100%)) [8.8.10] (1-117) -Homo sapiens IGHG1*03v,
G1m3>G1m17, nG1m1 (CH1 R120>K (214) (118-
215), hinge (216-230), CH2 (231-340), CH3 E12 (356),
M14 (358) (341-445), CHS K2>del (446)) (118-446)],
(220-214)-disulfide with kappa light chain humanized
(1’-214’) [V-KAPPA (Homo sapiens IGKV1-33*01
(85.3%) -IGKJ4*01 (100%)) [6.3.9] (1’-107’) -Homo
sapiens IGKC*01 (100%), Km3 A45.1 (153), V101
(191) (108’-214’)]; dimer (226-226’-:229-229”)-
bisdisulfide

nadunolimab

Immunoglobulin G1-kappa, anti-[Homo sapiens
IL1RAP (interleukin-1 receptor accessory protein)],
humanized monoclonal antibody;
gamma1 heavy chain humanized (1-446) [VH (Homo
sapiens IGHV1-69*02 (85.4%) -IGHD -IGHJ4*01
(100%)) [8.8.10] (1-117) -Homo sapiens IGHG1*03v,
G1m3>G1m17, nG1m1 (CH1 R120>K (214) (118-
215), hinge (216-230), CH2 (231-340), CH3 E12 (356),
M14 (358) (341-445), CHS K2>del (446)) (118-446)],
(220-214)-disulfide with kappa light chain humanized
(1’-214’) [V-KAPPA (Homo sapiens IGKV1-33*01
(85.3%) -IGKJ4*01 (100%)) [6.3.9] (1’-107’) -Homo
sapiens IGKC*01 (100%), Km3 A45.1 (153), V101
(191) (108’-214’)]; dimer (226-226”-:229-229”)-
bisdisulfide
nadunolimab

immunoglobulin G1-kappa, anti-[Homo sapiens IL1RAP (interleukin-1 receptor accessory protein)], humanized monoclonal antibody; gamma1 heavy chain humanized (1-446) [VH (Homo sapiens IGHV1-69*02 (85.4%) -IGHD -IGHJ4*01 (100%)) [8.8.10] (1-117) -Homo sapiens IGKJ1*03v, G1m3>G1m17, nG1m1 (Ch1 R120>K (214) (118-215), hinge (216-230), CH2 (231-340), CH3 E12 (356), M14 (358) (341-445), CHS K2>del (446)) (118-446)], (220-214')-disulfide with kappa light chain humanized (1'-214') [V-KAPPA (Homo sapiens IGKV1-33*01 (85.3%) -IGKJ4*01 (100%)) [6.3.9] (1'-107') -Homo sapiens IGKJ4*01 (100%), Km3 A45.1 (153), V101 (191) (108'-214')]; dimer (226-226'':229-229'')-bisdisulfide

Heavy chain / Chaîne lourde / Cadena pesada

VQQLVQSGAE VKKPGSSVKV SCKASGYAFT SSWMNWVRQA PGQGLEWMGR 50
IYPGDGNTHY AQRPQGKRTV TADKSTSMAY MTESQSLGTD SYRKLQRVTQ 100
LLQMPWQGQQ TVLVTFEASHT KGSFVFPLAP ESSKRGSDQA ALLGVKQTYF 150
PEPRTYQGGG ELGAVGTVSF PAVSQAESGLY SSLSYYLVPE SSLQGQYTVC 200
VNYKPGSKTP TDKKVVPKKEK CKTVHCPCPF APELGGGPSV YLFFPKDPKTD 250
LMNQSKPEIV CVVGDVHSED PEWKFMYMDT QVEVHNAKTK PKEQNYSTNT 300
RPIVQTVLYL QMLNQKTEYK CVQVNLKFAPI FTTIEMKQA QQKEPRQVTY 350
LPFSKREMKT NGQSLCTLYK GFYEMTAVKE MEEQGQIIPE YKXTTPVYLDS 400

Light chain / Chaîne légère / Cadena ligera

DIQMTQSPES LSASVGDRTV ITCQASQGIN NYIVWQQKRP GAKPFLISHY 50
TESSLKAVGVPSEFSEGSEQDTDD TTVQISELPEP EUVATYYCQY YSLFPPFKGG 100
GTPYRTFTKTV AAFQVVFIFTP SDEQKLQGTA SYVVLCLNHY QPEQVQNNVY 150
DNALQGNGHQ ESVEQDSKDK STYSLSSSTLT LKADYEKHK VYACEVTVQGO 200
LESSVTVKSPF RGEC 214

Post-translational modifications
Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfur
Intra-H (C23-C104) 22-96 144-200 261-321 367-425
22''-96'' 144''- 200'' 261''-321'' 367''-425''
Intra-L (C23-C104) 23'-88' 134'-194'
23'''-88''' 134'''- 194'''
Inter-H-L (h 5-CL 126) 229-214'' 220-214''
Inter-H-H (h 11, h14) 226-226'' 229-229''

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
H CH2 N84.4: 297, 297'
Afucosylated complex bi-antennary CHO-type glycans / glycanes de type CHO bi-antennaires complexes afucosilados.

C 18H18N4O4

nesolicaftor
nesolicaftor
N-(trans-3-[(5-{(1R)-1-hydroxyethyl}-1,3,4-oxadiazol-2-yl)cyclobutyl]-3-phenyl-1,2-oxazole-5-carboxamide

nésolicaftor
nésolicaftor
N-(trans-3-[(5-{(1R)-1-hydroxyéthyl}-1,3,4-oxadiazol-2-yl)cyclobutyl]-3-phenyl-1,2-oxazole-5-carboxamide

nesolicaftor
nesolicaftor
3-fenil-N-(trans-3-[(5-{(1R)-1-hidroxietil}-1,3,4-oxadiazol-2-il)ciclobutil]-1,2-oxazol-5-carboxamida

C_{18}H_{19}N_4O_4
nipocalimab

immunoglobulin G1-lambda, anti-[Homo sapiens FCGRT (Fc fragment of IgG receptor and transporter, neonatal Fc receptor, FcRn, transmembrane alpha chain of the neonatal receptor)], Homo sapiens monoclonal antibody; gamma1 heavy chain Homo sapiens (1-445) [VD Homo sapiens IGHV3-23*01 (90.8%) - (IGHD) - IGHJ3*01 (100%)) CDR-IMGT [8.8.9] (26-33.51-58.97-105) (1-116) - Homo sapiens IGHG1*03 G1m3>G1m17, nG1m1, G1v29 CH2 A84.4 (CH1 R120-K (213) (117-214), hinge 1-15 (215-229), CH2 N84.4->A (296) (230-339), CH3 E12 (355), M14 (357) (340-444), CHS K2>del (445) (117-445)), (219-215)-disulfide with lambda light chain Homo sapiens (1'216) [V-LAMBDA (Homo sapiens IGLV2-23*01 (94.8%) - IGLJ1*01 (100%)) CDR-IMGT [9.3.10] (26-34.52-54.91-100 (1'110) - Homo sapiens IGLC3*03 (100%) (111'-216']) dimer (225-225''228-228'')-bisdisulfide, produced in Chinese hamster ovary (CHO) cells, glycoform alpha

nipocalimab

immunoglobuline G1-lambda, anti-[Homo sapiens FCGRT (transporteur et récepteur du fragment Fc des IgG, récepteur Fc néonatal, FcRn, chaîne alpha transmembranaire du récepteur néonatal)], anticorps monoclonal Homo sapiens; chaîne lourde gamma1 Homo sapiens (1-445) [VD Homo sapiens IGHV3-23*01 (90.8%) - (IGHD) - IGHJ3*01 (100%)) CDR-IMGT [8.8.9] (26-33.51-58.97-105) (1-116) - Homo sapiens IGHG1*03 G1m3>G1m17, nG1m1, G1v29 CH2 A84.4 (CH1 R120-K (213) (117-214), charnière 1-15 (215-229), CH2 N84.4->A (296) (230-339), CH3 E12 (355), M14 (357) (340-444), CHS K2>del (445) (117-445)], (219-215)-disulfure avec la chaîne légère lambda Homo sapiens (1'216) [V-LAMBDA (Homo sapiens IGLV2-23*01 (94.8%) - IGLJ1*01 (100%)) CDR-IMGT [9.3.10] (26-34.52-54.91-100 (1'110) - Homo sapiens IGLC3*03 (100%) (111'-216]) dímero (225-225'228-228'')-bisdisulfuro, producida por células ováricas de hamster chino (CHO), glicoform alfa

nipocalimab

inmunglobulina G1-lambda, anti-[Homo sapiens FCGRT (transportador y receptor del fragmento Fc de las IgG, receptor Fc neonatal, FcRn, cadena alfa transmembranaria del receptor neonatal)], anticuerpo monoclonal Homo sapiens; cadena pesada gamma1 Homo sapiens (1-445) [VD Homo sapiens IGHV3-23*01 (90.8%) - (IGHD) - IGHJ3*01 (100%)) CDR-IMGT [8.8.9] (26-33.51-58.97-105) (1-116) - Homo sapiens IGHG1*03 G1m3>G1m17, nG1m1, G1v29 CH2 A84.4 (CH1 R120-K (213) (117-214), bisagra 1-15 (215-229), CH2 N84.4->A (296) (230-339), CH3 E12 (355), M14 (357) (340-444), CHS K2>del (445) (117-445)], (219-215)-disulfuro con la cadena ligera lambda Homo sapiens (1'-216) [V-LAMBDA (Homo sapiens IGLV2-23*01 (94.8%) - IGLJ1*01 (100%)) CDR-IMGT [9.3.10] (26-34.52-54.91-100 (1'-110) - Homo sapiens IGLC3*03 (100%) (111'-216]) dímero (225-225'228-228'')-bisdisulfuro, producido dans des cellules ovariennes de hamster chinois (CHO), glicoforme alfa
Recommended INN: List 84

WHO Drug Information, Vol. 34, No. 3, 2020

Heavy chain / Chaîne lourde / Cadena pesada

EVQLVESGGG LVTQSPLRLS SCAASGRTFYS TAYAGKNVRQA PKGKLEKVVSS 50
IGASGSEGTQRY ADSVEKVFTH SKGNSTLY LQNSILRAED TAAYVKCARLA 100
YGGQNYQGCTQ YVQTVSSATR GSPQVLALPS LikEGTGAAT LGLVYKQTPP 150
EPVTWYMASS ALTSGVHTFPP AVLQSQSGLYS LSLYTVVPSS SLQ6GT6LC 200
VHHRPSVTYY DKKVDSRPSCED KTVTCCPCPDFA ELLGSGDPSV LFPPFKQKDLTL 250
MISRTKHEVC VKDSVTRSDK EKPWNYQOG VEOGEHARTK BEMRQASYER 300
VVDDLVTIQH DLNKKYKVC KVKKALRAP IEKTIS6RQ FURPEPVYTL 350
PPSREEMTPF YQSLTCLVEG FFPSEPDAVEN ESFQEPFNYK EKTPFVLEDQ 400
GSPFY5EYLT YOSSQQQQQN YPPCMMBA LEHWTYK6L SLEPG 445

Light chain / Chaîne légère / Cadena liger a

QUALITPQAVV ESSQPEVTI SOTRGHSGV SYNLVS6WQ SYHL6AP6K 50
YGQERPSGCV SRPSG6KRSK6 NTASLISGL 6AE6D6YK CSYAG6S6YV 100
FSTVTVYTVL GQPRAPAVST LFPO666KOK6 AMK6TLVVL 6STFP6GATV 150
AMRA66P6K AY6ETTPTPK USN.heading SKY6C6YQT6K 200
HEG6T6KTV G6P6C 216

Post-translational modifications

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro

Intra-H (C23-C104) 22-96 143-199 260-320 366-424
Intra-L (C23-C104) 22'-90' 138'-197'
Inter-H-L (h 5-CL 126) 219-215' 219'-215'
Inter-H-H (h 11, h 14) 225-225' 228-228'

No N-glycosylation sites / pas de sites de N-glycosylation / ningún posición de N-glicosilación

H CH2 N84.4>A: 296, 296''

olverembatinib

olverembatinib 4-methyl-N-[4-[(4-methylpiperazin-1-yl)methyl]-3-(trifluoromethyl)phenyl]-3-[(1H-pyrazolo[3,4-b]pyridin-5-yl)ethynyl]benzamide

olvérembatinib

4-méthyl-N-[4-[(4-méthylpiperazin-1-yl)méthyl]-3-(trifluorométhyl)phényl]-3-[(1H-pyrazolo[3,4-b]pyridin-5-yl)éthynyl]benzamide

olverembatinib

4-metil-N-[4-[(4-metilpiperazin-1-il)métil]-3-(trifluorometil)fenil]-3-[(1H-pirazolo[3,4-b]piridin-5-il)etil]benzamide

olvimulogenum nanivacirepvecum #

olvimulogene nanivacirepvec

A recombinant replication-competent oncolytic vaccinia virus (strain LIVP) comprising the genes encoding a Renilla luciferase - green fluorescent protein fusion protein (ruc-gfp) and enzymes beta-galactosidase (lacZ) and beta-glucuronidase (gusA), inserted into the F14.5L, J2R (thymidine kinase) and A56R (hemagglutinin) loci, respectively. Expression of the three proteins is driven by a synthetic early/late promoter (pSEL), a vaccinia virus strain Western Reserve early/late p7.5 promoter and a vaccinia virus strain Western Reserve late p11 promoter, respectively. A human transferrin receptor gene has also been inserted in the J2R locus but is not expressed.
olvimulogène nanivacirépvec

Virus de la vaccine recombinant répliquant oncolytique (souche LIVP) contenant les gènes codant pour une protéine de fusion luciférase de Renilla - protéine fluorescente verte (ruc-gfp) et des enzymes galactosidase bêta (lacZ) et glucuronidase bêta (gusA), insérés dans les loci F14.5L, J2R (thymidine kinase) and A56R (hémagglutinine), respectivement. L'expression des trois protéines est sous le contrôle d'un promoteur synthétique précoce/tardif (pSEL), d'un promoteur p7.5 précoce/tardif du virus de la vaccine souche Western Reserve et d'un promoteur p11 tardif du virus de la vaccine souche Western Reserve, respectivement. Un gène du récepteur de transférine humain a aussi été inséré dans le locus J2R mais n'est pas exprimé.

olvimulogén nanivacirepvec

Un virus vaccinia recombinante (souche LIVP) compétent para replicación, oncolítico, que contiene los genes que codifican para una proteína de fusión de la luciferasa de Renilla y la proteína fluorescente verde (ruc-gfp) y para las enzimas beta-galactosidasa (LacZ) y beta-glucuronidasa (gusA), insertados en los loci F14.5L, J2R (timidina quinasea) y A56R (hemaglutinina), respectivamente. La expresión de las tres proteínas está dirigida por un promotor temprano/tardío sintético (pSEL), un promotor p7.5 precoz/tardío de la cepa Western Reserve del virus vaccinia y un promotor p11 tardío de la cepa Western Reserve del virus vaccinia, respectivamente. Se ha insertado también un gen del receptor de transferrina humana en el locus J2R pero éste no se expresa.

omfiloctocogum alfa #

omfiloctocog alfa

Human coagulation factor VIII (FVIII, antihemophilic factor, AHF, procoagulant component) with deleted B-domain (746-1639)-sequence: single-chain recombinant FVIII composed of domains A1-a1-A2-a2 (1-740), the B-domain N- and C-terminal fragments (741-745) and 1640-1648 (746-754) and domains a3-A3-C1-C2 1649-2332 (755-1438), produced in Chinese hamster ovary (CHO) cells, glycoform alfa

omfiloctocog alfa

Facteur de coagulation VIII humain (FVIII, facteur antihémophilique, AHF, composant procoagulant) dont le domaine B a été supprimé (746-1639): chaîne unique du FVIII humain recombinant composé des domaines A1-a1-A2-a2 (1-740), des fragments N- and C-terminaux du domaine B (741-745) et 1640-1648 (746-754) et des domaines a3-A3-C1-C2 1649-2332 (755-1438), produit par des cellules ovariiennes de hamster chinois (CHO), glycoforme alfa

omfiloctocog alfa

Factor de coagulación VIII humano (FVIII, factor antihemofílico, AHF, componente procoagulante) con el dominio B que ha sido suprimido (746-1639):
cadena única del FVIII humano recombinante compuesto de los dominios A1-a1-A2-a2 (1-740), de los fragmentos N- y C-terminal del dominio B (741-745) y de los dominios A3-A3-C1-C2 1649-2332 (755-1438), producido por las células ováricas de hamster chino (CHO), glicofoma alfa

**Sequence / Séquence / Secuencia**

ATRYYLGLAV ELSEWYMQSD LGELPVDAFP PPRPKSFSPF NTSVYKRTL 50  
FVFYTPDRLNF IAKRPFPMMK LGLPQTQAEV YOTCVTLIK MAERPVSLHA 100  
VYYTMYKAGE GAEYDIQTOQ RKEKVDRTYF GSSTTVQYGV LKEGNGSMAQ 150  
PCLTVSYLS HYDVKVLNQL GLIGAVLCCR ECGLAEKTQ TLHKFILLFA 200  
VFDEQKRMHS ETNLSMKQR DDASAARNPK MVHTNYGNVR LSGPLIGCHR 250  
KSYWHRQVQG GTPRQKSVSP LCHRFTYURN HRQASLIEISP ITTLAQGIL 300  
NOLQLQPLFC HSSQHQGHGN EAYVKVSDSC EEOQLMRKN RNADQGDDOL 350  
TSDENQVRVF DODSFSFPIQ IRSVAKKHPR TWYHLYAEAE EYNWYAFVLV 400  
APQGYRQYKQ YNLNDQORIG NHXKKVFRMA VTDEFTPKRE AIQKKGMLG 450  
FLYGEQVQIT LIILFQKQAS RPYNTYPHIQ TDQRPYSLRR LPRQKVKEIQ 500  
FPPPLQPREEPK YPKWTVTVQED PTKDEPRCIL RYESSPVPNNE RQAGSLGIL 550  
LLICFRKXSV QDRGQIQMDR RQVLESSVFPD ENRQYFICEN SQRQFVRQAG 600  
VQLESDQFQGA SNNMCSIYNG VFPSQSLNVC LHEAVYKYL SIGAQTFQFLS 650  
VFDESGTYFR PKVNYEDTLTL FFFSGEVTYM SNQPGSRLIM GCHEDSFPRHR 700  
GGTAKQXVQG KQCGDIKDYE DSYEKISAYL LSSKIKNQQF SRFGPSSPVL 750  
HRQHEETRTT LQESQIEIED DOTISVEMKK EODPVEDE MQSQPSQFKQK 800  
TRKYPFAAVE RLWSQGEMSS WYRSNRRXRS QSPQYQPQKV YQFPDQSOFT 850  
PHEQGELINE HIGLQGYPFR ARVDENITYV PRASQARPPS FYYSSLTVHE 900  
DOQCAPEKRX PKVFQNPETRT YFKWHQHIMA PTQEDCOKA MAYSQVQLE 950  
KVRQSLGILP LLVCHTYLNN PAEGRQVTQV EALPTFTTED EUKSNYFTTEN 1000  
MERCONAPCN IOMQDITPKRK RNPVPHIYQ IMGPGLVLQ AQGQIRKMYL 1050  
LSGCHENNH STHFSQGVTY VRKREYRHYA LLYLHVPE TEVQPLSPRAR 1100  
INWREVEEDQ HSLKQHDFLF LLTHSNQGQTP LMOSAHQIRI FTQASQCOGQ 1150  
QMÑ lapseV LQCGNMAST EEPFEPKIVP LLLPRHGH IG RPQAQPSPNL 1200  
SLVQIPFQIM YSDLCKKHQVT YRGBNQTICM VPPQFQDSQG IKMNFPKPP 1250  
IARYLRLHPT BYSIRETLMK ELMOQICAC NELPMESQA IESQATQASE 1300  
TYFPRNTEHG SYFMRLLQGQQGNNRQPR YPPQELQVQ QKTQKMTQVQ 1350  
TQGQKSLTTS MYQREFLISS SQHQXHTLF FQHYKQVQV QMGQDSTPVV 1400  
NSDOPFLTR LRLYHDRQGWV HATALMNEVL GXAUDLY 1438

**Post-translational modifications**

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro  
153-179, 248-329, 528-554, 630-711, 938-964, 1005-1009, 1127-1275, 1280-1432  
(Cys-SH: 310, 692, 1106)

Glycosylation sites / Sites de glycosylation / Posiciones de glicosilación  
N41, N239, N916, N1224

Fucosylated complex bi-antennary CHO-type glycans / Glycanes de type CHO bi-antennaires complejos fucosilados  

Tyr-sulfation sites / Sites de Tyr-sulfation / Posiciones de Tyr-sulfación  
346, 718, 719, 723, 770, 786  

**onatasertib**

7-[6-(2-hydroxypropan-2-yl)pyridin-3-yl]-1-(trans-4-methoxy cyclohexyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one

**onatasertib**

7-[6-(2-hydroxypropan-2-yl)pyridin-3-yl]-1-(trans-4- methoxy cyclohexyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one

**onatasertib**

7-[6-(2-hidroxipropan-2-il)piridin-3-il]-1-(trans-4- metoxiciclohexil)-3,4-dihidropirazino[2,3-b]-pirazin-2(1H)-ona

