WHO Vision for Safety of Medicinal Products
No country left behind: worldwide pharmacovigilance for safer medicinal products, safer patients

The aim of the newsletter is to disseminate regulatory information on the safety of medicinal products, based on communications received from our network of national pharmacovigilance centres and other sources such as specialized bulletins and journals, as well as partners in WHO.

The information is produced in the form of résumés in English, full texts of which may be obtained on request from:

Pharmacovigilance,  
MHP/RPQ,  
World Health Organization,  
1211 Geneva 27, Switzerland,  
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This newsletter is also available at: https://www.who.int/teams/regulation-prequalification

The WHO pharmaceuticals newsletter provides you with the latest information on the safety of medicinal products and regulatory actions taken by authorities around the world.

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#### Safety of medicinal products

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All the previous issues of the WHO Pharmaceuticals Newsletter can be accessed from our website.
Denosumab

Risk of severe hypocalcemia

1. United States. The US Food and Drug Administration (FDA) has concluded that the osteoporosis medicine denosumab (Prolia®) increases the risk of severe hypocalcemia, very low blood calcium levels, in patients with advanced chronic kidney disease (CKD), particularly patients on dialysis. Severe hypocalcemia appears to be more common in patients with CKD who also have a condition known as mineral and bone disorder (CKD-MBD). In patients with advanced CKD taking denosumab, severe hypocalcemia resulted in serious harm, including hospitalization, life-threatening events, and death.

Denosumab is a monoclonal antibody initially developed for the treatment of osteoporosis in postmenopausal women at increased risk of fracture or who are refractory to or cannot tolerate other therapies. Denosumab was later approved to increase bone mass in men with osteoporosis; to treat men with high risk for fracture receiving androgen deprivation therapy for prostate cancer; to treat women at high risk for fracture receiving aromatase inhibitor therapy for breast cancer; and, to treat men and women with glucocorticoid-induced osteoporosis.

FDA is adding a Boxed Warning to the denosumab prescribing information about the significant risk of developing severe hypocalcemia in patients with advanced CKD. This warning and new labelling contains information to help reduce this risk, including appropriate patient selection for denosumab treatment, increased monitoring of blood calcium levels, and other strategies. The FDA is adding this updated information to the patient Medication Guide and the denosumab Risk Evaluation and Mitigation Strategy (REMS).

Reference:
Drug safety communication, US FDA, 19 January 2024 (link to the source within www.fda.gov)
(See also WHO Pharmaceuticals Newsletter No.1, 2023: Denosumab and potential risk of severe hypocalcemia in patients on dialysis)

2. Canada. Health Canada has alerted health-care professionals that the Indications, Warnings and Precautions, Adverse Reactions (Post-Market Adverse Reactions), Clinical Pharmacology (Pharmacokinetics, Special Populations and Conditions), and Patient Medication Information sections of the Canadian product monograph for denosumab (Prolia®) have been updated with additional information on the risk of severe symptomatic hypocalcemia and safety in paediatric patients.

In the post-market setting, severe symptomatic hypocalcemia (resulting in hospitalization, life-threatening events and fatal cases) have been reported. This is particularly observed in patients with severe renal impairment, receiving dialysis or treatment with other calcium-lowering drugs. While most cases occurred in the first weeks of initiating therapy, it can also occur later. Examples of the clinical manifestations of severe symptomatic hypocalcemia have included QT interval prolongation, tetany, convulsions and altered mental status.

Based on the data submitted and reviewed by Health Canada, the safety and efficacy of denosumab (Prolia®) in paediatric patients has not been established; therefore, Health Canada has not authorized an indication for paediatric use. In clinical trials, hypercalcemia has been reported in paediatric patients with osteogenesis imperfecta treated with denosumab. Some cases required hospitalization and were complicated by acute renal injury.

Reference:
Health Product InfoWatch, Health Canada, 25 January 2024 (link to the source within www.hc-sc.gc.ca)

Finasteride

Risk of mood alterations

Canada. Health Canada has alerted health-care professionals that the Warnings, Precautions and Patient Medication Information sections of the Canadian product monographs for finasteride (Propecia® and Proscar®)
have been updated with the risk of mood alterations including depressed mood, depression, self-harm injury and suicidal ideation.

Finasteride is indicated the treatment and control of prostate gland enlargement (benign prostatic hyperplasia), and for the treatment of male pattern hair loss (androgenetic alopecia).

There have been post-marketing reports of serious psychiatric symptoms in patients treated with finasteride that sometimes continued after treatment discontinuation. Mood alterations including depressed mood, depression, self-harm injury, suicidal ideation, as well as worsening of pre-existing depression have been reported in patients treated with finasteride.

It is recommended that all patients be screened for suicidal ideation, self-harm, and depression and/or associated risk factors before treatment initiation. Clinical monitoring of all patients for signs and symptoms of psychiatric disorders should continue throughout treatment and afterward.

(See also WHO Pharmaceuticals Newsletter No.2, 2023: Fluoroquinolone antibiotics and potential risk of suicidal ideation in Singapore)

### Fluoroquinolone antibiotics

**Further restrictions for use due to risk of disabling and potentially long-lasting or irreversible side effects**

**United Kingdom.** The Medicines and Healthcare Products Regulatory Agency (MHRA) has updated indications for systemic (by mouth, injection, or inhalation) fluoroquinolone antibiotics. It has been suggested that they must only be used in situations where other antibiotics, that are commonly recommended for the infection, are inappropriate, as they can cause long-lasting (up to months or years), disabling and potentially irreversible side effects, sometimes affecting multiple body systems and senses.