C₂₁H₂₇N₅O₃

![Structural diagram of onatasertib](image-url)
ongericimab #
ongericimab

Immunoglobulin G4-kappa, anti-[Homo sapiens PCSK9 (proprotein convertase subtilisin/kexin type 9, neural apoptosis-regulated convertase 1, NARC1, NARC-1, proprotein convertase 9, PC9)], humanized monoclonal antibody;
gamma4 heavy chain (1-438) [VH (Homo sapiens IGHV4-59*01 (79.2%) -IGHD -IGHJ1*01 (100%)) CDR-IMGT [8.7.5] (26-33.51-57.96-100) (1-111) - Homo sapiens IGHS4*01, G4v5 h P10 (CH1 (112-209), hinge 1-12 S10>P (219) (210-221), CH2 (222-331), CH3 (332-436), CHS (437-438)) (112-438)], (125-213')-disulfide with kappa light chain (1'-213') [V- KAPPA (Homo sapiens IGKV1-33*01 (85.1%) - IGKJ1*01 (100%)) CDR-IMGT [6.3.8] (27-32.50-52.89-96) (1'-106') - Homo sapiens IGKC*01 (100%) Km3 A45.1 (152), V101 (190) (107'-213')];
dimer (217-217''-220-220'')-bisdisulfide, produced in Chinese hamster ovary (CHO) cells, glycoform alpha

ongéricimab

Immunoglobuline G4-kappa, anti-[Homo sapiens PCSK9 (proprotéine convertase subtilisine/kexine type 9, convertase 1 régulée par l'apoptose neuronale, NARC1, NARC-1, proprotéine convertase 9, PC9)], anticorps monoclonal humanisé;
chaîne lourde gamma4 (1-438) [VH (Homo sapiens IGHV4-59*01 (79.2%) -IGHD - IGHJ1*01 (100%)) CDR-IMGT [8.7.5] (26-33.51-57.96-100) (1-111) - Homo sapiens IGHS4*01, G4v5 h P10 (CH1 (112-209), charnière 1-12 S10>P (219) (210-221), CH2 (222-331), CH3 (332-436), CHS (437-438)) (112-438)], (125-213')-disulfure avec la chaîne légère kappa (1'-213') [V-KAPPA (Homo sapiens IGKV1-33*01 (85.1%) - IGKJ1*01 (100%)) CDR-IMGT [6.3.8] (27-32.50-52.89-96) (1'-106') - Homo sapiens IGKC*01 (100%) Km3 A45.1 (152), V101 (190) (107'-213')];
dimère (217-217''-220-220'')-bisdisulfure, produite dans des cellules ovariennes de hamster chinois (CHO), glycoforme alpha

ongericimab

Inmunoglobulina G4-kappa, anti-[Homo sapiens PCSK9 (proprotein convertasa subtilisina/kexina tipo 9, convertasa 1 regulada por la apotoposa neuronal, NARC1, NARC-1, proprotein convertasa 9, PC9)], anticuerpo monoclonal humanizado;
cadena pesada gamma4 (1-438) [VH (Homo sapiens IGHV4-59*01 (79.2%) -IGHD - IGHJ1*01 (100%)) CDR-IMGT [8.7.5] (26-33.51-57.96-100) (1-111) - Homo sapiens IGHS4*01, G4v5 h P10 (CH1 (112-209), bisagra 1-12 S10>P (219) (210-221), CH2 (222-331), CH3 (332-436), CHS (437-438)) (112-438)], (125-213')-disulfuro con la cadena ligera kappa (1'-213') [V-KAPPA (Homo sapiens IGKV1-33*01 (85.1%) - IGKJ1*01 (100%)) CDR-IMGT [6.3.8] (27-32.50-52.89-96) (1'-106') - Homo sapiens IGKC*01 (100%) Km3 A45.1 (152), V101 (190) (107'-213')];
dímero (217-217''-220-220'')-bisdisulfuro, producida por células ováricas de hamster chino (CHO), glicosilada alfa
ontorpaceptum #

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proteína reguladora de señal alpha, humana (SIRPa), sustrato 1 de tipo no-receptor de la tirosina-proteína fosfatasa, receptor inhibidor SHPS-1), (L14>S, T20>S, T22>I, R24>H, A27>V, G45>A, D65>E, L66>S, N70>E, R77>S, G79>S, D101>del, V102>T101)-variante, fragmento N-terminal (1-118) [dominio unido al CD47 (inhibidor de la fagocitosis por los macrófagos)], fusionado con el fragmento Fc C-terminal de la inmunoglobulina G1 (119-345), dímero (124-124’:127-127’)-bisdisulfuro, producido en las células ováricas de hamster chino (CHO), glicoforma alfa
opucolimabum #
opucolimab

**Immunoglobulin G1-lambda, anti-[**Homo sapiens**]**

- **Opucolimab**
  - **CD274** (programmed death ligand 1, PD-L1, PD-L1, B7 homolog 1, B7H1), monoclonal antibody;
  - gamma1 heavy chain (1-453) [VH (Homo sapiens IGHV3-21*01 (94.9%) -IGHD -IGHJ3*01 (93.3%)) [8.8.16] (1-123) -**Homo sapiens** IGHG1*03v]
  - G1m3=G1m17, nG1m1 (CH1 R120>K (220) (124-221), hinge 1-15 (222-236), CH2 N84.4>A (303) (237-346), CH3 E12 (362), M14 (364) (347-451), CHS (452-453)) (124-453)), (226-214)-disulfide with lambda light chain humanized (1-214) [V-LAMDBA (**Homo sapiens** IGLV1-51*01 (82.3%) -IGLJ2*01 (100%)) [8.3.10] (1-109) -**Homo sapiens** IGLC3*03 (98.1%) K119>R (207), P123>L (211) (110-214))];
  - dimer (232-232**:235-235**)-bisdisulfide, produced in Chinese hamster ovary (CHO) cells

opucolimab

**Immunoglobulin G1-lambda, anti-[**Homo sapiens**]**

- **Opucolimab**
  - **CD274** (ligand 1 de mort programmée, PD-L1, PD-L1, homologue 1 de B7, B7H1)), anticorps monoclonal;
  - chaîne lourde gamma1 (1-453) [VH (**Homo sapiens** IGHV3-21*01 (94.9%) -IGHD -IGHJ3*01 (93.3%)) [8.8.16] (1-123) -**Homo sapiens** IGHG1*03v]
  - G1m3=G1m17, nG1m1 (CH1 R120>K (220) (124-221), charnière 1-15 (222-236), CH2 N84.4>A (303) (237-346), CH3 E12 (362), M14 (364) (347-451), CHS (452-453)) (124-453)), (226-214)-disulfide avec la chaîne légère (1-214) [V-LAMDBA (**Homo sapiens** IGLV1-51*01 (82.3%) -IGLJ2*01 (100%)) [8.3.10] (1-109) -**Homo sapiens** IGLC3*03 (98.1%) K119>R (207), P123>L (211) (110-214)];
  - dimère (232-232**:235-235**)-bisdisulfure, produit dans des cellules ovariennes de hamster chinois (CHO)

opucolimab

**Immunoglobulina G1-lambda, anti-[**Homo sapiens**]**

- **Opucolimab**
  - **CD274** (ligando 1 de muerte programada, PD-L1, PD-L1, homólogo 1 de B7, B7H1)), anticuerpo monoclonal;
cadena pesada gamma1 (1-453) [VH (Homo sapiens IGHV3-21*01 (94.9%) -IGHJ3*01 (93.3%)) [8.8.16] (1-123) -Homo sapiens IGHG1*03v G1m3>G1m17, nG1m1 (CH1 R120*K (220) (124-221), bisagra 1-15 (222-236), CH2 N84.4>A (347-451), CHS (452-453)] (124-243), (226-214*)-disulfuro con la cadena ligera lambda (1-214*) [V-LAMBDA (Homo sapiens IGLV1-51*01 (82.3%) -IGLJ2*01 (100%)) [B.3.10] (1-109*) -Homo sapiens IGLC3*03 (98.1%) K119>R (207), P123=L (211) (110-214*)]; dímero (232-232*:235-235*)-bisdisulfuro, producido por células ováricas de hamster chino (CHO)

Heavy chain / Chaîne lourde / Cadena pesada
EVQLVQSGG GVEPYDQGKL SQFSQDFTPS SYWHMVFAQ PCKLEWSS 50
ISSGSELYV ADSVQGPTI SRQKRMHLY LGSHRRAE TAYVCRNCE 100
LEWYQGQACAF SRQWQDQMTV VISASFKPS VYFLAPSSKS TSGTHAAGC 150
LVVGRYPFFV YMEMSAGLY SIVQPSAPQ GSSLYLSS LVTVAPSPEL 200
TQYICHEWH KPSNTVQDKK VEPECSQTHH TFCPQAPW LGGPSVFLPP 250
PKEKKTLSRSS TTEVVCTCVY QYHSVHEPK RMYQGVQVF IHAQXKPFKX 300
QVQATVYWVS VVTLQAGQML NSEXGHCKPS HKLLAPIT CHKSAQQPR 350
EQTVTLFES REMTKQKVS LTLVCRQFHP SDIAVRENSI GFFNYKETT 400
PPPILDDQQP FLYSKLTVQG SRRQGQNYTS CSGRHSLANS HYTQSSLSS 453

Light chain / Chaîne légère / Cadena ligera
QSVTVQPSPH SAAPQGKTVI SCGGSSSYIE SSVQQGQQL GTAPRSLIY 50
DDMRKPRSGP DRSFSKSDRT SATLTVQCG TSGQACTFCY IKRRSLQGVP 100
GQGTYVLS QFPAASPQTVI FFXPSFILQG KATVCLGSSLQGDPFQXVTV 150
MKASSSPQKA QYEVTPQPSQ SNKSAASYS LSLTPEQWKS HRSYSCQVTH 200
EGSTQKTVTA LTEC 214

Post-translational modifications
Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro
Intra-H (C23-C104) 22-96 22* 150-327 373-431
22* 150*-206* 267*-327* 373*-431*
Intra-L (C23-C104) 2218 137*-196*
22* 137*-196*
Inter-H-L (h 5-CL 126) 226-2142 226*-214*
Inter-H-H (h 11, h 14) 232-232* 235-235*
No N-glycosylation sites / Pas de sites de N-glycosylation / Ningún posición de N-glicosilación:
H CH2 N84.4>A: 303, 303!
C-terminal lysine clipping:
H CHS K2: 453, 453*

orelabrutinib

2-(4-phenoxyphenyl)-6-[1-(prop-2-enoyl)piperidin-4-yl]pyridine-3-carboxamide
**orvacabtagenum autoleucelum #**

autologous CD4+ and CD8+ T lymphocytes obtained from peripheral blood mononuclear cells (PBMC), transduced *ex vivo* with a replication-incompetent, self-inactivating (SIN) lentiviral vector, encoding a chimeric antigen receptor (CAR) consisting of the human B cell maturation antigen (BCMA)-specific scFv, an IgG4-CH2-CH3 hinge region, CD28 transmembrane domain, CD137 (4-1BB) co-stimulatory domain and CD3 zeta signalling domain, under the control of a hybrid Elongation Factor 1 alpha (EF1α) / Human T cell Leukemia Virus (HTLV) R element promoter. The vector also encodes a truncated human epidermal growth factor receptor (EGFRt) that is expressed separately from the CAR on the cell surface.

**orvacabtagene autoleucel**

lymphocytes T autologues CD4+ and CD8+ obtenus de cellules mononucléées du sang périphérique (PBMC), transduits *ex vivo* avec un vecteur lentiviral non-répliquant, auto-inactivant (SIN) codant pour un récepteur d’antigène chimérique (CAR) ciblant l’antigène spécifique du scFv de maturation des lymphocytes B (BCMA) humain, une région charnière IgG4-CH2-CH3, un domaine transmembranaire du CD28, un domaine co-stimulateur du CD137 (4-1BB), et un domaine de signalisation CD3 zéta, sous le contrôle d’un promoteur hybride du facteur d’élongation 1-alpha humain (EF1α) / élément R du virus du lymphome humain à cellules T (HTLV). Le vecteur exprime un récepteur du facteur de croissance des cellules épidermiques humain tronqué (EGFRt) qui est exprimé séparément du CAR à la surface de la cellule.

**orvacabtagén autoleucel**

linfocitos T CD4+ y CD8+ autólogos obtenidos de células mononucleares de sangre periférica, transducidos con un vector lentiviral auto inactivante e incompetente para replicación, que codifica un receptor para antígenos quimérico (CAR) consistente en un ssFv específico del antígeno de maduración de linfocitos B humano (BCMA), una región bisagra IgG4-CH2-CH3, un dominio transmembrana de CD28, un dominio coestimulador de CD137 (4-1BB) y un dominio de señalización de CD3 zeta, bajo el control de un promotor híbrido del Factor de Elongación 1 alfa (EF1α) / elemento R del virus de la leucemia de células T (HTLV) humana. El vector también codifica para una forma truncada del receptor del factor de crecimiento epidérmico (EGFRt) humano que se expresa separado del CAR en la superficie celular.

**osoressnontrinum**

1-(oxan-4-yl)-6-[(pyridin-2-yl)methyl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

1-(oxan-4-yl)-6-[(pyridin-2-yl)méthyl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

1-(oxan-4-il)-6-[(piridin-2-il)metil]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona
pelacarsen

all-P-ambo-5'-O-(28-[(2-acetamido-2-deoxy-β-D-galactopyranosyl)oxy]-16,16-bis[[3-{6-[(2-acetamido-2-deoxy-β-D-galactopyranosyl)oxy]hexyl}amino]-3-oxopropanyl]methyl]-1-hydroxy-1,10,14,21-tetraoxo-2,18-dioxo-9,15,22-tri-1α5-phosphoactocasan-1-yl]-2'-O-(2-methoxyethyl)-5-methyl-P-thiouridylyl-(3'→5')-2'-O-(2-methoxyethyl)guanylyl-(3'→5')-2'-O-(2-methoxyethyl)-5-methylcytidylyl-(3'→5')-2'-O-(2-methoxyethyl)-5-methylcytidylyl-(3'→5')-2'-deoxy-5-methyl-P-thiocytidylyl-(3'→5')-2'-deoxy-P-thioguanylyl-(3'→5')-P-thiocytidylyl-(3'→5')-P-thioguanylyl-(3'→5')-2'-deoxy-P-thioguanylyl-(3'→5')-2'-deoxy-P-thioguanylyl-(3'→5')-2'-deoxy-P-thiouridylyl-(3'→5')-2'O-(2-methoxyethyl)-5-methyl-P-thiocytidylyl-(3'→5')-P-thiocytidylyl-(3'→5')-2'-O-(2-methoxyethyl)-5-methyl-P-thiocytidylyl-(3'→5')-2'-O-(2-methoxyethyl)-5-methyl-P-thiouridylyl-(3'→5')-2'-O-(2-methoxyethyl)-5-methyl-P-thiouridylyl-(3'→5')-2'O-(2-methoxyethyl)-5-methyl-P-thiouridylyl-(3'→5')-2'-O-(2-methoxyethyl)-5-methyl-P-thiouridylyl-(3'→5')-2'-O-(2-methoxyethyl)-5-methyl-P-thiouridylyl-(3'→5')-2'-O-(2-methoxyethyl)-5-methyl-P-thiouridylyl-(3'→5')-2'-O-(2-methoxyethyl)-5-methyl-P-thiouridylyl-(3'→5')-2'-O-(2-methoxyethyl)-5-methylcytidine

pé lacarsen

tout-P-ambo-5'-O-(28-[(2-acétamido-2-désoxy-β-D-galactopyranosyl)oxy]-16,16-bis[[3-{6-[(2-acétamido-2-désoxy-β-D-galactopyranosyl)oxy]hexyl}amino]-3-oxopropanyl][méthyl]-1-hydroxy-1,10,14,21-tétraoxo-2,18-dioxo-9,15,22-tri-1α5-phosphoactocasan-1-yl]-2'-O-(2-méthoxyéthyl)-5-méthyl-P-thiouridylyl-(3'→5')-2'-O-(2-méthoxyéthyl)guanylyl-(3'→5')-2'-O-(2-méthoxyéthyl)-5-méthylcytidylyl-(3'→5')-2'-O-(2-méthoxyéthyl)-5-méthylcytidylyl-(3'→5')-2'-dés oxy-5-méthyl-P-thiocy tidylyl-(3'→5')-2'-dés oxy-P-thioguanylyl-(3'→5')-P-thiocy tidylyl-(3'→5')-2'-dés oxy-P-thioguanylyl-(3'→5')-2'-dés oxy-P-thioguanylyl-(3'→5')-P-thiothymidylyl-(3'→5')-2'-dés oxy-P-thioguanylyl-(3'→5')-2'-dés oxy-P-thioguanylyl-(3'→5')-2'-dés oxy-P-thioguanylyl-(3'→5')-5-méthyl-P-thiothymidylyl-(3'→5')-P-thiothymidylyl-(3'→5')-2'-O-(2-méthoxyéthyl)-5-méthyl-P-thiothymidylyl-(3'→5')-2'-O-(2-méthoxyéthyl)guanylyl-(3'→5')-2'-O-(2-méthoxyéthyl)-5-méthyl-P-thiouridylyl-(3'→5')-2'-O-(2-méthoxyéthyl)-5-méthyl-P-thiouridylyl-(3'→5')-2'-O-(2-méthoxyéthyl)-5-méthyl-P-thiouridylyl-(3'→5')-2'-O-(2-méthoxyéthyl)-5-méthyl-P-thiouridylyl-(3'→5')-2'-O-(2-méthoxyéthyl)-5-méthylcytidine
pelacarsén

todo-P-ambo-5’-O-(28-{[2-acetamido-2-desoxi-β-D-galactopiranosil]oxi}-16,16-bis[[3-{(6-{[2-acetamido-2-desoxi-β-D-galactopiranosil]oxi}hexil)amino]-3-oxopropoxi]metil]-1-hidroxi-1,10,14,21-tetraoxo-2,18-dioxia-9,15,22-triaza-1λ^6-fosfoacetacosen-1-il]-2’-O-(2-metotioxidil)-5-metil-P-tiouridil-(3’→5’)-2’-O-(2-metotioxidil)-5-metiltiouridil-(3’→5’)-2’-O-(2-metotioxidil)-5-metiltiouridil-(3’→5’)-2’-O-(2-metotioxidil)-5-metiltiouridil-(3’→5’)-2’-O-(2-metotioxidil)-5-metiltiouridil-(3’→5’)-2’-O-(2-metotioxidil)-5-metiltiouridil-(3’→5’)-2’-O-(2-metotioxidil)-5-metiltiouridil-(3’→5’)-2’-O-(2-metotioxidil)-5-metiltiouridil-(3’→5’)-2’-O-(2-metotioxidil)-5-metiltiouridil-(3’→5’)-2’-O-(2-metotioxidil)-5-metiltiouridil-(3’→5’)-2’-O-(2-metotioxidil)-5-metiltiouridil-(3’→5’)-2’-O-(2-metotioxidil)-5-metiltiouridil-(3’→5’)-2’-O-(2-metotioxidil)-5-metiltiouridil-(3’→5’)-2’-O-(2-metotioxidil)-5-metiltiouridil-(3’→5’)-2’-O-(2-metotioxidil)-5-metiltiouridil-(3’→5’)-2’-O-(2-metotioxidil)-5-metiltiouridil-(3’→5’)-2’-O-(2-metotioxidil)-5-metiltiouridil-(3’→5’)-2’-O-(2-metotioxidil)-5-metiltiouridil-(3’→5’)-2’-O-(2-metotioxidil)-5-metiltiouridil-(3’→5’)-2’-O-(2-metotioxidil)-5-metiltiouridil-(3’→5’)-2’-O-(2-metotioxidil)-5-metiltiouridil-(3’→5’)-2’-O-(2-metotioxidil)-5-metiltiouridil-(3’→5’)-2’-O-(2-metotioxidil)-5-metiltiouridil-(3’→5’)-2’-O-(2-metotioxidil)-5-metiltiouridil-(3’→5’)-2’-O-(2-metotioxidil)-5-metiltiouridil-(3’→5’)-2’-O-(2-metotioxidil)-5-metiltiouridil-(3’→5’)-2’-O-(2-metotioxidil)-5-metiltiouridil-(3’→5’)-2’-O-(2-metotioxidil)-5-metiltiouridil-

guanilil-(3’→5’)-2’-O-(2-metotioxidil)-5-metiltiouridil-(3’→5’)-2’-O-(2-metotioxidil)-5-metiltiouridil-(3’→5’)-2’-O-(2-metotioxidil)-5-metiltiouridil-(3’→5’)-2’-O-(2-metotioxidil)-5-metiltiouridil-(3’→5’)-2’-O-(2-metotioxidil)-5-metiltiouridil-(3’→5’)-2’-O-(2-metotioxidil)-5-metiltiouridil-(3’→5’)-2’-O-(2-metotioxidil)-5-metiltiouridil-(3’→5’)-2’-O-(2-metotioxidil)-5-metiltiouridil-(3’→5’)-2’-O-(2-metotioxidil)-5-metiltiouridil-(3’→5’)-2’-O-(2-metotioxidil)-5-metiltiouridil-(3’→5’)-2’-O-(2-metotioxidil)-5-metiltiouridil-(3’→5’)-2’-O-(2-metotioxidil)-5-metiltiouridil-(3’→5’)-2’-O-(2-metotioxidil)-5-metiltiouridil-(3’→5’)-2’-O-(2-metotioxidil)-5-metiltiouridil-(3’→5’)-2’-O-(2-metotioxidil)-5-metiltiouridil-(3’→5’)-2’-O-(2-metotioxidil)-5-metiltiouridil-(3’→5’)-2’-O-(2-metotioxidil)-5-metiltiouridil-(3’→5’)-2’-O-(2-metotioxidil)-5-metiltiouridil-(3’→5’)-2’-O-(2-metotioxidil)-5-metiltiouridil-(3’→5’)-2’-O-(2-metotioxidil)-5-metiltiouridil-(3’→5’)-2’-O-(2-metotioxidil)-5-metiltiouridil-(3’→5’)-2’-O-(2-metotioxidil)-5-metiltiouridil-(3’→5’)-2’-O-(2-metotioxidil)-5-metiltiouridil-(3’→5’)-2’-O-(2-metotioxidil)-5-metiltiouridil-(3’→5’)-2’-O-(2-metotioxidil)-5-metiltiouridil-(3’→5’)-2’-O-(2-metotioxidil)-5-metiltiouridil-(3’→5’)-2’-O-(2-metotioxidil)-5-metiltiouridil-(3’→5’)-2’-O-(2-metotioxidil)-5-metiltiouridil-(3’→5’)-2’-O-(2-metotioxidil)-5-metiltiouridil-(3’→5’)-2’-O-(2-metotioxidil)-5-metiltiouridil-(3’→5’)-2’-O-(2-metotioxidil)-5-metiltiouridil-(3’→5’)-2’-O-(2-metotioxidil)-5-metiltiouridil-(3’→5’)-2’-O-(2-metotioxidil)-5-metiltiouridil-(3’→5’)-2’-O-(2-metotioxidil)-5-metiltiouridil-(3’→5’)-2’-O-(2-metotioxidil)-5-metiltiouridil-(3’→5’)-2’-O-(2-metotioxidil)-5-metiltiouridil-(3’→5’)-2’-O-(2-metotioxidil)-5-metiltiouridil-(3’→5’)-2’-O-(2-metotioxidil)-5-metiltiouridil-(3’→5’)-2’-O-(2-metotioxidil)-5-metiltiouridil-(3’→5’)-2’-O-(2-metotioxidil)-5-metiltiouridil-(3’→5’)-2’-O-(2-metotioxidil)-5-metiltiouridil-(3’→5’)-2’-O-(2-metotioxidil)-5-metiltiouridil-(3’→5’)-2’-O-(2-metotioxidil)-5-metiltiouridil-(3’→5’)-2’-O-(2-metotioxidil)-5-metiltiouridil-(3’→5’)-2’-O-(2-metotioxidil)-5-metiltiouridil-(3’→5’)-2’-O-(2-metotioxidil)-5-metiltiouridil-(3’→5’)-2’-O-(2-metotioxidil)-5-metiltiouridil-(3’→5’)-2’-O-(2-metotioxidil)-5-metiltiouridil-(3’→5’)-2’-O-(2-metotioxidil)-5-metiltiouridil-(3’→5’)-2’-O-(2-metotioxidil)-5-metiltiouridil-(3’→5’)-2’-O-(2-metotioxidil)-5-metiltiouridil-

C_{296}H_{439}N_{71}O_{163}P_{20}S_{13}

Legend: C & U: 2’-O-(2-methoxyethyl)-5-methyl nucleotide

pelcitoclaxum

pelcitoclax

(3’→5’)-{[(10R)-14-chloro-35-fluoro-24-(methanesulfonyl)-25-

methyl-7,7-dioxo-10-[(phenylsulfanyl)methyl]-21-

(propan-2-yl)-83-(trifluoromethanesulfonyl)-21-

H7λ^6-

thia-6,9-diaza-4(1,4)-piperazina-13(1)-piperidina-

2(2,3)-pyrrola-1(1),3(1,3),5,8(1,4)-

tetrazenatriudecaphane-13-

carbonyl][oxy]propyl]phosphonic acid

pelcitoclax

acide (3’→(10R)-14-chloro-35-fluoro-24-

(methanesulfonyl)-25-

méthyl-7,7-dioxo-10-[(phénylsulfanyl)méthyl]-21-

(propan-2-yl)-83-(trifluorométhanesulfonyl)-21-

H7λ^6-thia-6,9-diaza-4(1,4)-pipérazina-13(1)-pipéridina-

2(2,3)-pyrrola-1(1),3(1,3),5,8(1,4)-
tétrabenzenatriédécaphane-13-

carbonyl][oxy]propyl]phosphonique

pelcitoclax

ácido (3’→(10R)-14-cloro-10-[(fenilsulfanil)metil]-35-

fluoro-24-(metanosulfonil)-25-

metil-7,7-dixo-21-

(propan-2-il)-83-(triflurometanosulfonil)-21-

H7λ^6-thia-6,9-diaza-4(1,4)-piperazina-13(1)-piperidina-

2(2,3)-pyrrola-1(1),3(1,3),5,8(1,4)-
tetrazenatriedicafano-13-

carbonil][oxy]propil]fosfónico
**Recommended INN: List 84**

C$_{57}$H$_{66}$ClF$_4$N$_6$O$_{11}$PS$_4$

![Chemical Structure](image)

**pexopiprantum**

pexopiprant

((8-chloro-3-[(4-chlorophenyl)methyl]-4-(difluoromethoxy)-2-ethylquinolin-5-yl)oxy)acetic acid

**pexopiprant**

acide ((8-chloro-3-[(4-chlorophényl)méthyl]-4-(difluorométhoxy)-2-éthylquinolin-5-yl)oxy)acétique

**pexopiprant**

ácido ((8-cloro-3-[(4-clorofenil)metil]-4-(difluorometoxi)-2-etilquinolin-5-il)oxi)acético

C$_{21}$H$_{17}$Cl$_2$F$_2$NO$_4$

![Chemical Structure](image)

**pimurutamabum #**

pimurutamab

immunoglobulin G1-kappa, anti-[*Homo sapiens* EGFR (epidermal growth factor receptor; receptor tyrosine-protein kinase erbB-1, ERBB1, HER1, HER-1, ERBB)], humanized monoclonal antibody; gamma1 heavy chain humanized (1-449) [VH (*Homo sapiens* IGHV3-48*03 (78.6%) -(IGHD) -IGHJ3*01 (85.7%)) [8.7.13] (1-119) -*Homo sapiens* IGHG1*03 (100%) G1m3, nG1m1 (CH1 R120 (216) (120-217), hinge 1-15 (218-232), CH2 (233-342), CH3 E12 (358), M14 (360) (343-447), CHS (448-449)) (120-449)], (222-214')-disulfide with kappa light chain humanized (1'-214') [V-KAPPA (*Homo sapiens* IGKV3-11*01 (85.3%) -IGKJ4*01 (90.9%)) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01 (100%) Km3 A45.1 (153), V101 (191) (108'-214')]; dimer (228-228'':231-231'')-bisdisulfide, produced in Chinese hamster ovary (CHO) cells, glycoform alfa

**pimurutamab**

immunoglobuline G1-kappa, anti-[*Homo sapiens* EGFR (récepteur du facteur de croissance épidermique, récepteur tyrosine-protéine kinase erbB-1, ERBB1, HER1, HER-1, ERBB)], anticorps monoclonal humanisé;
pimurutamab

inmunoglobulina G1-kappa, anti-[Homo sapiens EGFR (receptor del factor de crecimiento epidermico, receptor tirosina-proteína kinasa erbB-1, ERBB1, HER1, HER-1, ERBB)], anticuerpo monoclonal humanizado;

cadena pesada gamma1 humanizada (1-449) [VH (Homo sapiens IGHV3-48*03 (78.6%) -IGHD -IGHJ3*01 (85.7%)) [8.7.13] (1-119) -Homo sapiens IGHG1*03 (100%) G1m3, nG1m1 (CH1 R120 (216) (120-217), charnière 1-15 (218-232), CH2 (233-342), CH3 E12 (358), M14 (360) (343-447), CHS (448-449)) (120-449)], (222-214°)-disulfure avec la chaîne légère kappa humanisée (1°-214°) [V-KAPPA (Homo sapiens IGKV3-11*01 (85.3%)-IGKJ4*01 (90.9%)) [6.3.9] (1°-107°) -Homo sapiens IGKC*01 (100%) Km3 A45.1 (153), V101 (191) (108°-214°)];
dimère (228-228°:231-231°)-bisdisulfure, produit dans des cellules ovaires de hamster chinois (CHO), glycoforme alfa
**Recommended INN: List 84**

**posenacaftorum**

8-methyl-2-(3-methyl-1-benzofuran-2-yl)-5-[(1R)-1-(oxan-4-yl)ethoxy]quinoline-4-carboxylic acid

**posénacaftor**

acide 8-méthyl-2-(3-méthyl-1-benzofuran-2-yl)-5-[(1R)-1-(oxan-4-yl)éthoxy]quinoléine-4-carboxylique

**posenacaftor**

ácido 8-metil-2-(3-metil-1-benzofuran-2-il)-5-[(1R)-1-(oxan-4-il)etoxi]quinolina-4-carboxilico

\[ C_{27}H_{27}NO_5 \]

---

**pudexacianini chloride**

pudexacianinium chloride


chlorure de pudexacianinium


cloruro de pudexacianinio


\[ C_{135}H_{197}ClN_4O_{73} \]
quavonlimabum #
quavonlimab

immunoglobulin G1-kappa, anti-[*Homo sapiens* CTLA4 (cytotoxic T-lymphocyte-associated protein 4, CD152)], humanized monoclonal antibody; gamma1 heavy chain humanized (1-445) [VH (*Homo sapiens* IGVH3-72*01 (84.7%) -(IGHD) -IGHJ4*01 (92.9%)) CDR-IMGT [8.10.6] (26-33.51-60.99-104) (1-115) - *Homo sapiens* IGHG1*01 (100%) G1m17,1 (CH1 K120 (212) (116-213), hinge 1-15 (214-228), CH2 (229-338), CH3 D12 (354), L14 (356) (339-443), CHS (444-445)) (116-445)], (224-214")-disulfide with kappa light chain humanized (1'-214") [V-KAPPA (*Homo sapiens* IGKV1-6*01 (81.6%) -IGKJ2*02 (90.9%)) CDR-IMGT [6.3.9] (27-32.50-52.89-97) (1'-107") - *Homo sapiens* IGKC*01 (100%) Km3 A45.1 (153), V101 (191) (108'-214")]; dimer (224-224":227-227")-bisdisulfide, produced in Chinese hamster ovary (CHO) cells, glycoform alfa

quavonlimab

immunoglobuline G1-kappa, anti-[*Homo sapiens* CTLA4 (protéine 4 associée aux lymphocytes T cytotoxiques, CD152)], anticorps monoclonal humanisé; chaîne lourde gamma1 humanisée (1-445) [VH (*Homo sapiens* IGVH3-72*01 (84.7%) -(IGHD) -IGHJ4*01 (92.9%)) CDR-IMGT [8.10.6] (26-33.51-60.99-104) (1-115) - *Homo sapiens* IGHG1*01 (100%) G1m17,1 (CH1 K120 (212) (116-213), charnière 1-15 (214-228), CH2 (229-338), CH3 D12 (354), L14 (356) (339-443), CHS (444-445)) (116-445)], (224-214")-disulfure avec la chaîne légère kappa humanisée (1'-214") [V-KAPPA (*Homo sapiens* IGKV1-6*01 (81.6%) -IGKJ2*02 (90.9%)) CDR-IMGT [6.3.9] (27-32.50-52.89-97) (1'-107") - *Homo sapiens* IGKC*01 (100%) Km3 A45.1 (153), V101 (191) (108'-214")]; dimère (224-224":227-227")-bisdisulfure, produit dans des cellules ovariennes de hamster chinois (CHO), glycoforme alfa

quavonlimab

immunoglobulina G1-kappa, anti-[*Homo sapiens* CTLA4 (proteína 4 asociada a los linfocitos T citotóxicos, CD152)], anticuerpo monoclonal humanizado; cadena pesada gamma1 humanizada (1-445) [VH (*Homo sapiens* IGVH3-72*01 (84.7%) -(IGHD) -IGHJ4*01 (92.9%)) CDR-IMGT [8.10.6] (26-33.51-60.99-104) (1-115) - *Homo sapiens* IGHG1*01 (100%) G1m17,1 (CH1 K120 (212) (116-213), bisagra 1-15 (214-228), CH2 (229-338), CH3 D12 (354), L14 (356) (339-443), CHS (444-445)) (116-445)], (224-214")-disulfuro con la cadena ligera kappa humanizada (1'-214") [V-KAPPA (*Homo sapiens* IGKV1-6*01 (81.6%) -IGKJ2*02 (90.9%)) CDR-IMGT [6.3.9] (27-32.50-52.89-97) (1'-107") - *Homo sapiens* IGKC*01 (100%) Km3 A45.1 (153), V101 (191) (108'-214")]; dímero (224-224":227-227")-bisdisulfuro, producido por células ováricas de hamster chino (CHO), glicosilada alfa
ragifilimab #

immunoglobulin G1-kappa, anti-\([Homo sapiens TNFRSF18]\) (tumor necrosis factor receptor (TNFR) superfamily member 18, activation-inducible TNFR family receptor, AITR, glucocorticoid-induced TNFR-related, GITR, CD375), humanized monoclonal antibody:
gamma1 heavy chain humanized (1-447) [VH \((Homo sapiens IGHV1-2*02\) (80.6%) -\((IGHD) -IGHJ4*01\) (92.9%)) CDR-IMGT [8.8.11] (26-33.51-58.97-107) (1-118) -\(Homo sapiens IGK\) G1m3, nG1m1 (CH1 R120 (215) (119-216), hinge 1-15 (217-231), CH2 (232-341), CH3 E12 (357), M14 (359) (342-446), CHS K\(\delta\)del (447)) (119-447)], (221-220\)-disulfide with kappa light chain humanized (1-113) -\(Homo sapiens IGKC\) Km3 A45.1 (159), V101 (197) (114-220)];
dimer (227-227\(\delta\):230-230\)-bisdisulfide, produced in Chinese hamster ovary (CHO) cells, glycoform alfa

ragifilimab

immunoglobuline G1-kappa, anti-\([Homo sapiens TNFRSF18]\) (membre 18 de la super famille des récepteurs du TNF, récepteur de la famille TNFR induit par activation, AITR, récepteur apparenté au TNF et induit par les glucocorticoides, GITR, CD375), anticorps monoclonal humanisé:
chaine lourde gamma1 humanisée (1-447) [VH \((Homo sapiens IGHV1-2*02\) (80.6%) -\((IGHD) -IGHJ4*01\) (92.9%)) CDR-IMGT [8.8.11] (26-33.51-58.97-107) (1-118) -\(Homo sapiens IGK\) G1m3, nG1m1 (CH1 R120 (215) (119-216), chaîne 1-15 (217-231), CH2 (232-341), CH3 E12 (357), M14 (359) (342-446), CHS K\(\delta\)del (447)) (119-447)], (221-220\)-disulfure avec la chaîne légère kappa humanisée (1-220) \([V\text{-}KAPPA}\ (Homo sapiens IGKV4-1*01\) (91.1%) -\(IGKJ2*01\) (100%)) CDR-IMGT [12.3.9] (27-38.56-58.95-103) (1-113) -\(Homo sapiens IGKC\) Km3 A45.1 (159), V101 (197) (114-220)];
dimère (227-227\(\delta\):230-230\)-bisdisulfure, produit dans des cellules ovariennes de hamster chinois (CHO), glycoforme alfa
Ragifilimab is an immunoglobulin G1-kappa, anti-[Homo sapiens TNFRSF18 (member 18 of the TNF family, TNF receptor induced by activation, AITR, TNF receptor related induced by glucocorticoids, GITR, CD375), monoclonal humanized antibody; heavy chain gamma1 humanized (1-447) [VH (Homo sapiens IGHV1-2*02 (80.6%)-(IGHD) - IGHJ4*01 (92.9%)) CDR-IMGT [8.8.11] (26-33.51-58.97-107) (1-118) -Homo sapiens IGHGI*03 (100%) G1m3, nG1m1 (CH1 R120 (215) (119-216), bisagra 1-15 (217-231), CH2 (232-341), CH3 E12 (357), M14 (359) (342-446), CHS K-del (447)) (119-447)], (221-220)-disulfide with the light chain kappa humanized (1-220) [V-KAPPA (Homo sapiens IGKV4-1*01 (91.1%)-IGKJ2*01 (100%)) CDR-IMGT [12.3.9] (27-38.56-58.95-103) (1-113) -Homo sapiens IGKC*01 (100%) Km3 A45.1 (159), V101 (197) (114'-220')] dimero (227'-227*):230-230*):-bisdisulfide, produced by cellular ovary of hamster chino (CHO), forma glicosilada alfa

Heavy chain / Chaîne lourde / Cadena pesada

```
QVQLVQSGAE VKKPGASVKVS CKGSGYTFT DYAMYWVRQA PGQGLEWIGV 50
IRTYSGDVTY NQKFQRATM TVDKEISAYT MELSLSRDSD WAVYCALRSG 100
TVYFQGWGQG GLTVVQSASG TGPSVYFLA PSESIGGSGT AALSCLVGEQ 150
FFPQVPSSSH GALTSGQFTG FAVLQLSGQ YLESLTVYTP PHYSTDQTYY 200
CNWHRGPIHT KYDFVEFPEK CDKHTCFCPP PAFELLGLPS VLPFPPKDP 250
TLMHSPTEV YCVVVSQVHE DEPYFPFMNV GDEYHART KPFRQHYNHT 300
YRPSVLTVNL IGQHRSGEQK KGQKSLNPQ APIEKTISKA KGQPREPQVY 350
TLPFFKREMT RQQLSSLTVLV KGFYPSDIAV EWSNGQOFN YFVKGTVVLD 400
SDGSFLISK LTVDKSNMQQ GMVFSCSVMM EALNHTHTGQ SLSLSPG 447
```

Light chain / Chaîne légère / Cadena ligera

```
DIVMTQSPDS LAVSLGERAT INCKSSQSLL NSGNQKNYLT WYQQKPGQPS 50
KLLYVASTTR ESQDPQPSG SGGTSPFILT ISSLQAEDVA VYHCQNDYSY 100
PYTFGQGTKL EIKRTVAAPS VFIFPPSDEQ LKSGTASVVC LLNNFYPREA 150
KVQWKVDNAL QSGNSQESVT EQDSKDSTYS LSSTLTLSKA DYEKHKVYAC 200
EVQWQLSSP VTKSFHRGC 220
```

Post-translational modifications

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro

Intra-H (C23-C104) 22-96 262-322 368-426

22'-96' 262'-322' 368'-426'

Intra-L (C23-C104) 23'-94' 221'-220'

Inter-H-L (h 5-CL 126) 221-220 227-230

Inter-H-H (h 11, h14) 230-230*

N-terminal glutaminyl cyclization to pyroglutamyl (pE, 5-oxoprolly)

H VH Q1:
1, 1'

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación

H CH2 N84.4:
298, 298'

Fucosylated complex bi-antennary CHO-type glycans / glycanes de type CHO biantennaires complejos fucosilados

Recifercept fragment (1-336)-(401-413) of the receptor 3 of fibroblast growth factor 3 (FGFR-3, CD333) (1-336)-(401-413) fragment (1-349) [soluble isoform (337-400>del, 414-784>del)-sFGFR3], produced in Chinese hamster ovary (CHO) cells, glycoform alfa

Recifercept #

Recifercept

Human fibroblast growth factor receptor 3 (FGFR-3, CD333) (1-336)-(401-413) fragment (1-349) [soluble isoform (337-400>del, 414-784>del)-sFGFR3], produced in Chinese hamster ovary (CHO) cells, glycoform alfa

Recifercept

Fragment (1-336)-(401-413) of the receptor 3 of the factor of croissance of the fibroblasts human (FGFR-3, CD333) (1-336) [soluble soluble (337-400>del, 414-784>del)-sFGFR3], produit dans des cellules ovariennes de hamster chino (CHO), glycoforme alfa
recifercept

fragmento (1-336)-(401-413) del receptor 3 del factor de crecimiento de los fibroblastos humanos (FGFR-3, CD333) (1-349) [isóforma soluble (337-400>del, 414-784>del)-sFGFR3], producido en las células ováricas de hamster chino (CHO), glicoforina alfa

Sequence / Séquence / Secuencia
ESLGTEQRVV GRAAEVPGPE PGQQEQLVFG SGDAVELSCP PPGGGPMGPT 50
VWVKDGTGLV PSERVLVGPQ RLQVLNASHE DSGAYSCRQR LTQRVLCHFS 100
VRVTDAPSG DGEDDGEA DTSVDGTGAP MTRPPMOK LLAPPAANTV 150
RPCCPAAOPH TPSISWKLKG RFEPRGHIG GIRHLIQPSM LOMSVPSID 200
RNVTYCVREN PFQOIQRYYT LVQILFPLR PIQAGTLPAN QTVVLDOVE 250
FEKVYIDAG PSQKLHVEV NSDESVFGDG TPYTVLALAT GANTOKELE 300
VLSLVHITTE SAGTYTCLAG NQOFSIHSA MLVYPYVSE SHADSST 349

Post-translational modifications
Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro
intra-chain 39-97 154-206 253-317
(
Cys-SH: 
87)

Glycosylation sites / Sites de glycosylation / Posiciones de glicosilación
N76, N203, N240, N272, N293, N306, N342
Fucosylated complex bi-antennary CHO-type glycans / Glycans de type CHO bi-antennaires complexes fucosilés / Glicanos de tipo CHO biantenarios complejos fucosilados

relzomostatum
relzomostat

(3R,4S,5S,6R)-5-methoxy-4-[(2R,3R)-2-methyl-3-(3-methylbut-2-en-1-yl)oxiran-2-yl]-1-oxaspiro[2.5]octan-6-yl 6-(2,2-difluoroethyl)-2,6-diazaspiro[3.3]heptane-2-carboxylate

relzomostat


relzomostat

6-(2,2-difluoroétil)-2,6-diazaspiro[3.3]heptano-2-carboxilato de (3R,4S,5S,6R)-5-métoxi-4-[(2R,3R)-2-métil-3-(3-métilbut-2-en-1-il)oxiran-2-il]-1-oxaspiro[2.5]octan-6-il

C_{24}H_{36}F_{2}N_{2}O_{5}

resiquimodum pegolum
resiquimod pegol


résiquimod pégol


resiquimod pegol

revdofilimab

immunoglobulin G1-kappa, anti-[Homo sapiens TNFRSF4 (tumor necrosis factor receptor (TNFR) superfamily member 4, ACT35, OX40, CD134)], monoclonal antibody;
gamma1 heavy chain (1-450) [VH (Mus musculus IGHV5-6-3*01 (88.8%) -IGHJ4*01 (93.8%)/Homo sapiens IGHV3-7*01 (88.8%) -IGHD -IGHJ4*01 (92.3%)) CDR-IMGT [8.8.13] (26-33.51-58.97-109) (1-120) -Homo sapiens IGHG1*03v, G1m3-G1m17, nG1m1 (CH1 R120>K (217) (121-218), hinge 1-15 (219-233), CH2 (234-343), CH3 E12 (359), M14 (361) (344-448), CHS (449-450)) (121-450)], (223-218')-disulfide with kappa light chain (1'-218') [V-KAPPA (Mus musculus IGKV3-4*01 (83.8%) -IGKJ1*01 (90.9%)/Homo sapiens IGKV4-1*01 (83.2%) -IGKJ4*01 (100%)) CDR-IMGT [10.3.9] (27-36.54-56.93-101) (1'-111') -Homo sapiens IGKC*01 (100%) Km3 A45.1 (157), V101 (195) (112'-218');
dimer (229-229":232-232")-bisdisulfide, produced in Chinese hamster ovary (CHO) cells, glycoform alfa

revdofilimab

immunoglobe G1-kappa, anti-[Homo sapiens TNFRSF4 (membre 4 de la super famille des récepteurs du facteur de nécrose tumorale, ACT35, OX40, CD134)], anticorps monoclonal;
chaîne lourde gamma1 (1-450) [VH (Mus musculus IGHV5-6-3*01 (88.8%) -IGHJ4*01 (93.8%)/Homo sapiens IGHV3-7*01 (88.8%) -IGHD -IGHJ4*01 (92.3%)) CDR-IMGT [8.8.13] (26-33.51-58.97-109) (1-120) -Homo sapiens IGHG1*03v, G1m3-G1m17, nG1m1 (CH1 R120>K (217) (121-218), chaîne 1-15 (219-233), CH2 (234-343), CH3 E12 (359), M14 (361) (344-448), CHS (449-450)) (121-450)], (223-218')-disulfure avec la chaîne légère kappa (1'-218') [V-KAPPA (Mus musculus IGKV3-4*01 (83.8%) -IGKJ1*01 (90.9%)/Homo sapiens IGKV4-1*01 (83.2%) -IGKJ4*01 (100%)) CDR-IMGT [10.3.9] (27-36.54-56.93-101) (1'-111') -Homo sapiens IGKC*01 (100%) Km3 A45.1 (157), V101 (195) (112'-218');
dimère (229-229":232-232")-bisdisulfure, produit dans des cellules ovarienes de hamster chinois (CHO), glycoforme alfa

revdofilimab

inmunoglobulina G1-kappa, anti-[Homo sapiens TNFRSF4 (miembro 4 de la super familia de los receptores del factor de necrosis tumoral, ACT35, OX40, CD134)], anticuerpo monoclonal;
cadena pesada gamma1 (1-450) [VH (Mus musculus IGHV5-6-3*01 (86.8%) -IGHJ4*01 (93.8%)/Homo sapiens IGHV3-7*01 (86.8%) -IGHD -IGHJ4*01 (92.3%)) CDR-IMGT [8.8.13] (26-33.51-58.97-109) (1-120) -Homo sapiens IGHG1*03v, G1m3-G1m17, nG1m1 (CH1 R120-K (217) (121-218), bisagra 1-15 (219-233), CH2 (234-343), CH3 E12 (359), M14 (361) (344-448), CHS (449-450)) (121-450)], (223-218°)-disulfuro con la cadena ligera kappa (1°-218°) [VKappa (Mus musculus IGHV3-4*01 (86.8%) -IGKJ1*01 (90.9%) Homo sapiens IGHV4-1*01 (83.2%) -IGKJ4*01 (100%)) CDR-IMGT [10.3.9] (27-36.54-56.93-101) (1°-111°) -Homo sapiens IGKC*01 (100%) Km3 A45.1 (157), V101 (195) (112°-218°)], dimero (229-229°:232-232°)-bisdisulfuro, producido por células ováricas de hamster chino (CHO), forma glicosilada alfa.

**rezivertinib**

rezivertinib

\[N-(2-[2-(dimethylamino)ethoxy]-4-methoxy-5-[[4-(1-methyl-1H-indol-3-yl)pyrimidin-2-yl]amino]phenyl)prop-2-enamide\]

\(\text{C}_{27}\text{H}_{30}\text{N}_{6}\text{O}_{3}\)
rilematovir

3-((5-chloro-1-[3-(methanesulfonyl)propyl]-1H-indol-2-yl)methyl)-1-(2,2,2-trifluoroethyl)-1,3-dihydro-2H-imidazo[4,5-c]pyridin-2-one

rilématovir

3-((5-chloro-1-[3-(méthanesulfonyl)propyl]-1H-indol-2-yl)méthyl)-1-(2,2,2-trifluoroéthyl)-1,3-dihydro-2H-imidazo[4,5-c]pyridin-2-one

rilematovir

3-((5-cloro-1-[3-(metanosulfonil)propi]-1H-indol-2-il)métil)-1-(2,2,2-trifluoroetil)-1,3-dihidro-2H-imidazo[4,5-c]piridin-2-ona

C₂₁H₂₀ClF₃N₄O₃S

ripafollitropinum alfa (bovinum) #
ripafollitropin alfa (bovine)

bovine follicle-stimulating hormone (synthetic analog):
[follitropin (Bos taurus) subunit β (1-109)]-[human chorionic gonadotropin (hCG) C-terminal 28-peptide linker (110-137)]-[glycoprotein hormones α chain (follitropin subunit α) (Bos taurus) (138-233)] fusion protein, produced in Chinese hamster ovary (CHO) cells, glycoform alfa

ripafollitropine alfa (bovine)
hormone folliculostimulante bovine (analogue synthétique):
protéine de fusion [folitropine (Bos taurus) sous-unité β (1-109)]-[peptide liant: 28-peptide C-terminal de la gonadotrophine chorionique humaine (hCG) (110-137)]-[chaîne α des hormones glycoprotéiques (folitropine sous-unité α) (Bos taurus) (138-233)], produit par des cellules ovariennes de hamster chinois (CHO), forme glycosylée alfa

ripafollitropina alfa (bovina)
hormona estimulante del folículo bovina (análogo sintético):
proteina de fusión [folitropina (Bos taurus) subunidad β (1-109)]-[conector: 28-péptido C-terminal de la gonadotropina coriónica humana (hCG) (110-137)]-[cadena α de las hormonas glicoproteicas (folitropina subunidad α) (Bos taurus) (138-233)], producida por células ováricas de hamster chino (CHO), forma glicosilada alfa
Recommended INN: List 84

WHO Drug Information, Vol. 34, No. 3, 2020

Sequence/Secuencia:
CETLTVTVY EEKQGFCIS IHTMCGAGY TETQVLYRPP ARHIQECTCT 5
FRELYTVY VFGAVASKH LITMYTPC KCSCGSDST CCTVQGGLPS 11
YCEFREIKES SSSKAPPPFL PESRILIQPS UTFILQFPD GEFTMQSGPE 1
CEKREMYF KPAEFLYUCCGQKSAIPF PARSEKTV PVNITSEUAG 24
CVNASAPAF AYQVOYVHIFT TCHQTTY 3


Glycosylation sites / Sitios de glycosilación / Posisiciones de glycosilación:
potential N-glycosylation: N3, N22, N193, N219
potential O-glycosylation: S113, S119, S124, S130

Other post-translational modifications:
potential deamidation: N5, N22, N44, Q46, Q137, Q146, N156, Q168, N193, N214, N219
potential S-oxidation: M145, M170, M188, M212


teratamabum #
teratamab

immunoglobulin G1-kappa, anti-[*Homo sapiens* MS4A1 (membrane-spanning 4-domains subfamily A member 1, CD20)], chimeric monoclonal antibody; gamma1 heavy chain chimeric (1-451) [VH (*Mus musculus* IGHV1-12*01* (91.8%) -(IGHD) -IGHJ1*01* (87.5%)) CDR-IMGT [8.8.14] (26-33.51-58.97-110) (1-121) -*Homo sapiens* IGHG1*01* (100%) G1m17,1 (CH1 K120 (218) (122-219), hinge 1-15 (220-234), CH2 (235-344), CH3 D12 (360), L14 (362) (345-449), CHS (450-451)) (122-451), (224-213')-disulfide with kappa light chain chimeric (1'-213') [V-KAPPA (*Mus musculus* IGKV4-72*01* (95.8%) -IGKJ1*01* (100%)) CDR-IMGT [5.3.9] (27-31.49-51.88-96) (1'-106') -*Homo sapiens* IGKC*01* (100%), Km3 A45.1 (152), V101 (190) (107'-213')]; dimer (230-230'':233-233'')-bisdisulfide, produced in Chinese hamster ovary (CHO) cells, glycoform alfa


teratamab

immunoglobuline G1-kappa, anti-[*Homo sapiens* MS4A1 (membre 1 de la sous-famille A à 4 domaines transmembranaires, CD20)], anticorps monoclonal chimérique; chaîne lourde gamma1 chimérique (1-451) [VH (*Mus musculus* IGHV1-12*01* (91.8%) -(IGHD) -IGHJ1*01* (87.5%)) CDR-IMGT [8.8.14] (26-33.51-58.97-110) (1-121) -*Homo sapiens* IGHG1*01* (100%) G1m17,1 (CH1 K120 (218) (122-219), charnière 1-15 (220-234), CH2 (235-344), CH3 D12 (360), L14 (362) (345-449), CHS (450-451)) (122-451), (224-213')-disulfure avec la chaîne légère kappa chimérique (1'-213') [V-KAPPA (*Mus musculus* IGKV4-72*01* (95.8%) -IGKJ1*01* (100%)) CDR-IMGT [5.3.9] (27-31.49-51.88-96) (1'-106') -*Homo sapiens* IGKC*01* (100%), Km3 A45.1 (152), V101 (190) (107'-213')]; dimère (230-230'':233-233'')-bisdisulfure, produite dans des cellules ovariennes de hamster chinois (CHO), glycoforme alfa


teratamab

immunoglobulina G1-kappa, anti-[*Homo sapiens* MS4A1 (miembro 1 de la subfamilia A con 4 dominios transmembranarios, CD20)], anticuerpo monoclonal quimérico;
rocafinogenum sifuclasmidum

rocafinogene sifuclasmid

A DNA plasmid encoding both subunits of human interleukin-12 (IL12), subunit alpha (IL12A, IL-12 subunit p35) and subunit beta (IL12B; IL-12 subunit p40), under the control of a human cytomegalovirus (CMV) immediate-early 1 (IE1) promoter and a simian cytomegalovirus (sCMV) promoter, respectively.

rocafinogène sifuclasmide

plasmide dont l’ADN code pour les deux sous-unités de l’interleukine 12 humaine (IL-12), sous-unité alpha (IL12A, sous-unité p35 de l’IL-12) et sous-unité bêta (IL12B; sous-unité p40 de l’IL-12), sous le contrôle d’un activateur/promoteur immédiate-précoce 1 (IE1) du cytomegalovirus (CMV) et d’un promoteur du cytomegalovirus simiesque (sCMV), respectivement.

rocafinogén sifuclasmida

Un plásmido de DNA que codifica para ambas subunidades de la interleucina 12 (IL12) humana, la subunidad alfa (IL12A, IL-12 subunidad p35) y la subunidad beta (IL12B; IL-12 subunidad p40), bajo el control de un promotor inmediato-temprano 1 (IE1) del citomegalovirus (CMV) humano y un promotor del citomegalovirus de simio (sCMV), respectivamente.
Rosopatamab

**Recommended INN: List 84**

**WHO Drug Information, Vol. 34, No. 3, 2020**

**Rosopatamab**

*Rosopatamab immunoglobulin G1-kappa, anti-[Homo sapiens FOLH1 (folate hydrolase, prostate specific membrane antigen, PSMA)], monoclonal antibody; gamma1 heavy chain (1-445) [VH (Mus musculus IGHV1-26*01 (78.4%)-(IGHD)-IGHJ2*01 (92.9%)]/Homo sapiens IGHV1-69-2*01 (76.3%)-(IGHD)-IGHJ4*01 (92.9%)) [8.8.8] (1-115) -Homo sapiens IGHG1*01 (100%) G1m17.1 (CH1 K120 (212) (116-213), hinge 1-15 (214-228), CH2 (229-338), CH3 D12 (354), L14 (356) (339-443), CHS (444-445)) (116-445), (218-214')-disulfide with kappa light chain (1'-(214')] [V-KAPPA (Mus musculus IGKV6-23*01 (80.9%)] -IGKJ2*03 (72.7%)/Homo sapiens IGKV1-13*02 (78.7%)-IGKJ3*01 (91.7%)) [6.3.9] (1'-107') -Homo sapiens IGKC*01 (100%) Km3 A45.1 (153), V101 (191) (108'-214');
dimer (224-224':227-227')-bisdisulfide, produced in Chinese hamster ovary (CHO) cells, glycoform alfa

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**Rosopatamab**

*Rosopatamab immunoglobuline G1-kappa, anti-[Homo sapiens FOLH1 (folate hydrolase, antigène membranaire spécifique de la prostate, PSMA)], anticorps monoclonal; chaîne lourde gamma1 (1-445) [VH (Mus musculus IGHV1-26*01 (78.4%)-(IGHD)-IGHJ2*01 (92.9%)]/Homo sapiens IGHV1-69-2*01 (76.3%)-(IGHD)-IGHJ4*01 (92.9%)) [8.8.8] (1-115) -Homo sapiens IGHG1*01 (100%) G1m17.1 (CH1 K120 (212) (116-213), charnière 1-15 (214-228), CH2 (229-338), CH3 D12 (354), L14 (356) (339-443), CHS (444-445)) (116-445), (218-214')-disulfure avec la chaîne légère kappa (1'-(214')] [V-KAPPA Mus musculus IGKV6-23*01 (80.9%)] -IGKJ2*03 (72.7%)/Homo sapiens IGKV1-13*02 (78.7%)-IGKJ3*01 (91.7%)) [6.3.9] (1'-107') -Homo sapiens IGKC*01 (100%) Km3 A45.1 (153), V101 (191) (108'-214');
dimère (224-224':227-227')-bisdisulfure, produit dans des cellules ovariennes de hamster chinois (CHO), glycoforme alfa

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**Rosopatamab**

*Rosopatamab inmunoglobulina G1-kappa, anti-[Homo sapiens FOLH1 (folato hidrolasa, antígeno membranario específico de la próstata, PSMA)], anticuerpo monoclonal; cadena pesada gamma1 (1-445) [VH (Mus musculus IGHV1-26*01 (78.4%)-(IGHD)-IGHJ2*01 (92.9%)]/Homo sapiens IGHV1-69-2*01 (76.3%)-(IGHD)-IGHJ4*01 (92.9%)) [8.8.8] (1-115) -Homo sapiens IGHG1*01 (100%) G1m17.1 (CH1 K120 (212) (116-213), bisagra 1-15 (214-228), CH2 (229-338), CH3 D12 (354), L14 (356) (339-443), CHS (444-445)) (116-445), (218-214')-disulfuro con la cadena ligera kappa (1'-(214')] [V-KAPPA Mus musculus IGKV6-23*01 (80.9%)] -IGKJ2*03 (72.7%)/Homo sapiens IGKV1-13*02 (78.7%)-IGKJ3*01 (91.7%)) [6.3.9] (1'-107') -Homo sapiens IGKC*01 (100%) Km3 A45.1 (153), V101 (191) (108'-214');
dímero (224-224':227-227')-bisdisulfuro, producido por células ováricas de hamster chino (CHO), forma glicosilada alfa
rosopatamab tetraxetanum #
rosopatamab tetraxetan

immunoglobulin G1-kappa, anti-[Homo sapiens FOLH1 (folate hydrolase, prostate specific membrane antigen, PSMA)], monoclonal antibody, tetraxetan conjugate; gamma1 heavy chain (1-445) [VH (Mus musculus IGHV1-26*01 (78.4%) -(IGHD) -IGHJ2*01 (92.9%)/Homo sapiens IGHV1-69-2*01 (76.3%) -(IGHD) -IGHJ4*01 (92.9%)) [8.8.8] (1-115) -Homo sapiens IGHG1*01 (100%) G1m17,1 (CH1 K120 (212) (116-213), hinge 1-15 (214-228), CH2 (229-338), CH3 D12 (354), L14 (356) (339-443), CHS (444-445)) (116-445), (218-214')-disulfide with kappa light chain (1'-214') [V-KAPPA (Mus musculus IGKV1-13*02 (78.7%) -(IGHJ3*01 (91.7%)) [6.3.9] (1'-107) -Homo sapiens IGKC*01 (100%) Km3 A45.1 (153), V101 (191) (108-214')] ; dimer (224-224*:227-227*)-bisdisulfide; produced in Chinese hamster ovary (CHO) cells, glycoform alfa, tetraxetan (DOTA) conjugate (on an average of 3 to 5 lysyl, linked to the chelator by their N6)

rosopatamab têtaxétan

immunoglobuline G1-kappa, anti-[Homo sapiens FOLH1 (folate hydrolase, antígeno membrana specific de la prostate, PSMA)], anticorps monoclonal, conjugué au têtaxétan; chaîne lourde gamma1 (1-445) [VH (Mus musculus IGHV1-26*01 (78.4%) -(IGHD) -IGHJ2*01 (92.9%)/Homo sapiens IGHV1-69-2*01 (76.3%) -(IGHD) -IGHJ4*01 (92.9%)) [8.8.8] (1-115) -Homo sapiens IGHG1*01 (100%) G1m17,1 (CH1 K120 (212) (116-213), charnière 1-15 (214-228), CH2 (229-338), CH3 D12 (354), L14 (356) (339-443), CHS (444-445)) (116-445), (218-214')-disulfure avec la chaîne légère kappa (1'-214') [V-KAPPA (Mus musculus IGKV1-13*02 (78.7%) -(IGHJ3*01 (91.7%)) [6.3.9] (1'-107) -Homo sapiens IGKC*01 (100%) Km3 A45.1 (153), V101 (191) (108-214')] ; dimère (224-224*:227-227*)-bisdisulfure; produit en cellules de hamster chinois ovary (CHO) cells, glycoform alfa, têtaxétan (DOTA) conjugate (sur une moyenne de 3 à 5 lysyl, lié à l’chelateur par leur N6)
dimère (224-224";227-227")-bisdisulfure; produit dans des cellules ovariennes de hamster chinois (CHO), glycoforme alfa, conjugué au tétraxétan (DOTA) (avec une moyenne de 3 à 5 lysyl liés au chélateur par leur N6)

rosopatamab tetraxétan

inmunoglobulina G1-kappa, anti-[Homo sapiens FOLH1 (folato hidrolasa, antígeno membranario específico de la próstata, PSA)], anticuerpo monoclonal, conjugado con tetraxétan ; cadena pesada gamma1 (1-445) [IGH (Mus musculus IGHV1-26*01 (76.4%) - (IGHD) -IGHJ2*01 (92.9%)/Homo sapiens IGHV1-69-2*01 (76.3%) - (IGHD) -IGHJ4*01 (92.9%)) [8.8.8] (1-115) - Homo sapiens IGHG1*01 (100%) G1m17,1 (CH1 K120 (212) (116-213), bisagra 1-15 (214-228), CH2 (229-338), CH3 D12 (354), L14 (356) (339-443), CHS (444-445)) (218-214")-disulfur con la cadena ligera kappa (1-214") [V-KAPPA Mus musculus IGKV6-23*01 (80.9%) -IGJK2*03 (72.7%)|(Homo sapiens IGKV1-13*02 (78.7%) -IGJK3*01 (91.7%)) [6.3.9] (1-107") - Homo sapiens IGKC*01 (100%) Km3 A45.1 (153), V101 (191) (108-214")], dimérome (224-224";227-227")-bisdisulfure; producido por células ováricas de hamster chino (CHO), forma glicosilada alfa, conjugado con tetraxétan (DOTA) (con una media de 3 a 5 restos lisil unidos al quelante por sus respectivos N6)

Heavy chain / Chaîne lourde / Cadena pesada
EVQLVQSGPE VRHPSQTPKVE SCKSGTVPFT ETYTHWKVQA PGESLMNQN 50
INENNQGQTYY QKPEINEGLAT TTVNTSFDQY MELALLSRAH TAVCYNAMG 100
NPQMWQGQTY LTVSSASEKRG PVYYFAALPS KESRGGTAL GCLVKEAFFY 150
PPVSFNGGSG LTSQGWTPFA VLSQSEGQYL SSVVTSPSS LSQVTQICNY 200
NRHPSMTKVD KVPKPSDRCR WYCTCPCFAP ELLQGSLFIV LFPKFQFPDT 250
IEKSTPTCV YQSYSHDDPE FRTNFQTMGC YWEQVTRRPE EQQYSNHDR 300
VSDTVGLOWD WKGKEVYVRK MESNLAPAPI ERTSISAKQG PNSQVLTLP 350
PERDELMNQG VSLCLVRGKP YSFDILAVHE SHQPEBNKK Y77PVFLSDG 400
STPSGLKTLY DESQWQERYQ FCSYVHYMAAL HNHPQGKLS LERFX 445

Light chain / Chaîne légère / Cadena ligera
DIQMTQSPSS LSSTYGSPSV LTRASQAVQG TAYMVYQQKP GSSPEVLLY 50
ASTHRTYCPFP RFGGGEQGTD PFLTISQLQF EDFADYVCQ YNHFPLPGD 100
GTKPSLITKVP APPFPVIFPP SFQKLSQTA SVCCLVNLFY PREDVFQKTV 150
DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG 200
DHLLQGQKSQ KSYEVRGQSD STYSLSTLT LEKADYEHVK VYACEVTHQG 224

Post-translational modifications
Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro
Intra-H (C23-C104) 22-96 142-198 259-319 365-423
22"-96" 142"-198" 259"-319" 365"-423"
Inter-H (C23-C104) 23'88" 134'-194'
Inter-H-L (b 5-CL 126) 218'-214" 219'-214"
Inte-H-H (b 11, h 14) 224'-224" 227'-227"

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
H CH2 N84.4: 295, 295"

Fucosylated complex bi-antennary CHO-type glycans / glycanes de tipo CHO bi-antennaires complexes fucosilés / glicanos de tipo CHO biantenarios complejos fucosilados.

Potential modified residues / résidus modifiés potentiels / restos modificados potenciales

3 to 5 lysyl (K)
3 a 5 lisil (K)
3 a 5 lysyl (K)

Nα-(tetraxétan)-l-lysyl
sabatolimab

immunoglobulin G4-kappa, anti-[Homo sapiens HAVCR2 (hepatitis A virus cellular receptor 2, T-cell immunoglobulin mucin family member 3, Tim-3, TimD3, CD366)], humanized monoclonal antibody; gamma4 heavy chain humanized (1-444) [VH (Homo sapiens IGHV1-46*01 (87.8%) -IGHD -IGHJ4*01 (92.3%)) CDR-IMGT [8.8.11] (26-33.51-58.97-107) (1-118)-Homo sapiens IGHG4*01, G4v5 h P10 (CH1 (119-216), hinge 1-12 S10>P (226) (217-228), CH2 (229-338), CH3 (339-443), CHS K>del (444)) (119-444), (132-218')-disulfide with kappa light chain humanized (1'-218') [V-KAPPA (Homo sapiens IGKV1-39*01 (81.6%) -IGKJ4*01 (100%)) CDR-IMGT [10.3.9] (27-36.54-56.93-101) (1'-111') -Homo sapiens IGKC*01 (100%), Km3 A45.1 (157), V101 (195) (112'-218')]; dimer (224-224";227-227")-bisdisulfide, produced in Chinese hamster ovary (CHO) cells, glycoform alpha

sabatolimab

immunoglobuline G4-kappa, anti-[Homo sapiens HAVCR2 (récepteur cellulaire 2 du virus de l'hépatite A, CD366, membre 3 de la famille mucine immunoglobuline des cellules T, Tim-3, TimD3, CD366)], anticorps monoclonal humanisé; chaîne lourde gamma4 humanisée (1-444) [VH (Homo sapiens IGHV1-46*01 (87.8%) -IGHD -IGHJ4*01 (92.3%)) CDR-IMGT [8.8.11] (26-33.51-58.97-107) (1-118)-Homo sapiens IGHG4*01, G4v5 h P10 (CH1 (119-216), charnière 1-12 S10>P (226) (217-228), CH2 (229-338), CH3 (339-443), CHS K>del (444)) (119-444), (132-218')-disulfure avec la chaîne légère kappa humanisée (1'-218') [V-KAPPA (Homo sapiens IGKV1-39*01 (81.6%) -IGKJ4*01 (100%)) CDR-IMGT [10.3.9] (27-36.54-56.93-101) (1'-111') -Homo sapiens IGKC*01 (100%), Km3 A45.1 (157), V101 (195) (112'-218')]; dimère (224-224";227-227")-bisdisulfure, produit dans des cellules ovariennes de hamster chinois (CHO), glycoforme alpha

sabatolimab

imunoglobulina G4-kappa, anti-[Homo sapiens HAVCR2 (receptor celular 2 del virus de la hepatitis A, CD366, miembro 3 de la familia mucina immunoglobulina de las células T, Tim-3, TimD3, CD366)], anticuerpo monoclonal humanizado; cadena pesada gamma4 humanizada (1-444) [VH (Homo sapiens IGHV1-46*01 (87.8%) -IGHD -IGHJ4*01 (92.3%)) CDR-IMGT [8.8.11] (26-33.51-58.97-107) (1-118)-Homo sapiens IGHG4*01, G4v5 h P10 (CH1 (119-216), bisagra 1-12 S10>P (226) (217-228), CH2 (229-338), CH3 (339-443), CHS K>del (444)) (119-444), (132-218')-disulfuro con la cadena ligera kappa humanizada (1'-218') [V-KAPPA (Homo sapiens IGKV1-39*01 (81.6%) -IGKJ4*01 (100%)) CDR-IMGT [10.3.9] (27-36.54-56.93-101) (1'-111') -Homo sapiens IGKC*01 (100%), Km3 A45.1 (157), V101 (195) (112'-218')]; dimero (224-224";227-227")-bisdisulfuro, producido por células ováricas de hamster chino (CHO), forma glicosilada alfa
**samelisantum**

*samelisant*

\[N\{4\{1-cyclobutylpiperidin-4-yl\}oxy\{phenyl\}\}2-(morpholin-4-yl)acetamide\]

**samélisant**

\[N\{4\{1-cyclobutylpiperidin-4-yl\}oxy\{phényl\}\}2-(morpholin-4-yl)acetamide\]

**samelisant**

\[N\{4\{1-ciclobutilpiperidin-4-il\}oxi\{fenil\}\}2-(morfolin-4-il)acetamida\]

\[C_{21}H_{31}N_{3}O_{3}\]

**samuraciclibum**

*samuraciclib*

\[(3R,4R)-4-\{[7-(benzylamino)-3-(propan-2-yl)pyrazolo[1,5-a]pyrimidin-5-yl]amino\}methyl)piperidin-3-ol\]

**samuraciclib**

\[(3R,4R)-4-\{[7-(benzylamino)-3-(propan-2-yl)pyrazolo[1,5-a]pyrimidin-5-yl]amino\}méthyl)pipéridin-3-ol\]

**samuraciclib**

\[(3R,4R)-4-\{[7-(benzilamino)-3-(propan-2-il)pirazolo[1,5-a]pirimidin-5-il]amino\}metil)piperidin-3-ol\]
seralutinibum

seralutinib

\[N\{-3\{[(1S)-1\{-[6\{(3,4\text{-dimethoxyphenyl})\text{pyrazin-2-yl}\text{amino}]}\text{ethyl}][phenyl]\}-5\text{-methylpyridine-3-carboxamide}\}

\[C_{22}\text{H}_{30}\text{N}_{6}\text{O}\]

séralutinib

\[N\{-3\{[(1S)-1\{-[6\{(3,4\text{-diméthoxyphényl})\text{pyrazin-2-yl}\text{amino}]}\text{éthyl}][phényl]\}-5\text{-méthylpyridine-3-carboxamide}\}

\[C_{22}\text{H}_{27}\text{N}_{5}\text{O}_{3}\]

seralutinib

\[N\{-3\{[(1S)-1\{-[6\{(3,4\text{-dimetoxyfenil})\text{pirazin-2-yl}\text{amino}]}\text{etil}][fenil]\}-5\text{-metilpiridina-3-carboxamida}\}

\[C_{22}\text{H}_{30}\text{N}_{6}\text{O}\]

simoladagenum autotemcelum #

simoladagene autotemcel

autologous CD34+ hematopoietic stem cells (HSC), obtained by leukapheresis or from bone marrow, transduced \textit{ex vivo} with a non-replicating, self-inactivating (SIN) lentiviral vector encoding codon optimised human adenosine deaminase (ADA) under the internal control of elongation factor 1α short promoter (EFS)

simoladagène autotemcel

cellules souches hématopoïétiques CD34+ autologues obtenues par leucophérèse ou de la moëlle osseuse, transduites \textit{ex vivo} avec un vecteur lentiviral non-répliquant, auto-inactivant (SIN) codant pour l’adénosine déaminase (ADA) humaine codon optimisé sous le contrôle interne d’un promoteur court du facteur d’élongation 1α (EFS)

simoladagén autotemcel

células madre hematopoyéticas CD34+ autólogas obtenidas por leucoaféresis o de médula ósea, transducidas \textit{ex vivo} con un vector lentiviral no replicativo y auto inactivante (SIN), que codifica para la adenosina deaminasa (ADA) humana con codones optimizados bajo el control interno del promotor corto del factor de elongación 1α (EFS)

sisunatovirum

sisunatovir

1\'\{-[5\{(aminomethyl)-1\{-[4,4,4\text{-trifluorobutyl}]-1H-benzimidazol-2-yl\}methyl]-6\'-fluorospiro[cyclopropane-1,3\'-indol]-2\'(1'H\)-one

sisunatovir

1\'\{-[5\{(aminomethyl)-1\{-[4,4,4\text{-trifluorobutyl}]-1H-benzimidazol-2-yl\}methyl]-6\'-fluorospiro[cyclopropane-1,3\'-indol]-2\'(1'H\)-one
sisunatovir
1'-{(5-(aminomethyl)-1-(4,4,4-trifluorobutyl)-1H-benzimidazol-2-yl)ethyl}-6'-fluoro-spiro[cyclopropane-1,3'-[3H]indol]-2'(1'H)-one

C_{23}H_{22}F_{4}N_{4}O

sovesudilum
sovesudil
propyl 2'-((aminomethyl)-5'-[(3-fluoropyridin-4-yl)carbamoyl][1,1'-biphenyl]-3-carboxylate

sovésdil
2'-((aminométhyl)-5'-[(3-fluoropyridin-4-yl)carbamoyl][1,1'-biphényl]-3-carboxylic acid of propyle

sovesudil
2'-((aminometil)-5'-[(3-fluoropiridin-4-il)carbamoil][1,1'-bifenil]-3-carboxilato de propilo

C_{23}H_{22}FN_{3}O_{3}

sugemalimabum #
sugemalimab
immunoglobulin G4-lambda, anti-[\textit{Homo sapiens} CD274 (programmed death ligand 1, PDL1, PD-L1, B7 homolog 1, B7H1)], \textit{Homo sapiens} monoclonal antibody, gamma4 heavy chain \textit{Homo sapiens} (1-448) [VH (\textit{Homo sapiens} IGHV3-23*01 (98.0%) - (IGHD) - IGHJ4*01 (100%)) [8.8.14] (1-121) -\textit{Homo sapiens} IGHG4*01, G4v5 h P10 (CH1 (122-219), hinge 1-12 S10>P (229) (220-231), CH2 (232-341), CH3 (342-446), CHS (447-448)) (122-448)], (135-213')-disulfide with lambda light chain \textit{Homo sapiens} (1'-214') [\textit{\lambda}-LAMBDA (\textit{Homo sapiens} IGLV3-21*02 (100%) - IGLJ2*01 (100%)) [6.3.11] (1'-108') -\textit{Homo sapiens} IGLC2*01 (100%)] (109'-214')] - dimer (227-227' :230-230")-bisdisulfide, produced in Chinese hamster ovary (CHO) cells, glycoform alfa

sugémalimab
immunoglobuline G4-lambda, anti-[\textit{Homo sapiens} CD274 (ligand 1 de mort programmée, PDL1, PD-L1, homologue 1 de B7, B7H1)], anticorps monoclonal \textit{Homo sapiens};
chaîne lourde gamma4 Homo sapiens (1-448) [VH (Homo sapiens IGHV3-23*01 (98.0%) -IGHD) - IGHJ4*01 (100%)) [8.8.14] (1-121) -Homo sapiens IGHG4*01, G4v5 h P10 (CH1 (122-219), chaîne 1-12 S10>P (229) (220-231), CH2 (232-341), CH3 (342-446), CHS (447-448)) (122-448)], (135-213)-disulfure avec la chaîne légère lambda Homo sapiens (1-214) [V-LAMBDA (Homo sapiens IGLV3-21*02 (100%) - IGLJ2*01 (100%)) [6.3.11] (1-108) -Homo sapiens IGLC2*01 (100%) (109-214)];
dimère (227-227'':230-230'')-bisdisulfure, produit dans des cellules ovariennes de hamster chinois (CHO), glycoforme alfa

sugemalimab

inmunoglobulina G4-lambda, anti-[Homo sapiens CD274 (ligando 1 de muerte programada, PDL1, PD-L1, homólogo 1 de B7, B7H1)], anticuerpo monoclonal Homo sapiens;
cadena pesada gamma4 Homo sapiens (1-448) [VH (Homo sapiens IGHV3-23*01 (98.0%) -IGHD) - IGHJ4*01 (100%)) [8.8.14] (1-121) -Homo sapiens IGHG4*01, G4v5 h P10 (CH1 (122-219), bisagra 1-12 S10>P (229) (220-231), CH2 (232-341), CH3 (342-446), CHS (447-448)) (122-448)], (135-213)-disulfuro con la cadena ligera lambda Homo sapiens (1-214) [V-LAMBDA (Homo sapiens IGLV3-21*02 (100%) - IGLJ2*01 (100%)) [6.3.11] (1-108) -Homo sapiens IGLC2*01 (100%) (109-214)];
dímero (227-227'':230-230'')-bisdisulfuro, producido por células ováricas de hamster chino (CHO), forma glicosilada alfa

Heavy chain / Chaîne lourde / Cadena pesada

SYVLQPSVES SVAVQIYAQR TVGQGNGSEK SYWVQVPQFG GPAVLVPYDD 50
IDVRKPRFVY WQGQTVFITS SASTGQPSFP PLMPCSRTST ESYALGSLN 100
TQIYGFHPR YVGRPVAVDS KTSTVQPGPS YVQYVYQVVE QPSKYPWVS 150
TQVSGLTVLY MVQMLNGEY KCVVKGNGLP SIEKTIKSA KGQFDPQVY 200
TYVQFSQKMT RNQLYSLCIV GKFYPIDJAV NEMSNQGQEN MYKTTVPVLV 250
SYSDIFFLYS LVQDSQHMKQ GMNVLCSYVM EALNNHQTGQ SSILNLGQ 300
Light chain / Chaîne légère / Cadena ligera

SYVLQPSVES SVAVQIYAQR TVGQGNGSEK SYWVQVPQFG GPAVLVPYDD 50
IDVRKPRFVY WQGQTVFITS SASTGQPSFP PLMPCSRTST ESYALGSLN 100
TQIYGFHPR YVGRPVAVDS KTSTVQPGPS YVQYVYQVVE QPSKYPWVS 150
TQVSGLTVLY MVQMLNGEY KCVVKGNGLP SIEKTIKSA KGQFDPQVY 200
SYSDIFFLYS LVQDSQHMKQ GMNVLCSYVM EALNNHQTGQ SSILNLGQ 300

Post-translational modifications

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro
Intra-H (C23-C104) 22-96 148-204 368-426
22''-96'' 148''-204'' 368''-426''
Intra-L (C23-C104) 22-87 135-195
22''-87'' 135''-195''
Inter-H-L (CH1 10-CL126) 135-213 135'-213' 230-230'
Inter-H-H (b 8, b 11) 227-227'' 230-230''

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
H CH2 N84.4: 298, 298'
H CH3 N114: 435, 435'

Deamidation sites / Sites de déamidation / Posiciones de desamidación
H CH2 N84.4: 298, 298'
H CH3 N114: 435, 435'

Oxidation sites / Sites de oxydation / Posiciones de oxidación
H CH2 M15.1: 253, 253'
H CH3 M107: 429, 429''
suvecaltamidum

suvecaltamide 2-(4-(propan-2-yl)phenyl)-N-[(1R)-1-[5-(2,2,2-trifluoroethoxy)pyridin-2-yl]ethyl]acetamide

suvécaltamide 2-(4-(propan-2-yl)phényl)-N-[(1R)-1-[5-(2,2,2-trifluoroéthoxy)pyridin-2-yl]éthyl]acetamide

suvécaltamida 2-(4-(propan-2-il)fenil)-N-{(1R)-1-[5-(2,2,2-trifluoroetoxi)piridin-2-il]etil}acetamida

C₂₀H₂₃F₃N₂O₂

C₂₀H₂₃F₃N₂O₂

tebotelimabum #

tebotelimab

immunoglobulin G4-kappa, anti-[Homo sapiens PDCD1 (programmed cell death 1, PD-1, PD1, CD279)] and anti-[Homo sapiens LAG3 (lymphocyte activating 3, lymphocyte-activation 3, CD223)], humanized monoclonal antibody, bispecific tetravalent; gamma4 heavy chain scFv-h-CH2-CH3 humanized (1-496) [V-KAPPA anti-LAG3 (Homo sapiens IGKV1-39*01 (88.4%) -IGKJ4*01 (90.9%)) [6.3.9] (1-107) -8-mer linker (108-115)-VH anti-PDCD1 (Homo sapiens IGHV1-46*01 (81.6%) -IGHD -IGHJ4*01 (92.9%)) [8.8.12] (116-234) 6-mer diglycyl-cysteinyl-triglycyl linker (235-240)-E-coil motif (241-268) -Homo sapiens IGHG4*01, G4v5 h P10, G4v21 CH2 Y15.1, T16, E18 (hinge 1-12 S10>P (278) (269-280), CH2 M15.1>Y (302), S16>T (304), T18>E (306) (281-390), CH3 (391-495), CHS K>del (496) (269-496)), (237-240:245-248)’-bisdisulfide with kappa light chain humanized (1’-271’) [V-KAPPA anti-PDCD1 (Homo sapiens IGKV3D-11*02 (77.7%) -IGKJ4*01 (100%)) [10.3.9] (1’-111’) 6-mer linker (112’-119’) -VH anti LAG3 (Homo sapiens IGHV1-18*01 (86.7%) -IGHD -IGHJ4*01 (82.7%)) [8.8.11] (120’-237’) 6-mer diglycyl-cystéinyl-triglycyl linker (238’-243’) -K-coil motif (244’-271’); dimer (276’-276”:279’-279”)-bisdisulfide, produced in Chinese hamster ovary (CHO) cells, glycoforme alfa

tébotélimab

immunoglobuline G4-kappa, anti-[Homo sapiens PDCD1 (protéine 1 de mort cellulaire programmée, PD-1, PD1, CD279)] et anti-[Homo sapiens LAG3 (activateur 3 des lymphocytes, lymphocyte-activation 3, CD223)], anticorps monoclonal humanisé, bispécifique tétravalent; chaîne lourde gamma4 scFv-h-CH2-CH3 humanisée (1-496) [V-KAPPA anti-LAG3 (Homo sapiens IGKV1-39*01 (88.4%) -IGKJ4*01 (90.9%)) [6.3.9] (1-107) -8-mer linker (108-115)-VH anti-PDCD1 (Homo sapiens IGHV1-46*01 (81.6%) -IGHD -IGHJ4*01 (92.9%)) [8.8.12] (116-234) 6-mer diglycyl-cystéinyl-triglycyl linker (235-240)-E-coil motif (241-268) -Homo sapiens IGHG4*01, G4v5 h P10, G4v21 CH2 Y15.1, T16, E18 (charnière 1-12 S10>P (278) (269-280), CH2 M15.1>Y (302), S16>T (304), T18>E (306) (281-390), CH3 (391-495), CHS K>del (496) (269-496)), (237-240:245-248')-bisdisulfure avec la chaîne légère kappa humanisée (1’-271’) [V-KAPPA anti-PDCD1 (Homo sapiens IGKV3D-11*02 (77.7%) -IGHJ4*01 (100%)) [10.3.9] (1’-111’) 6-mer linker (112’-119’) -VH anti LAG3 (Homo sapiens IGHV1-18*01 (86.7%) -IGHD -IGHJ4*01 (82.7%)) [8.8.11] (120’-237’) 6-mer diglycyl-cystéinyl-triglycyl linker (238’-243’) -K-coil motif (244’-271’); dimère (276’-276”:279’-279”)-bisdisulfure, produit dans des cellules ovariennes de hamster chinois (CHO), glycoforme alfa
tebotelimab

la inmunoglobulina G4-kappa, anti-[*Homo sapiens* PDCD1 (proteína 1 de muerte celular programada, PD-1, PD1, CD279)] y anti-[*Homo sapiens* LAG3 (activador 3 de los linfocitos, linfocito-activación 3, CD223)], anticuerpo monoclonal humanizado, biespecífico tetravalente; cadena pesada gamma4 scFv-h-CH2-CH3 humanizada (1-496) [V-KAPPA anti-LAG3 (*Homo sapiens* IGKV1-39*01 (88.4%)) -IGJK*4*01 (90.9%) [6.3.9] (1-107) -conector octámero (108-115) -VH anti-PDCD1 (*Homo sapiens* IGKV1-46*01 (81.6%)) -IGH -IGHJ*4*01 (92.9%)) [8.8.12] (116-234) -conector sexámero diglicil-cisteinil-triglicil (235-240) -E-coil motíf (241-268) -Homo sapiens iGHG4*01, G4v5 h P10, G4v21 CH2 Y15.1, T16, E18 (bisagra 1-12 S10>P (269-280), CH2 M15.1>T (304), T16>E (306) (281-390), CH3 (391-495), CHS K>del (496) (269-496)), (237-240:244-248")-bisdisulfuro con la cadena ligera kappa humanizada (1'-271) [V-KAPPA anti-PDCD1 (*Homo sapiens* IGKV3D-11*02 (77.7%)) -IGJK*4*01 (100%)) [10.3.9] (1-111) -conector octámero (112-119)-VH anti-LAG3 (*Homo sapiens* IGHV1-18*01 (86.7%)) -IGH -IGHJ*4*01 (82.7%) [8.8.11] (120'-237) -conector sexámero diglicil-cisteinil-triglicil (238'-243")-K-coil motíf (244'-270") dímero (276'-276"-279'-279")-bisdisulfuro, producido por células ováricas de hamster chino (CHO), forma glicosilada alfa

**Heavy chain / Chaîne lourde / Cadena pesada**

<table>
<thead>
<tr>
<th>Post-translational modifications</th>
<th>Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro</th>
<th>N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación</th>
<th>Fucosylated complex bi-antennary CHO-type glycans / glycanes de type CHO bi-antennaires complexes fucosilés / glicanos de tipo CHO biantenarios complejos fucosilados</th>
</tr>
</thead>
<tbody>
<tr>
<td>N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación</td>
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<td>H CH2 N84.4:</td>
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<td>347, 347&quot;</td>
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<tr>
<td>Fucosylated complex bi-antennary CHO-type glycans / glycanes de type CHO bi-antennaires complexes fucosilés / glicanos de tipo CHO biantenarios complejos fucosilados</td>
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</tr>
</tbody>
</table>

**Light chain / Chaîne légère / Cadena ligera**

**Post-translational modifications**

**Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro**

**N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación**

**Fucosylated complex bi-antennary CHO-type glycans / glycanes de type CHO bi-antennaires complexes fucosilés / glicanos de tipo CHO biantenarios complejos fucosilados**
télazorlimab

immunoglobuline G1-kappa, anti-[Homo sapiens TNFRSF4 (membre 4 de la super famille des récepteurs du facteur de nécrose tumorale, ACT35, OX40, CD134)], anticorps monoclonal humanisé;

chaîne lourde gamma1 humanisée (1-448) [VH (Homo sapiens IGHV2-70*10 (93.0%) -IGHJ4*01 (92.9%)) CDR-IMGT [10.7.10] (26-35-53-59-98-107) (1-118) -Homo sapiens IGHG1*01 (100%), G1m17, 1 (CH1 K120 (215) (119-216), charnière 1-15 (217-231), CH2 (232-341), CH3 D12 (357), L14 (359) (342-446), CHS (447-448) (119-448)), (221-213′)-disulfure avec la chaîne légère kappa humanisée (1-213′) [V-KAPPA (Homo sapiens IGKV3-11*01 (97.4%) -IGKJ1*01 (100%)) CDR-IMGT [5.3.9] (27-31.49-51.38-46) (1-106′) -Homo sapiens IGKC*01 (100%) Km3 A45.1 (152), V101 (190) (107′-213′)];

dimère (227-227′-230-230′)-bisdisulfure, produit dans des cellules ovariennes de hamster chinois (CHO), glycoforme alfa

Heavy chain / Chaîne lourde / Cadena pesada

QVTLKESGPA LVKPTQTLTL TCSFSGFSLS TSQGQVVKIR QFFQKALEWI 50

ASHWGWQDQKV YNTALKRTIL IEKDESKQNV VLMTINMDPV EATATYCAR1 100

DONGPFAQVQ GTVTSUGAVE TKPGPVYPLA PESKTSGQTOG AALGCWVQY 150

FPPRVYVYWN SGALTGQVTY PFAVQLQSSGL YLESSLVTFFV 200

CHVNWKPENV KTVNVEVPEK CDDTHICTCPP FCAPELLGFGPS VLFPPFGPPK 250

TLMKSLKTVPE VTVLSDWVHH DPWSFPWNYQ GOVSNWARK KGREYQYNET 300

RYVSVVITVL HQMNLGKEY KCVKSNKALPI APTKEXTIKA KQKPRFQVY 350

TLPSSDRLK7 KNQVSLCLV TCYGFPSDIAV EMEESNGQPNEN KYDTTPVVL 400

SDGDFFIISK LTVDKSMWQQ GNFVSCSVMAEALNHHYQK SSLSLPGK 448

Light chain / Chaîne légère / Cadena ligera

EIVLTQSPAT LSLPKPQHAT LSCKSS6YSV YNWWQYKQFG VAPFRWIYAT 50

SNRATIGIPAR FSGSGQGSTDV TLLSSLEKPE SFVYYQQQGM SNSWPFQEQ 100

TKVVEIRRTVA APSVFIFPSPS DQLQKGSTAS VYCLLNHYFP KFAPVYKVD 150

NAQSOINSE SVTQDSQRDSD TSYLSLSTLTE VACDIEHRLK FYCEYVHGQL 200

ASPVYQSPR GEC 213

Post-translational modifications

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro

Intra-H (C23-C104) 22-97 145-201 368-426 22°-87° 145°-201° 262°-322° 368°-426°

Intra-L (C23-C104) 23′-87′ 133°-193°

Inter-H-L (h 5-CL 126) 221-213F 221-213

Inter-H-H (h 11, h 114) 227-227′ 230-230′

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación

H CH2 N84.4:

298, 298′

Fucosylated complex bi-antennary CHO-type glycans / glycanes de type CHO bi-antennaires complejos fucosilados / glicanos de tipo CHO biantenarios complejos fucosilados

C-terminal lysine clipping:

H CH2 K2:

448, 448′
tesnatilimab

Immunoglobulin G4-kappa, anti-[Homo sapiens KLRK1 (killer cell lectin like receptor K1, NKG2D, KLR, NKG2-D, CD314)]. Homo sapiens monoclonal antibody; gamma4 heavy chain Homo sapiens (1-442) [VH (Homo sapiens IGHV4-59*01 (93.8%) -IGHD) -IGHJ3*02 (93.8%)) CDR-IMGT [8.7.9] (26-33.51-57.96-104) (1-115) -Homo sapiens IGHG4*01, G4v5 h P10 (CH1 (116-213), hinge S10>P (223) (214-225), CH2 (226-335), CH3 (336-440), CHS (441-442) (116-442)), (129-215')-disulfide with kappa light chain Homo sapiens (1'-215') [V-KAPPA (Homo sapiens IGKV3-20*01 (100%) -IGKJ1*01 (100%)) CDR-IMGT [7.3.9] (27-33.51-53.90-98) (1'-108') -Homo sapiens IGKC*01 (100%), Km3 A45.1 (154), V101 (192) (109'-215')]; dimer (221-221'':224-224'')-bisdisulfide, produced in Chinese hamster ovary (CHO) cells, glycoform alfa.
tezatabep matraxetanum #
tezatabep matraxetan

three-alpha-helix binding protein, derived from an immunoglobulin G (IgG)-binding domain of a staphylococcal protein A (SpA), designed to bind receptor tyrosine-protein kinase erbB-2 (ERBB2, Neu, HER2), produced by peptide synthesis, conjugated at the C-terminal Cys to one (3RS)-2,5-dioxo-1-(2-{2-[4,7,10-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecan-1-yl]acetamido}ethyl)pyrrolidin-3-yl (matraxetan) group

tézatabep matraxétan

protéine à trois hélices alpha, dérivée du domaine de l’immunoglobuline G (IgG) se liant à la protéine staphylocoque A (SpA), mise au point pour se lier au récepteur tyrosine-protéine kinase erbB-2 (ERBB2, Neu, HER2), produite par synthèse péptidique, conjuguée sur la Cys en sa partie C-terminale à un groupe (3RS)-2,5-dioxo-1-(2-[4,7,10-tris(carboxyméthyl)-1,4,7,10-téraazacyclododecan-1-yl]acétylamido)éthyl)pyrrolidin-3-yl (matraxétan)

tezatabep matraxétan

proteina de tres hélices alfa, derivada del dominio de la inmunoglobulina G (IgG) que se une a la proteína estafilocócica A (SpA), diseñada para unirse al receptor tiroisina-proteína kinasas erbB-2 (ERBB2, Neu, HER2), producida por síntesis peptídica, conjugada con la Cys en su parte C-terminal a un grupo (3RS)-2,5-dioxo-1-(2-[4,7,10-tris(carboximetil)-1,4,7,10-tetraazaciclododecan-1-yl]acetamido)etil)pirrolidin-3-ilo (matraxétan)
tifalibepum #

**tifalibep**

Fusion protein composed of 3 binding domains, each consisting of a three-alpha-helix motif derived from the immunoglobulin (Ig)-binding Z-domain of staphylococcal protein A (SpA), engineered for binding to the human neonatal Fc receptor (FcRn) with the two identical N- and C-terminal domains (1-58, 116-173), and for binding to the domain II of human serum albumin (HSA) with the central domain (59-110), connected via a G4S peptide linker (111-115); [FcRn-binding engineered SpA peptide (1-58)]-[HSA-binding engineered SpA peptide (59-110)]-[G4S linker (111-115)]-[FcRn-binding engineered SpA peptide (116-173)] fusion protein; produced in *Escherichia coli*

tifalibep

Protéine de fusion composée de 3 domaines liants, chacun consistant en un motif à 3 hélices alfa dérivé du domaine Z de la protéine staphylococcique A (SpA) se liant à l’immunoglobuline (Ig), mis au point pour se lier au récepteur Fc néonatal humain (FcRn) avec les deux domaines N- et C-terminals identiques (1-58, 116-173), et au domaine II de l’albumine sérique humaine (ASH, HSA) avec le domaine central (59-110), connecté via un peptide liant G4S (111-115) ; protéine de fusion [peptide SpA mis au point pour se lier au FcRn (1-58)]-[peptide SpA mis au point pour se lier au HSA (59-110)]-[peptide liant G4S (111-115)]- [peptide SpA mis au point pour se lier au FcRn (116-173)]; produite par *Escherichia coli*

tifalibep

Proteína de fusión compuesta de 3 dominios de unión, cada uno consistente en un motivo con 3 hélices alfa derivado del dominio Z de la proteína estafilocócica A (SpA) que se une a la inmunoglobulina (Ig), diseñada para unirse al receptor Fc neonatal humano (FcRn) con los dos dominios N- y C-terminal idénticos (1-58, 116-173), y con el dominio II de la albúmina sérica humana (ASH, HSA) con el dominio central (59-110), conectado a través de un péptido linker G4S (111-115) ; proteína de fusión [péptido SpA diseñado para unirse al FcRn (1-58)]-[péptido SpA diseñado para unirse al HSA (59-110)]-[péptido G4S linker (111-115)]-[péptido SpA diseñado para unirse al FcRn (116-173)]; producida por *Escherichia coli*
**tilogotamab #**

**tilogotamab**

**Recommended INN: List 84**

WHO Drug Information, Vol. 34, No. 3, 2020

**Sequence:**

```
AJAKQAYQGQQHQRHPFSLWKQQFQKFG1HFHDFLYQVRVAKQIQiel0g1gQIQLS
IAKQAPKASGIAGGAGIDH66QYGVGVYHAQREEQNYD5EQYGFVAI100
DAIAGQKOHQGSGCGYLPFAMGQQAGHE1NMFLN1PQQQFQRVAPMG150
DPQEQGLSLGERLQGSGQGAP
```

Post-translation/modifications/ Modifications post-traductionnelles/ Modificaciones posttraducción

**Note:**

acucine / ninguno

** imitationgulin G1-kappa, anti-**

**Homo sapiens**

TNFRSF10B (tumor necrosis factor receptor (TNFR)

superfamily member 10B, death receptor 5, DR5, TNF-

related apoptosis-inducing ligand receptor 2, TRAILR2,

TRAIL-R2, TR-2, CD262)], humanized monoclonal antibody;

gamma1 heavy chain humanized (1-447) [VH (*Homo sapiens* IGHV1-3*01 (84.7%) -IGHD -IGHJ4*01

(93.3%)) CDR-IMGT [8.8.11] (26-33.51-58.97-107) (1-

118) -*Homo sapiens* IGHG1*03, G1m3, nG1m1,

G1v34 C1H3 G109 (CH1 R120 (215) (119-216), hinge

1-15 (217-231), CH2 (232-341), CH3 E12 (357), M14

(359), E109>G (431) (342-446), CHS K>del (447)

(119-447)), [221-213)-disulfide with kappa light chain

humanized (1'-213') [V-KAPPA (*Homo sapiens* IGKV1-

16*01 (83.2%) -IGKJ4*01 (100%)) CDR-IMGT [5.3.9]

(27-31.49-51.88-96) (1'-106') -*Homo sapiens* IGKC*01

(100%) Km3 A45.1 (152), V101 (190) (107'-213'));

dimer (227-227":230-230")-bisdisulfide, produced in

Chinese hamster ovary (CHO) cells, glycoform alfa

**tilogotamab**

**tilogotamab**

**tilogotamab**

**tilogotamab**

**tilogotamab**

**tilogotamab**

**tilogotamab**

immunoglobuline G1-kappa, anti-**

**Homo sapiens**

TNFRSF10B (membre 10B de la super famille des

récepteurs du facteur de nécrose tumorale (TNFR),

récepteur de mort 5, DR5, TRAILR2, TRAIL-R2, TR-2,

CD262)), anticorps monoclonal humanisé;

chaîne lourde gamma1 humanisée (1-447) [VH (**Homo sapiens** IGHV1-3*01 (84.7%) -IGHD -IGHJ4*01

(93.3%)) CDR-IMGT [8.8.11] (26-33.51-58.97-107) (1-

118) -*Homo sapiens* IGHG1*03, G1m3, nG1m1,

G1v34 C1H3 G109 (CH1 R120 (215) (119-216), charnière

1-15 (217-231), CH2 (232-341), CH3 E12 (357), M14

(359), E109>G (431) (342-446), CHS K>del (447)

(119-447)), [221-213)-disulfide avec la chaîne légère kappa humanisée (1'-213') [V-KAPPA (**Homo sapiens** IGKV1-

16*01 (83.2%) -IGKJ4*01 (100%)) CDR-IMGT [5.3.9]

(27-31.49-51.88-96) (1'-106') -*Homo sapiens* IGKC*01

(100%) Km3 A45.1 (152), V101 (190) (107'-213'));

dimère (227-227":230-230")-bisdisulfure, produit dans

des cellules ovariennes de hamster chinois (CHO),

glycoforme alfa

immunoglobulina G1-kappa, anti-**

**Homo sapiens**

TNFRSF10B (miembro 10B de la super familia de los

receptores del factor de necrosis tumoral (TNFR),

receptor de muerte 5, DR5, TRAILR2, TRAIL-R2, TR-

2, CD262)), anticuerpo monoclonal humanizado;
tolebrutinib

tolebrutinib

tolébrutinib

tolebrutinib

cadena pesada gamma1 humanizada (1-447) [VH (Homo sapiens IGHV1-3*01 (84.7%)) -IGHD - IGHJ4*01 (93.3%)) CDR-IMGT [8.8.11] (26-33.51-58.97-107) (1-118) -Homo sapiens IGHG1*03, G1m3, G1v34 CH3 G109 (CH1 R120 (215) (119-216), bisagra 1-15 (217-231), CH2 (232-341), CH3 E12 (357), M14 (359), E109>G (431) (342-446), CHS K>del (447) (119-447)), (221-213”)-disulfuro con la cadena ligera kappa humanizada (1’-213”) [V-KAPPA (Homo sapiens IGKV1-16*01 (83.2%) -IGKJ4*01 (100%)) CDR-IMGT [5.3.9] (27-31.49-51.88-96) (1’-106’) -Homo sapiens IGKC*01 (100%) Km3 A45.1 (152), V101 (190) (107”-213”));
dímero (227-227”::230-230”)-bisdisulfuro, producido por células ováricas de hamster chino (CHO), forma glicosilada alfa

\[
\text{tolebrutinib} = 4\text{-amino-3-(4-phenoxyphenyl)-1-[(3R)-1-(prop-2-enoyl)piperidin-3-yl]-1,3-dihydro-2H-imidazo[4,5-c]pyridin-2-one}
\]

\[
\text{C}_{26}\text{H}_{25}\text{N}_{5}\text{O}_{3}
\]
tovinontrinum

tovinontrine

6-{(3S,4S)-4-methyl-1-[(pyrimidin-2-yl)methyl]pyrrolidin-3-yl}-3-(oxan-4-yl)imidazo[1,5-a]pyrazin-8(7H)-one

tovinontrine

6-{(3S,4S)-4-méthyl-1-[(pyrimidin-2-yl)méthyl]pyrrolidin-3-yl}-3-(oxan-4-yl)imidazo[1,5-a]pyrazin-8(7H)-one

tovinontrina

6-{(3S,4S)-4-metil-1-[(pirimidin-2-il)metil]pirrolidin-3-il}-3-(oxan-4-il)imidazo[1,5-a]pirazin-8(7H)-ona

udonitrectagum

udonitrectag

(1S,4R,5R,7S)-3,4-dibenzyl-2-oxo-6,8-dioxa-3-azabicyclo[3.2.1]octane-7-carboxylic acid

udonitrectag

acide (1S,4R,5R,7S)-3,4-dibenzyl-2-oxo-6,8-dioxa-3-azabicyclo[3.2.1]octane-7-carboxyle

udonitrectag

ácido (1S,4R,5R,7S)-3,4-dibencil-2-oxo-6,8-dioxa-3-azabicielo[3.2.1]octano-7-carboxilico

upifitamab #

upifitamab

immunoglobulin G1-kappa, anti-[Homo sapiens SLC34A2 (solute carrier family 34 (sodium phosphate) member 2, sodium/phosphate cotransporter 2B, NaPi2b, NaPi3b)], monoclonal antibody; gamma1 heavy chain (1-449) [VH (Homo sapiens IGHV1-46*01 (81.6%)-(IGHD)-IGHJ4*01 (92.9%)) [8.8.12] (1-119) -glycyll (120) -Homo sapiens IGHG1*03, G1m3, nG1m1 (CH1 R120 (217) (121-218), hinge 1-15 (219-233), CH2 (234-343), CH3 E12 (359), M14 (361) (344-448), CHS K>del (449)) (121-449)], (223-215')-disulfide with kappa light chain (1'-215') [V-KAPPA (Mus musculus IGKV10-94*01 (84.2%)-IGKJ5*01 (91.7%)/Homo sapiens IGKV1-16*01 (83.2%)-IGKJ2*01 (90.9%)) [6.3.9] (1'-107') -arginyll (108') -Homo sapiens IGKC*01 (100%) Km3 A45.1 (154), V101 (192) (109'-215')] dimer (229-229":232-232")-bisdisulfide, produced in Chinese hamster ovary (CHO) cells, glycoform alfa
upifitamab
immunoglobuline G1-kappa, anti-[Homo sapiens SLC34A2 (membre 2 de la famille 34 (phosphate de sodium) de transporteurs de solutés, cotransporteur 2B de sodium/phosphate, NaPi2b, NaPi3b)], anticorps monoclonal; chaîne lourde gamma1 (1-449) [VH (Homo sapiens IGHV1-46*01 (81.6%) -IGHD -IGHJ4*01 (92.9%)) [8.8.12] (1-119) -glycil (120) -Homo sapiens IGHG1*03, G1m3, nG1m1 (CH1 R120 (217) (121-218), charnière 1-15 (219-233), CH2 (234-343), CH3 E12 (359), M14 (361) (344-448), CHS K-del (449) (121-449), (223-215')-disulfure avec la chaîne légère kappa (1'-215') [V-KAPPA (Mus musculus IGKV10-94*01 (84.2%) -IGKJ5*01 (91.7%)/Homo sapiens IGK1-16*01 (83.2%) -IGKJ2*01 (90.9%)) [6.3.9] (1'-107') -arginyl (108') -Homo sapiens IGKC*01 (100%) Km3 A45.1 (154), V101 (192) (109'-215')];
dimère (229-229".232-232")-bisdisulfure, produit dans des cellules ovariennes de hamster chinois (CHO), glycoforme alfa

upifitamab
immunoglobulina G1-kappa, anti-[Homo sapiens SLC34A2 (miembro 2 de la familia 34 (fósforo de sodio) de transportadores de solutos, cotransportador 2B de sodio/fósforo, NaPi2b, NaPi3b)], antígeno monoclonal; cadena pesada gamma1 (1-449) [VH (Homo sapiens IGHV1-46*01 (81.6%) -IGHD -IGHJ4*01 (92.9%)) [8.8.12] (1-119) -glicil (120) -Homo sapiens IGHG1*03, G1m3, nG1m1 (CH1 R120 (217) (121-218), bisagra 1-15 (219-233), CH2 (234-343), CH3 E12 (359), M14 (361) (344-448), CHS K-del (449) (121-449), (223-215')-disulfuro con la cadena ligera kappa (1'-215') [V-KAPPA (Mus musculus IGKV10-94*01 (84.2%) -IGKJ5*01 (91.7%)/Homo sapiens IGK1-16*01 (83.2%) -IGKJ2*01 (90.9%)) [6.3.9] (1'-107') -arginil (108') -Homo sapiens IGKC*01 (100%) Km3 A45.1 (154), V101 (192) (109'-215')];
dímero (229-229".232-232")-bisdisulfuro, producido por células ováricas de hamster chino (CHO), forma glicosilada alfa
urabrelimabum #
urabrelimab

immunoglobulin G4-kappa, anti-[*Homo sapiens* CD47 (integrin associated protein, IAP, MER6, OA3)], *Homo sapiens* monoclonal antibody; gamma4 heavy chain *Homo sapiens* (1-452) [VH (*Homo sapiens* IGHV4-4*02 (94.9%) -IGHD - IGHJ6*01 (94.7%)) CDR-IMGT [9.7.18] (26-34.52-58.97-114) (1-125)-*Homo sapiens* IGHG4*01 (CH1 (126-223), hinge 1-12 (224-235), CH2 (236-345), CH3 (346-450), CHS (451-452)) (126-452)], (139-212']-disulfide with kappa light chain *Homo sapiens* (1'-212') [V-KAPPA (*Homo sapiens* IGKV3-11*01 (94.7%) -IGKJ4*01 (91.7%)) CDR-IMGT [6.3.8] (27-32.50-52.89-96) (1'-106')-*Homo sapiens* IGKC*01 (100%), Km3 A45.1 (151), V101 (189) (107'-212')]; dimer (231-231':234-234")-bisdisulfide, produced in Chinese hamster ovary (CHO) cells, glycoform alfa

urabrélimab

immunoglobuline G4-kappa, anti-[*Homo sapiens* CD47 (protéine associée à l’intégrine, IAP, MER6, OA3)], anticorps monoclonal *Homo sapiens*; chaîne lourde gamma4 *Homo sapiens* (1-452) [VH (*Homo sapiens* IGHV4-4*02 (94.9%) -IGHD - IGHJ6*01 (94.7%)) CDR-IMGT [9.7.18] (26-34.52-58.97-114) (1-125)-*Homo sapiens* IGHG4*01 (CH1 (126-223), charnière 1-12 (224-235), CH2 (236-345), CH3 (346-450), CHS (451-452)) (126-452)], (139-212')-disulfure avec la chaîne légère kappa *Homo sapiens* (1'-212') [V-KAPPA (*Homo sapiens* IGKV3-11*01 (94.7%) -IGKJ4*01 (91.7%)) CDR-IMGT [6.3.8] (27-32.50-52.89-96) (1'-106')-*Homo sapiens* IGKC*01 (100%), Km3 A45.1 (151), V101 (189) (107'-212')]; dimère (231-231':234-234")-bisdisulfure, produit dans des cellules ovariennes de hamster chinois (CHO), glycoforme alfa

urabrélimab

inmunoglobulina G4-kappa, anti-[*Homo sapiens* CD47 (proteína asociada a la integrina, IAP, MER6, OA3)], anticuerpo monoclonal *Homo sapiens*; cadena pesada gamma4 *Homo sapiens* (1-452) [VH (*Homo sapiens* IGHV4-4*02 (94.9%) -IGHD - IGHJ6*01 (94.7%)) CDR-IMGT [9.7.18] (26-34.52-58.97-114) (1-125)-*Homo sapiens* IGHG4*01 (CH1 (126-223), bisagra 1-12 (224-235), CH2 (236-345), CH3 (346-450), CHS (451-452)) (126-452)], (139-212')-disulfuro con la cadena ligera kappa *Homo sapiens* (1'-212') [V-KAPPA (*Homo sapiens* IGKV3-11*01 (94.7%) -IGKJ4*01 (91.7%)) CDR-IMGT [6.3.8] (27-32.50-52.89-96) (1'-106')-*Homo sapiens* IGKC*01 (100%), Km3 A45.1 (151), V101 (189) (107'-212')]; dimero (231-231':234-234")-bisdisulfuro, producido por células ováricas de hamster chino (CHO), forma glicosilada alfa
uzansertib

**uzansertib**

\[\text{uzansertib} \quad \text{N-}\{(7\,R)-4-[(3\,R,4\,R,5\,S)-3\text{-amino-4-hydroxy-5-methylpiperidin-1-yl}]\text{-}7\text{-hydroxy-6,7-dihydro-5H-cyclopenta[}\text{b}\text{]}\text{pyrindin-3-yl}]\text{-}6\text{-}(2,6\text{-difluorophenyl})\text{-}5\text{-fluoropyridine-2-carboxamide}\]

\[\text{uzansertib} \quad \text{N-}\{(7\,R)-4-[(3\,R,4\,R,5\,S)-3\text{-amino-4-hydroxy-5-methylpiperidin-1-yl}]\text{-}7\text{-hydroxy-6,7-dihydro-5H-cyclopenta[}\text{b}\text{]}\text{pyrindin-3-yl}]\text{-}6\text{-}(2,6\text{-difluorophenyl})\text{-}5\text{-fluoropyridine-2-carboxamide}\]

\[\text{uzansertib} \quad \text{N-}\{(7\,R)-4-[(3\,R,4\,R,5\,S)-3\text{-amino-4-hidroxi-5-metilpiperidin-1-il}]\text{-}7\text{-hidroxi-6,7-dihidro-5H-ciclopenta[}\text{b}\text{]}\text{piridin-3-il}]\text{-}6\text{-}(2,6-difluorofenil})\text{-}5\text{-fluoropiridina-2-carboxamida}\]

\[\text{uzansertib} \quad \text{N-}\{(7\,R)-4-[(3\,R,4\,R,5\,S)-3\text{-amino-4-hidroxi-5-metilpiperidin-1-il}]\text{-}7\text{-hidroxi-6,7-dihidro-5H-ciclopenta[}\text{b}\text{]}\text{piridin-3-il}]\text{-}6\text{-}(2,6-difluorofenil})\text{-}5\text{-fluoropiridina-2-carboxamida}\]

\[\text{vebicorvir} \quad \text{5,5,11-trioxo-N-\{(2-(trifluoromethyl)-1,3-thiazol-5-yl)methyl\}-10,11-dihydro-5H-5A\text{-dibenzo[}\text{b,}\text{f}]\text{[1,4]thiazepine-8-carboxamide}\]

\[\text{vebicorvir} \quad \text{5,5,11-trioxo-N-\{(2-(trifluorométhyl)-1,3-thiazol-5-yl)méthyl\}-10,11-dihydro-5H-5A\text{-dibenzo[}\text{b,}\text{f}]\text{[1,4]thiazépine-8-carboxamide}\]

\[\text{vebicorvir} \quad \text{5,5,11-trioxo-N-\{(2-(trifluoromethyl)-1,3-thiazol-5-yl)méthyl\}-10,11-dihydro-5H-5A\text{-dibenzo[}\text{b,}\text{f}]\text{[1,4]thiazépine-8-carboxamide}\]

\[\text{vebicorvir} \quad \text{5,5,11-trioxo-N-\{(2-(trifluorométhyl)-1,3-thiazol-5-yl)méthyl\}-10,11-dihydro-5H-5A\text{-dibenzo[}\text{b,}\text{f}]\text{[1,4]thiazépine-8-carboxamide}\]
**Recommended INN: List 84**

**vebicorvir**

5,5,11-trioxo-N-[(2-(trifluorometil)-1,3-tiazol-5-il)metil]-10,11-dihidro-5H-5λ6-dibenzo[b,f][1,4]tiazepina-8-carboxamida

\[ \text{C}_{19}\text{H}_{12}\text{F}_{3}\text{N}_{3}\text{O}_{4}\text{S}_{2} \]

**velmupressinum**

**velmupressin**

1,5-anhydro\{(4-chloro-L-phenylalanyl-3-(thiophen-2-yl)-L-alanyl-L-valyl-L-asparaginyl-S-(3-carboxypropyl)-L-cysteil-N\{4-(carbamimidoylamino)butyl\}-L-prolinamide\}

\[ \text{C}_{42}\text{H}_{60}\text{ClN}_{11}\text{O}_{8}\text{S}_{2} \]

**velmupressine**

1,5-anhydro\{(4-chloro-L-défénilalanyln-3-(thiophén-2-yl)-L-alanyl-L-valyl-L-asparagín-S-(3-carboxipyropyl)-L-cysténil-N\{4-(carbamimidoylamino)butyl\}-L-prolinamide\}

**velmupresina**

1,5-anhidro\{(4-cloro-L-fenilalañl-3-(tiofen-2-il)-L-alanil-L-valil-L-asparagin-S\{3-carboxipropil\}-L-cistéinil-N\{4-(carbmamidoilamino)butil\}-L-prolinámde\}

\[ \text{C}_{42}\text{H}_{60}\text{ClN}_{11}\text{O}_{8}\text{S}_{2} \]

**velufenacinum**

**velufenacin**

\([\{(3\text{R})-1\text{-methy[pyrrolidin-3-yl]}\text{methyl (3'-chloor-4'-fluoro[1,1'-biphenyl]-2-il)carbamate}\]

\[ \text{C}_{19}\text{H}_{20}\text{ClFN}_{2}\text{O}_{2} \]

**vélufrénacine**

\((3\text{'}\text{-cloro-4\text{'-fluoro[1,1\text{'-biphényl]}-2-il)carbamate de \{(3\text{R})-1\text{-méthy[pyrrolidin-3-yl]}\text{méthyle}\} \]

**velufenacina**

\((3\text{'}\text{-cloro-4\text{'-fluoro[1,1\text{'-bifenil]}-2-il)carbamat de \{(3\text{R})-1\text{-metilpirrolidin-3-il}\text{metilo}\} \]

\[ \text{C}_{19}\text{H}_{20}\text{ClFN}_{2}\text{O}_{2} \]
verbrinacogenum setparvovecum

A recombinant non-replicating adeno-associated virus of a modified liver-tropic serotype (S3) (rAAVS3) vector, encoding a gain-of-function variant (R338L; Padua) of codon-optimised human coagulation factor IX (hFIX) under the control of a liver-specific promoter (FRE1) comprising a truncated version of the human apolipoprotein E locus control region (i.e. enhancer) with a truncated version of the human alpha-1-antitrypsin promoter.

verbrinacogene setparvovec

vecteur viral adéno-associé recombinant, non-répliquant, d’un sérotype hépatotropique modifié (S3) (rAAVS3), codant pour le variant Padua (R338L; Padua) du facteur de coagulation IX humain (F9, Facteur IX, FIX) dont les codons sont optimisés, sous le contrôle du promoteur spécifique du foie (FRE1) comprenant une version tronquée de la région de contrôle du locus de l’apoprotéine E humaine (c.-à-d. amplificateur) avec une version tronquée du promoteur de l’antitrypsine alpha-1 humaine.

verbrinacogène setparvovec

Un vector de virus adeno-asociado recombinante, no replicativo, de un serotipo hepatotrópico modificado (S3) (rAAVS3), que codifica una variante de ganancia de función (R338L; Padua) del factor de coagulación IX humano (hFIX) con codones optimizados, bajo el control de un promotor específico de hígado (FRE1) que consta de una versión truncada de la región de control del locus de la apoliproteína E humana (es decir, potenciador) con una versión truncada del promotor de la alfa-1-antitripsina humana.

vilobelimabum

immunoglobulin G4-kappa, anti-[Homo sapiens C5 (complement 5) anaphylatoxin (C5a, C5 Pr678-751)], chimeric monoclonal antibody; gamma4 heavy chain chimeric (1-446) [VH (Mus musculus IGHV1-61*01 (81.6%) -IGHD) -IGHJ3*01 (92.9%)/Homo sapiens IGHV1-46*01 (62.2%) -IGHD) -IGHJ4*01 (92.9%)] [8.8.13] (1-119) -Homo sapiens IGHG4*01 (CH1 (120-217), hinge 1-12 (218-229), CH2 (230-339), CH3 (340-444), CHS (445-446)) (120-446)], (133-218')-disulfide with kappa light chain chimeric (1'-218') [V-KAPPA (Mus musculus IGKV3-4*01 (98.0%) -IGKJ2*01 (100%)/Homo sapiensIGKV3D-11*02 (69.1%) -IGKJ2*01 (91.7%)) [10.3.9] (1'-111') -Homo sapiens IGKC*01 (100%), Km3 A45.1 (157), V101 (195) (112'-218')]; dimer (225-225":228-228")-bisdisulfide, produced in Chinese hamster ovary (CHO) cells, glycoform alfa

vilobelimab

immunoglobuline G4-kappa, anti-[Homo sapiens C5 (complément 5) anaphylatoxine (C5a, C5 Pr678-751)], anticorps monoclonal chimérique;
chaîne lourde gamma4 chimérique (1-446) [VH (Mus musculus IGHV1-61*01 (81.6%)-(IGHD) -IGHJ3*01 (92.9%)/Homo sapiens IGHV1-46*01 (62.2%)-(IGHD) -IGHJ4*01 (92.9%))] [8.8.13] (1-119) -Homo sapiens IGH4*01 (CH1 (120-217), châssis 1-12 (218-229), CH2 (230-339), CH3 (340-444), CHS (445-446)) (120-446), (133-218)-disulfure avec la chaîne légère kappa chimérique (1-218) [V-KAPPA (Mus musculus IKGV3-4*01 (98.0%)-IgLJ2*01 (100%)/Homo sapiens IKGV3D-11*02 (69.1%)-IgLJ2'01 (91.7%))] [10.3.9] (1-111) -Homo sapiens IGKC*01 (100%), Km3 A45.1 (157), V101 (195) (112-218)];
dimère (225-225:228-228)-bisdisulfure, produit dans des cellules ovariennes de hamster chinois (CHO), glycoforme alfa

vilobelimbab

inmunoglobulina G4-kappa, anti-[Homo sapiens C5 (complemento 5) anafilatoxina (C5a, C5 Pr678-751)], anticuerpo monoclonal químérico;
cadena pesada gamma4 químérica (1-446) [VH (Mus musculus IGHV1-61*01 (81.6%)-(IGHD) -IGHJ3*01 (92.9%)/Homo sapiens IGHV1-46*01 (62.2%)-(IGHD) -IGHJ4*01 (92.9%))] [8.8.13] (1-119) -Homo sapiens IGH4*01 (CH1 (120-217), bisagra 1-12 (218-229), CH2 (230-339), CH3 (340-444), CHS (445-446)) (120-446), (133-218)-disulfiro con la cadena ligera kappa químérica (1-218) [V-KAPPA (Mus musculus IKGV3-4*01 (98.0%)-IgLJ2*01 (100%)/Homo sapiens IKGV3D-11*02 (69.1%)-IgLJ2*01 (91.7%))] [10.3.9] (1-111) -Homo sapiens IGKC*01 (100%), Km3 A45.1 (157), V101 (195) (112-218)];
dímero (225-225:228-228)-bisdisulfuro, producido por células ováricas de hamster chino (CHO), forma glicosilada alfa

Heavy chain/Chaine lourde/Cadernogenesis

**VH**

`**QGKLQSQS QYQKDFW**` (1-119) - HOMO HUMAN

`**EODGQSGS QYQKDFW**` (120-217) - HOMO HUMAN

`**TESSYYQ**` (218-229) - HOMO HUMAN

`**GKQ**` (230-339) - HOMO HUMAN

`**GQ**` (340-444) - HOMO HUMAN

`**R**` (445-446) - HOMO HUMAN

Light chain/Chaine légère/Cadenetigénes

**VK**

`**QGKLQSQS QYQKDFW**` (1-111) - HOMO HUMAN

`**EODGQSGS QYQKDFW**` (120-218) - HOMO HUMAN

`**TESSYYQ**` (219-228) - HOMO HUMAN

`**GKQ**` (230-339) - HOMO HUMAN

`**GQ**` (340-444) - HOMO HUMAN

`**R**` (445-446) - HOMO HUMAN

Post-translational modifications:

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro

intra-H (C23-C104) 22-96 146-202 260-320 366-424

intra-L (C23-C104) 23-92 138-198

N-glycosylation sites / Sites de N-glycosylation / Posisiciones de N-glicosilación

HCH12n44.4; 296,296'

N-acetylated complex bi-antennary CHO-glycosylated glycan / glycosylés complexe bio-antennaire CHO-N-acétylés / N-acetilado complejo bi-antennario CHO-n-acetilado

C-terminal (cleavage)

HCH12n44.4; 296,296'
vonafexorum
vonafexor
4-chloro-5-[4-(2,6-dichlorobenzene-1-sulfonyl)piperazin-1-yl]-1-benzofuran-2-carboxylic acid
vonafexor
acide 4-chloro-5-[4-(2,6-dichlorobenzéne-1-sulfonyl)pipérazin-1-yl]-1-benzofuran-2-carboxylique
vonafexor
ácido 4-cloro-5-[4-(2,6-diclorobenceno-1-sulfonil)piperazin-1-il]-1-benzofuran-2-carboxílico

C₁₉H₁₅Cl₃N₂O₅S

vosilasarmum
vosilasarm
2-chloro-4-(((1R,2S)-1-{5-(4-cyanophenyl)-1,3,4-oxadiazol-2-yl}-2-hydroxypropyl)amino)-3-methylbenzonitrile
vosilasarm
2-chloro-4-(((1R,2S)-1-{5-(4-cyanophényl)-1,3,4-oxadiazol-2-yl}-2-hydroxypropyl)amino)-3-méthylbenzonitrile
vosilasarm
4-(((1R,2S)-1-{5-(4-cianofenil)-1,3,4-oxadiazol-2-il}-2-hidroxipropil)amino)-2-cloro-3-metilbenzonitrilo

C₂₀H₁₆ClN₅O₂

vulinacimabum #
vulinacimab
immunoglobulin G1-kappa, anti-[Homo sapiens VEGFR2 (vascular endothelial growth factor receptor 2, KDR, kinase insert domain receptor, FLK1, CD309)], Homo sapiens monoclonal antibody; gamma1 heavy chain Homo sapiens (1-447) [VH (Homo sapiens IGHV3-23*04 (90.8%) -IGHD) -IGHJ1*01 (100%)) [8.8.10] (1-117) -Homo sapiens IGHG1*03v, G1m3>G1m17, nG1m1 (CH1 R120>K (214) (118-215), hinge 1-15 (216-230), CH2 (231-340), CH3 E12 (356), M14 (358) (341-445), CHS (446-457) (118-447)], (220-219')-disulfide with kappa light chain Homo sapiens (1'-219') [V-KAPPA (Homo sapiens IGKV2-30*01 (83.0%) -IGKJ2*01 (100%)) [11.3.9] (1'-112') -Homo sapiens IGKC*01 (100%) Km3 A45.1 (158), V101 (196) (113'-219'); dimer (226-226":229-229")-bisdisulfide, produced in Chinese hamster ovary (CHO) cells, glycoform alfa
vulinacimab

immunoglobuline G1-kappa, anti-[Homo sapiens VEGFR2 (récepteur 2 du facteur de croissance endothélial vasculaire, KDR, récepteur à domaine insert kinase, FLK1, CD309)], Homo sapiens anticorps monoclonal;
chaîne lourde gamma1 Homo sapiens (1-447) [VH (Homo sapiens IGVS3-23*04 (90.8%) -(IGHD) -IGHJ1*01 (100%)) [8.8.10] (1-117) -Homo sapiens IGCH1*03v, G1m3>G1m17, nG1m1 (CH1 R120-K (214) (118-215), chamière 1-15 (216-230), CH2 (231-340), CH3 E12 (356), M14 (358) (341-445), CHS (446-457)) (118-447)], (220-219")-disulfure avec la chaîne légère kappa Homo sapiens (1-219") [V-KAPPA (Homo sapiens IGKV2-30*01 (83.0%) -IGKJ2*01 (100%))] [11.3.9] (1-112") -Homo sapiens IGK*01 (100%) Km3 A45.1 (158), V101 (196) (113"-219")];
dimère (226-226";229-229")-bisdisulfure, produit dans des cellules ovariennes de hamster chinois (CHO), glycoforme alfa

vulinacimab

immunoglobuline G1-kappa, anti-[Homo sapiens VEGFR2 (receptor 2 del factor de crecimiento endotelial vascular, KDR, receptor con dominio inserto kinasas, FLK1, CD309)], Homo sapiens anticuerpo monoclonal;
cadena pesada gamma1 Homo sapiens (1-447) [VH (Homo sapiens IGVS3-23*04 (90.8%) -(IGHD) -IGHJ1*01 (100%)) [8.8.10] (1-117) -Homo sapiens IGCH1*03v, G1m3>G1m17, nG1m1 (CH1 R120-K (214) (118-215), bisagra 1-15 (216-230), CH2 (231-340), CH3 E12 (356), M14 (358) (341-445), CHS (446-457)) (118-447)], (220-219")-disulfuro con la cadena ligera kappa Homo sapiens (1-219") [V-KAPPA (Homo sapiens IGKV2-30*01 (83.0%) -IGKJ2*01 (100%))] [11.3.9] (1-112") -Homo sapiens IGK*01 (100%) Km3 A45.1 (158), V101 (196) (113"-219")];
dímero (226-226";229-229")-bisdisulfuro, producido por células ováricas de hamster chino (CHO), forma glicosilada alfa

Heavy chain / Chaîne lourde / Cadena pesada
QVQLVQSGGS LVQPQPSGLKL SCAASGFPSF YTVNSKVRQ PDAKLEHSG 50
ISGGOTGTHY ADKVGRFTSI KREKHMVNTG LMNESLRADD TAVYCYGKSL 100
NAGEGILMGKQ VTVSAGAGAV GQSSVFYAPD SGRKSEGTQA ALCGLVQYK 150
PRPVTGSNENL GALTGQYTFV PWLGSLQSLF SLSVLTVCSG 200
NVHRPSNMTK WTVKVRPEKC DHTHICCPCF ASELDDLGSVGF LEPFPEPMT 250
LMKSHPFTVF CVPGVHSDRE PEPFYKVI GVHGWATK FREDQHYY 300
RPSVLTVLHQ CHMNGKEYK CVKSNKAPF PITEKSFQRGQFQVQVY 350
LPFSKRFMTK QWQTSCLVYK GYPSIDAVE MNSQOPPPEN YKTTTFVLDS 400
LGQVQYKILY TVOKSPMQQQQ NNVFSCHVLE ALHNNHTRGQK LSLFPG 447

Light chain / Chaîne légère / Cadena ligera
DVVMTQSPLS LPVTLGQPAS ISCRSSLQSY YRSOTFTLQM YQKPQPSQG 50
LLYIQQSERDF GPDYTSGS GCTGDPLFLR SKEADEOVV YGQDFQWTRP 100
YTFQGQTLPE IRKTVAAPF YFPPSRDQGL RGQASVCSL IENQFPEAK 150
VQWYRQNLQA SQPQSVTLE QGSQDSTYDL SSSLTILAK YERKIVYACE 200
TVQWQLSFVY TQSFPRGEC 219

Post-translational modifications
Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro
Intra-H (C23-C104) 22-96 144-200 261-321 367-425
22"-96" 144"-200" 261"-321" 367"-425"
Intra-L (C23-C104) 23'-'93' 139'-199' 23"-'93" 139"-'199"
Inter-H-L (h 5-CL 126) 228-219 228-219' 229-229" 228-219" 229-229"
Inter-H-H (h 11, h 14) 226-226' 226-226" 229-229" 226-226" 229-229"

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
H CH2 N84:4
297, 297"**
Fucosylated complex bi-antennary CHO-type glycans / glycanes de tipo CHO bi-antennaires complejos fucosilados
C-terminal lysine clipping:
H CHS K2:
447, 447**
xevinapantum
xevinapant  
\((5S,8S,10aR)-N-(diphenylmethyl)-5-\{(2S)-2-(methylamino)propanamido\}-3-(3-methylbutanoyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocine-8-carboxamide

xévinapant  
\((5S,8S,10aR)-N-(dipénylméthyl)-5-\{(2S)-2-(méthylamino)propanamido\}-3-(3-méthylbutanoyl)-6-oxodécahydropyrrolo[1,2-a][1,5]diazocine-8-carboxamide

xevinapant  
\((5S,8S,10aR)-N-(difenilmetil)-5-\{(2S)-2-(metilamino)propanamido\}-3-(3-metilbutanoil)-6-oxodecahidropirrolo[1,2-a][1,5]diazocina-8-carboxamida

\[
\text{C}_{32}\text{H}_{43}\text{N}_{5}\text{O}_{4}
\]

zandelisibum
zandelisib  
4-\{2-(difluoromethyl)-1H-benzimidazol-1-yl\}-N-\{(2-methyl-1-[2-(1-methylpiperidin-4-yl)phenyl]propan-2-yl)\}-6-(morpholin-4-yl)-1,3,5-triazin-2-amine

zandélisib  
4-\{2-(difluorométhyl)-1H-benzimidazol-1-yl\}-N-\{(2-méthyl-1-[2-(1-méthylpipéridin-4-yl)phényl]propan-2-yl)\}-6-(morfolin-4-yl)-1,3,5-triazin-2-amine

zandelisib  
4-\{2-(difluorometil)-1H-benzimidazol-1-il\}-N-\{(2-metil-1-[2-(1-metilpiperidin-4-il)fenil]propan-2-il)\}-6-(morfolin-4-il)-1,3,5-triazin-2-amina

\[
\text{C}_{31}\text{H}_{38}\text{F}_{2}\text{N}_{8}\text{O}
\]

zoligratinibum
zoligratinib  
[5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl](1H-indol-2-yl)methanone

zoligratinib  
[5-amino-1-(2-méthyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-il](1H-indol-2-yl)méthane
zoligratinib

[5-amino-1-(2-metil-1H-benzimidazol-5-il)-1H-pirazol-4-il](1H-indol-2-il)metanona  

\[ \text{C}_{20}\text{H}_{16}\text{N}_{6}\text{O} \]

zotiraciclibum

zotiraciclib  

(8E)-6-méthyl-12-oxa-3,6-diaza-2(4,2)-pyrimidina-1,4(1,3)-dibenzénacyclodécaphan-8-ène

\[ \text{C}_{23}\text{H}_{24}\text{N}_{4}\text{O} \]

zuberitamabum #

zuberitamab

immunoglobulin G1-kappa, anti-[Homo sapiens MS4A1 (membrane spanning 4-domains subfamily A member 1, CD20)], chimeric monoclonal antibody; gamma1 heavy chain chimeric (1-452) [VH (Mus musculus IGHV1-12*01 (96.9%) -(IGHD) -IGHJ1*03 (100%)/Homo sapiens IGHV1-46*01 (70.4%) -(IGHD) -IGHJ1*03 (85.7%)) [8.8.15] (1-122) -Homo sapiens IGHG1*01 (100%) G1m17,1 (CH1 K120 (219) (123-220), hinge 1-15 (221-235), CH2 (236-345), CH3 D12 (361), L14 (363) (346-450), CHS (451-452)) (123-452)], (225-213')-disulfide with kappa light chain chimeric (1'-213') [V-KAPPA (Mus musculus IGKV4-72*01 (96.8%) -IGKJ1*01 (90.9 %)/Homo sapiens IGKV3-11*01 (64.9%) -IGKJ2*01 (90.9%)) [5.3.9] (1'-106') -Homo sapiens IGKC*01 (100%), Km3 A45.1 (152), V101 (190) (107'-213')); dimer (231-231'':234-234'')-bisdisulfide, produced in Chinese hamster ovary (CHO) cells, glycoform alfa

zubéritamab

immunoglobuline G1-kappa, anti-[Homo sapiens MS4A1 (membre 1 de la sous-famille A à 4 domaines transmembranaires, CD20)], anticorps monoclonal chimérique;
zuberitamab

inmunoglobulina G1-kappa, anti-[Homo sapiens MS4A1 (miembro 1 de la subfamilia A con 4 dominios transmembranarios, CD20)], anticuerpo monoclonal quimérico;

cadena pesada gamma1 quimérica (1-452) [VH (Mus musculus IGHV1-12*01 (96.9%) -IGHD -IGHJ1*03 (100%)/Homo sapiens IGHV1-46*01 (70.4%) -IGHD -IGHJ1*03 (85.7%)) [8.8.15] (1-122) -Homo sapiens IGHG1*01 (100%) G1m17,1 (CH1 K120 (219) (123-220), charnière 1-15 (221-235), CH2 (236-345), CH3 D12 (361), L14 (363) (346-450), CHS (451-452)) (123-452)], (225-213')-disulfure con la cadena ligera kappa quimérica (1'-213') [VKAPPA (Mus musculus IGKV4-72*01 (96.8%) -IGKJ1*01 (90.9%)/Homo sapiens IGKV3-11*01 (64.9%) -IGKJ2*01 (90.9%)) [5.3.9] (1'-106') -Homo sapiens IGKC*01 (100%), Km3 A45.1 (152), V101 (190) (190-213)];
dимер (231-231'-234-234')-disulfure, producido por células ováricas de hamster chino (CHO), forma glicosilada alfa
Recommended International Nonproprietary Names (Rec. INN): List 63
Dénominations communes internationales recommandées (DCI Rec.): Liste 63
Denominaciones Comunes Internacionales Recomendadas (DCI Rec.): Lista 63
(WHO Drug Information, Vol. 24, No. 1, 2010)

p.45  bardoxololum  
      bardoxole  replace the molecular formula by the following one
      bardoxole  remplace la formule moléculaire brute par la suivante
      bardoxolina  sustitúyase la fórmula molecular por la siguiente
      C31H41NO4

Recommended International Nonproprietary Names (Rec. INN): List 79
Dénominations communes internationales recommandées (DCI Rec.): Liste 79
Denominaciones Comunes Internacionales Recomendadas (DCI Rec.): Lista 79
(WHO Drug Information, Vol. 32, No. 1, 2018)

p.112  davamotecanum pegadexamerum  
       davamotécan pegadexamère  replace the structure by the following one
       davamotecán pegadexámero  sustitúyase la estructura por la siguiente

p.123  ianalumabum #  
       ianalumab  replace the description and the structure by the following ones
       ianalumab  remplacer la description et la structure par les suivantes
       ianalumab  sustitúyase la descripción y la estructura por las siguientes

immunoglobulin G1-kappa, anti-[Homo sapiens TNFRSF13C (tumor necrosis factor receptor (TNFR) superfamily member 13C, BAFF-R, BAFF-R, BR3, B cell activating factor receptor, CD268)], Homo sapiens monoclonal antibody;
gamma1 heavy chain (1-454) [Homo sapiens VH (IGHV6-1*01 (96.00%)-(IGHJ5*01) [10.9.14] (1-124) -Homo sapiens IGHG1*03, G1m3, nG1m1 (CH1 R120 (221) (125-222), hinge (223-237), CH2 (238-347), CH3 E12 (363), M14 (365) (348-452), CHS (453-454)) (125-454)], (227-215')-disulfide with kappa light chain (1'-215') [Homo sapiens V-KAPPA (IGKV3D-11*01 (89.00%)-IGKJ1*01) [7.3.9] (1'-108') -Homo sapiens IGKC*01, Km3 A45.1 (154), V101 (192) (109'-215')]; dimer (233-233'-236-236')-bisdisulfide;
produced in Chinese hamster ovary (CHO) cells, glycoform alfa
immunoglobuline G1-kappa, anti-[*Homo sapiens* TNFRSF13C (membre 13C de la super famille du récepteur du facteur de nécrose tumorale (TNFR), BAFFR, BAFF-R, BR3, récepteur du facteur d’activation des lymphocytes B, CD268), *Homo sapiens* anticorps monoclonal; chaîne lourde gamma1 (1-454) [*Homo sapiens* VH (IGHV6-1*01 (96.00%) -(IGHD) -IGHJ5*01 [10.9.14]) (1-124) -*Homo sapiens* IGHG1*03, G1m3, nG1m1 (CH1 R120 (221) (125-222), châssis (223-237), CH2 (238-347), CH3 E12 (363), M14 (365) (348-452), CHS (453-454)) (125-454)]] (227-215)-disulfure avec la chaîne légère (1'-215') [*Homo sapiens* V-KAPPA (IGKV3D-11*01 (89.00%) -IGKJ1*01 [7.3.9] (1'-108') -*Homo sapiens* IgKC*01, Km3 A45.1 (154), V101 (192) (109'-215')); dimère (233-233'*:236-236'-)bisdisulfure, produit dans des cellules de hamster chinois (CHO), glicoforme alfa

immunoglobulina G1-kappa, anti-[*Homo sapiens* TNFRSF13C (miembro 13C de la super familia del receptor del factor de necrosis tumoral (TNFR), BAFFR, BAFF-R, BR3, receptor del factor de activación de los linfocitos B, CD268), *Homo sapiens* anticuerpo monoclonal; cadena pesada gamma1 (1-454) [*Homo sapiens* VH (IGHV6-1*01 (96.00%) -(IGHD) -IGHJ5*01 [10.9.14]) (1-124) -*Homo sapiens* IGHG1*03, G1m3, nG1m1 (CH1 R120 (221) (125-222), bisagra (223-237), CH2 (238-347), CH3 E12 (363), M14 (365) (348-452), CHS (453-454)) (125-454)]] (227-215)-disulfuro con la cadena ligera (1'-215') [*Homo sapiens* V-KAPPA (IGKV3D-11*01 (89.00%) -IGKJ1*01 [7.3.9] (1'-108') -*Homo sapiens* IgKC*01, Km3 A45.1 (154), V101 (192) (109'-215')); dimero (233-233'*:236-236'-)bisdisulfuro, producido en las células ováricas de hamster chino (CHO), glicoforma alfa

<table>
<thead>
<tr>
<th>Heavy chain/Chaîne lourde/Cadena pesada</th>
<th>Light chain/Chaîne légère/Cadena ligera</th>
</tr>
</thead>
<tbody>
<tr>
<td>GYGGGGPD VLYFYFQTSL YIGGDGQGS YHQQMKHPEPQ FLWYF</td>
<td>DILYLSPLD LIQIGDQDSL IGLYQRTS YRQPRFLL PY</td>
</tr>
<tr>
<td>GTRICTLG EYGGYKDLYF TIGEDYMD YQDDYDYE NEDDDYDE</td>
<td>GOSRTPGEL LTSQGELQ DETILSDLQ QHDYDDYDE</td>
</tr>
<tr>
<td>GEDVDYTTY YVDDGMKL GQDQKVTQY DGTCTQG</td>
<td>GETGTVTHQ WADDGETD AQYCYLKL TGDTKQY</td>
</tr>
<tr>
<td>YGTVQYGLY VVQYQYQI GQDDLEQG DLKQYQYQ</td>
<td>YQQRQDQG DLKQYQYQ DLKQYQYQ</td>
</tr>
<tr>
<td>YGTVQYGLY VVQYQYQI GQDDLEQG DLKQYQYQ</td>
<td>YQQRQDQG DLKQYQYQ DLKQYQYQ</td>
</tr>
<tr>
<td>YGTVQYGLY VVQYQYQI GQDDLEQG DLKQYQYQ</td>
<td>YQQRQDQG DLKQYQYQ DLKQYQYQ</td>
</tr>
</tbody>
</table>

Post-translational modifications
Disulfide bridges/disulfure/Disulfuro/Disulfurs
Intra-H(C23-C304) 22-99 151-207 268-328 274-432
22-99 151-207 268-328 374-432
23-89 155-195 23-89 155-195
Inter-H(C23-C304) 22-99 151-207 268-328 274-432
22-99 151-207 268-328 374-432
Inter-H(C23-C304) 22-99 151-207 268-328 374-432
22-99 151-207 268-328 374-432

N-glycosylation sites/Sites de N-glycosylation/Posiciones de N-glicosilación
HCH2N44: 304 304'
M6Oglycosylation complex/bi-antennary CHO type glycans/ Glicosan detype CHO bi-antennarios complejos de glicanos/AA/De AA tipo CHO bi-antennarios
Non-glycosylation/fucose cyclisation/No glicosilación/ciclización de fucosa/ No glicosilación/ciclización de fucosa

H viQIQT: 1.1’

C-terminal lysine clipping
HCH2K2: 454, 454’
Recommended International Nonproprietary Names (Rec. INN): List 82

Dénominations communes internationales recommandées (DCI Rec.): Liste 82

Denominaciones Comunes Internacionales Recomendadas (DCI Rec.): Lista 82


p.606  
adlinacogenum civaparvovecum #

a recombinant non-replicating adeno-associated virus type 2/6 (rAAV6) vector, which contains a promoter-less human coagulation factor IX (hF9, Factor IX or FIX) transgene cassette, encoding exons 2-8 and splice acceptor site sequence (SA) from hF9 exon 2, flanked by a sequence homologous to the zinc-finger nuclease (ZFN) cleavage site of the human albumin (hALB) intron 1

vecteur viral adéno-associé de type 2/6 recombinant (rAAV6), non-répliquant, contenant la cassette avec le transgène du facteur de coagulation IX humain (hF9, Facteur IX, FIX) sans promoteur, codant pour les exons 2-8 et la séquence du site accepteur (SA) d’épissage de l’exon 2 de hF9, flanqué par une séquence homologue au site de clivage de la nucléase à doigts de zinc (ZFN) de l’intron 1 l’albumine humaine (hALB).

un vector de virus adeno asociado tipo 2/6 recombinante (rAAV6), no replicativo, que contiene un casete con el transgen del factor de coagulación IX (hF9, Factor IX o FIX) humano sin promotor, que codifica para los exones 2-8 y la secuencia del sitio acceptor (SA) del splicing del exon 2 de hF9, flanqueado por una secuencia homóloga al sitio de rotura por la nuclease con dedos de zinc (ZFN) del intron 1 de la albúmina humana (hALB)
a recombinant non-replicating adeno-associated virus type 2/6 (rAAV6) vector, which contains a promoter-less human alpha-L-iduronidase (hIDUA) transgene cassette, encoding partial exon 1 and full exons 2-14 with the first 28 amino acids removed, and splice acceptor site sequence (SA) from hIDUA exon 2, flanked by a sequence homologous to the zinc-finger nuclease (ZFN) cleavage site of the human albumin (hALB) intron 1.

un vector de virus adeno asociado tipo 2/6 recombinante (rAAV6), no replicativo, que contiene un casete con el transgen de la alfa-L-iduronidasa humana (hIDUA) sin promotor, que codifica para el exón 1 parcial y los exones 2-14 completos con los primeros 28 aminoácidos eliminados, y la secuencia del sitio aceptor (SA) del splicing del exón 2 de hIDUA, flanqueado por una secuencia homóloga al sitio de rotura por la nuclease con dedos de zinc (ZFN) del intrón 1 de la albúmina humana (hALB)

a recombinant non-replicating adeno-associated virus type 2/6 (rAAV6) vector, expressing a cDNA that targets 447-461 bp of the albumin locus (relative to the transcription initiation site), fused to the obligate heterodimeric FokI nuclease domain ELD, under the control of an apolipoprotein E hepatic control region and human alpha-1-antitrypsin promoter (ApoE/hAAT)

un vector de virus adeno asociado tipo 2/6 recombinante (rAAV6), no replicativo, que expresa un cDNA dirigido a unirse a los pares de bases 447-461 del locus de la albúmina (en relación con el sitio de iniciación de la transcripción), fusionado al dominio heterodimérico ELD de la nuclease FokI, bajo el control de una región de control de la apolipoproteína E (ApoE) específica del hígado y del promotor de la alfa1-antitripsina humana (ApoE/hAAT)
a recombinant non-replicating adeno-associated virus type 2/6 (rAAV6) vector, expressing a cDNA that targets 468-485 bp of the albumin locus (relative to the transcription initiation site), fused to the obligate heterodimeric FokI nuclease domain ELD, under the control of an apolipoprotein E hepatic control region and human alpha-1-antitrypsin promoter (ApoE/hAAT)

vecteur viral adéno-associé de type 2/6 recombinant (rAAV6), non-répliquant, exprimant un ADNc ciblant les paires de bases 468-485 du locus de l’albumine (en relation avec le site initial de transcription), fusionné au domaine hétérodimérique ELD de la nucléase FokI, sous le contrôle d’une région de contrôle de l’apolipoprotéine E (ApoE) spécifique du foie et du promoteur de l’alpha1-antitrypsine humaine (ApoE/hAAT)

un vector de virus adeno asociado tipo 2/6 recombinante (rAAV6), no replicativo, que expresa un cDNA dirigido a unirse a los pares de bases 468-485 (en relación al sitio de iniciación de la transcripción) del locus de la albúmina, fusionado al dominio heterodimérico ELD de la nuclease FokI, bajo el control de una región de control hepático de la apolipoproteína E y el promotor de la alfa 1 antitripsina humana (ApoE/hAAT)
A recombinant non-replicating adeno-associated virus type 2/8 (rAAV8) vector, encoding codon-optimized, wild-type human ornithine transcarbamylase (OTC) under the control of a hybrid human thyroxine-binding globulin (TBG) / human alpha 1-microglobulin/bikunin precursor (AMBP) promoter/enhancer. The vector genome is a head-to-head dimer, with the vector genome cassette located 5' of the mutated internal inverted terminal repeat (ITR) in a reverse orientation and the vector genome cassette located 3' of the mutated internal ITR in a forward orientation.

Un vector de virus adenoasociado recombinante no replicativo del serotipo 2/8 (rAAV8), que codifica para la ornitina transcarbamilasa silvestre humana (OTC) con codones optimizados, bajo el control de un promotor/potenciador híbrido de la globulina fijadora de tiroxina humana (TBG) / precursor de microglobulina alfa 1 humana/bicunina (AMBP). El genoma del vector es un dímero de cabeza con cabeza, con el casete del genoma del vector en posición 5' a la repetición terminal invertida (ITR) interna y mutada localizado en orientación inversa. y el casete del genoma del vector en posición 3' a la ITR localizado en orientación hacia adelante.
p.49  
epcoritamabum #
epcoritamab  
epcoritamab  
Replacement of the structure by the following one
remplacer la structure par la suivante
sustitúyase la estructura por la siguiente

Heavy chain / Chaîne lourde / Cadena pesada (anti-CD3E)
EVLYVESQSG LVQDPSDLR SCNASSTFY TYSWMMYQG PFKLDEWDR 50
LESTYNYTAT YTVMDVRF TIRREDSGL LLYSNLHLY TSTTSTCYTV 100
KGYGGNSYV KMSRFGSTTV VLYSASYAGK PSYFLEAPS KSTGSTD 150
GCLYKWSYFE PTTVWSSYK LSTSYVHTTVA VLSGSSLS YSSTVPS 200
LSYTVFYCH NHPRTSDE VGKESKDCR NTCTTCSPE AF EPPGSGFSLYF 250
FPKTNPLLM ISTRNTSSEN KVSSHVIDV KVSSHYHDS KVSHM 300
EWRNTHYFV SYTVLVLQGQ MNSKETECK VSHKAFARH KXTSKQAK 350
PREQYTFLE PSKREMEFQ VSULC/VYFG YESDIAYEE WNGFQZNYK 400
TYPFVLFSSG SFLHSLKTV DSAMQAPQFS SFCYMKSEL ANHITQESLS 450
LIPG 451

Light chain / Chaîne légère / Cadena ligera (anti-CD3E)
QVYTVFSTPE VSPSVSTTVT TCRSSDIST SVSTTYWQG TPQFRKDESL 50
GSTEMDFTPA PSHSSGSSD LSAKTVPTFT AAQESITDF CSAYKSEWWF 100
GGSTKTYLGQ GQAASSTTVF FPQPSELGQ MHTLIVSILH DSYFPAGTVA 150
WKDASSYFPGA GVVSTTPQSG AHRAYASMY LSTLPQGKWS HRSTYCVTH 200
EGSTVRYTA PTMC 253

Heavy chain / Chaîne lourde / Cadena pesada (anti-M5A1)
EVLYVESQSG LVQDPSDLR SCNASSTFY TYSWMMYQG PFKLDEWDR 50
ISNHYSTMY FYSQFSTV DHRAMESLY RNSHRASEAD TLTYCAKGD 100
PQYTVFYCH NHPRTSDE VGKESKDCR NTCTTCSPE AF EPPGSGFSLYF 250
NHLVYFFETV VSNSSSSALTS GVHTTAYVAG SGLLSSLSY VYXSSSLG 300
QYTVYCNRhR PSHSSGSSD LSAKTVPTFT AAQESITDF CSAYKSEWWF 400
KRESNHSQF TCRSCAIT KYGEKHPS KNTQFPEQQ 500
YNTRYVYG LPYRLEQGQG KETVQSNF PHLCHAGFYF LSHAGQFRE 550
PSTYVPQSF EMNTHYQVSL TCLYWFPQSF DIAMQHRGGQ HRNNYKTH 600
PLYTVLYSF LSYKLEVGDG RQWQGQYVFCS SSMCNEHNF YTTQSSLSLSP 650
G 651

Light chain / Chaîne légère / Cadena ligera (anti-M5A1)
EVLYVESQSG LVQDPSDLR SCNASSTFY TYSWMMYQG PFKLDEWDR 50
IYTVFSTPE VSPSVSTTVT TCRSSDIST SVSTTYWQG TPQFRKDESL 100
ASPMHSTMY FYSQFSTV DHRAMESLY RNSHRASEAD TLTYCAKGD 100
GSTMKTVFAP SPYSSGSSD LSAKTVPTFT AAQESITDF CSAYKSEWWF 200
GGSTKLYLGQ GQAASSTTVF FPQPSELGQ MHTLIVSILH DSYFPAGTVA 300
WKDYSSYFPGA VVVSTTPQSG AHRAYASMY LSTLPQGKWS HRSTYCVTH 400
EGSTVRYTA PTMC 453

Post-translational modifications
Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro
Intra-H (C23-C104) 22-98 152-208 269-329 375-433
27°-96° 149°-201° 266°-329° 377°-439°
Intra-L (C23-C104) 22-98 137-196
23°-88° 134°-196°
Inter-H4, (b1, 5-CL, 126) 228-214 255-214
Inter-L (b1, 11, 14) 234-213 237-214

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
H1 CH2N84-4: 305, 307°

Fucoseylated complex, bi-antennary CHO-type glycans / Glycans de type CHO bi-antennaires complejos, fucosilados / Glycans de tipo CHO bi-antennarios, complejos, fucosilados.

p.55  
giroctocogenum fitelparvovecum #
giroctocogene fitelparvovec  
giroctocogène fitelparvovec  
giroctocogén fitelparvovec
Replacement of the description by the following one
remplacer la description par la suivante
sustitúyase la descripción por la siguiente

A recombinant non-replicating adenovirus type 2/6 (rAAV6) vector, encoding human B-domain-deleted blood coagulation factor VIII (hF8, FVIII) under the control of a synthetic liver-specific promoter.

Vecteur viral adénó-associé de type 2/6 recombinant non-répliquant (rAAV6), codant pour le facteur de coagulation sanguine VIII humain (hF8, FVIII), dont le domaine B a été supprimé, sous le contrôle d’un promoteur synthétique spécifique du foie.
Un vector de virus adenoasociado recombinante no replicativo del tipo 2/6 (rAAV6), que codifica para el factor de coagulación sanguíneo VIII humano (hF8, FVIII) con el dominio B deletionado, bajo el control de un promotor sintético específico del hígado.

A recombinant non-replicating adeno-associated virus type 2/9 (rAAV9) vector, encoding human microdystrophin 5 (h-μD5) under control of CK8 muscle creatine kinase promoter and enhancer elements

A recombinant non(replicating adeno-associated virus type 2/9 (rAAV9) vector, encoding human microdystrophin 5 (h-μD5) under control of CK8 muscle creatine kinase promoter and enhancer elements

Un vector de virus adenoasociado recombinante no replicativo del tipo 2/9 (rAAV9), que codifica para la microdistrofina 5 humana (h-mD5) bajo el control del promotor y elementos potenciadores (enhancer) de la creatina quinasa CK8 de músculo.

Procedure and Guiding Principles / Procédure et Directives / Procedimientos y principios generales

The text of the Procedures for the Selection of Recommended International Nonproprietary Names for Pharmaceutical Substances and General Principles for Guidance in Devising International Nonproprietary Names for Pharmaceutical Substances will be reproduced in proposed INN lists only.

Les textes de la Procédure à suivre en vue du choix de dénominations communes internationales recommandées pour les substances pharmaceutiques et des Directives générales pour la formation de dénominations communes internationales applicables aux substances pharmaceutiques seront publiés seulement dans les listes des DCI proposées.

El texto de los Procedimientos de selección de denominaciones comunes internacionales recomendadas para las sustancias farmacéuticas y de los Principios generales de orientación para formar denominaciones comunes internacionales para sustancias farmacéuticas aparece solamente en las listas de DCI propuestas.
Selected WHO publications of related interest


**Quality assurance of pharmaceuticals 2018.** WHO guidelines, good practices, related regulatory guidance and GXP training materials. (CD-ROM, USB and online)


**International Nonproprietary Names (INN) for Pharmaceutical Substances.** CD-ROM. 2017

**The International Pharmacopoeia.** Eighth edition 2018. CD-ROM. (CD-ROM, USB and online)

**WHO Expert Committee on Biological Standardization.** Guidelines on management of blood and blood components as essential medicines. 2016. Adopted by the Committee at its Sixty-seventh Meeting; published as Annex 3 to the WHO Technical Report Series, No. 1004, 2017

**Council for International Organizations of Medical Sciences (CIOMS)**

International ethical guidelines for health-related research involving humans. 2016

CIOMS Guide to Active Vaccine Safety Surveillance. 2017

CIOMS Guide to Vaccine Safety Communication. 2018


CIOMS publications are also available at: http://cioms.ch/shop/

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