Fluoroquinolone antibiotics are a group of medicines that kill bacteria and have an important role in treating certain life-threatening infections. They include ciprofloxacin, delafloxacin, levofloxacin, moxifloxacin, and ofloxacin.

Restrictions to the use of fluoroquinolones were introduced in 2019 to minimise the risk of these reactions. In 2023 the MHRA reviewed the effectiveness of these measures in the UK and has taken additional action to further minimise the risk.

Situations in which other antibiotics are considered to be inappropriate and a fluoroquinolone may be indicated include:

- there is resistance to other first-line antibiotics recommended for the infection
- other first-line antibiotics are contraindicated in an individual patient
- other first-line antibiotics have caused side effects in the patient requiring treatment to be stopped
- treatment with other first-line antibiotics has failed

Reference: Drug Safety Update, MHRA, 22 January 2024 (link to the source within www.gov.uk)
(See also WHO Pharmaceuticals Newsletter No.4, 2023: Fluoroquinolone antibiotics and reminder of risk of long-lasting, disabling and potentially irreversible adverse reactions)

### Melphalan flufenamide

#### Withdrawal of approval

**United States.** US FDA announced its final decision to withdraw approval of melphalan flufenamide (Pepaxto®).

In February 2021, US FDA approved melphalan flufenamide under accelerated approval for use in combination with dexamethasone to treat adult patients with relapsed or refractory multiple myeloma who have received at least four prior lines of therapy and whose disease was refractory to at least one proteasome inhibitor, one immunomodulatory agent, and one CD38-directed monoclonal antibody. The manufacturer was required to conduct the post-approval confirmatory trial as a post-approval requirement under the accelerated approval program.

(See also WHO Pharmaceuticals Newsletter No.2, 2023: Finasteride and risk of suicidal ideation and self-injury, and No.4 2022: Finasteride and potential risk of suicidal ideation in Singapore)
The FDA determined the following grounds for withdrawal were met: (1) the confirmatory study conducted as a condition of accelerated approval did not confirm melphalan flufenamide's clinical benefit, and (2) the available evidence demonstrates that melphalan flufenamide is not shown to be safe or effective under its conditions of use.

Reference:
Drug safety and availability, US FDA, 23 February 2024 (link to the source within www.fda.gov)

**Montelukast**

New boxed warning for the risk of neuropsychiatric events

Ireland. The Health Products Regulatory Authority (HPRA) has announced that a new boxed warning will be included in both the Summary of Product Characteristics (SmPC) and the package leaflet of montelukast to raise further awareness of the risk of neuropsychiatric events, such as behavioural changes, depression and suicidality. The symptoms may be serious and can continue if treatment is not withdrawn.

Montelukast is an orally active leukotriene receptor antagonist indicated for use in the prophylaxis and treatment of asthmatic conditions.

The European Medicines Agency’s (EMA) Pharmacovigilance Risk Assessment Committee (PRAC), having completed a review of data related to the known risk of neuropsychiatric events with montelukast, has recommended a new boxed warning in product information to further raise awareness of this risk. Health-care professionals are advised that treatment with montelukast should be discontinued if neuropsychiatric symptoms occur during treatment.

Reference:
HPRA drug safety newsletter, HPRA, 21 December 2023 (link to the source within www.hpra.ie)
(See also WHO Pharmaceuticals Newsletter No.1, 2021: Montelukast and Risk of psychiatric effects)

**Oral anticoagulants**

Risk of acute kidney injury

Japan. The Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA) have issued a notification instructing the addition of “acute kidney injury” to the Clinically Significant Adverse Reactions section in the PRECAUTIONS of oral anticoagulants. The notification was in response to the cases reported in Japan for which a causal relationship between oral anticoagulants and acute kidney injury including anticoagulant-related nephropathy was reasonably possible.

Oral anticoagulants include apixaban, edoxaban tosilate hydrate, dabigatran etexilate methanesulfonate, rivaroxaban, and warfarin potassium. They are indicated for the prevention and treatment of thromboembolic conditions.

Health-care professionals are requested to pay sufficient attention to the onset of acute kidney injury related to the administration of oral anticoagulants as well as to take appropriate measures considering the possibility of anticoagulant-related nephropathy when acute kidney injury is noted in patients treated with oral anticoagulants.

Reference:
Pharmaceuticals and Medical Devices Safety Information, MHLW/PMDA, 19 December 2023 (link to the source within www.pmda.go.jp/english/)
(See also WHO Pharmaceuticals Newsletter No.4, 2023: Oral anticoagulants and potential risk of anticoagulant-related nephropathy (ARN))

**Promethazine hydrochloride injection**

Risk of severe chemical irritation and damage to tissues

United States. US FDA is alerting health care professionals of labelling updates intended to further reduce the risk of severe chemical irritation and damage to tissues from intravenous administration of promethazine hydrochloride injection. Promethazine hydrochloride injection is indicated to help manage
Regulatory matters

certain allergic reactions, motion sickness, post-operative nausea and vomiting, and as a sedative or adjunct to analgesics.

FDA recommends healthcare professionals administer promethazine hydrochloride injection by deep intramuscular administration instead of intravenous administration. If promethazine hydrochloride injection must be administered intravenously, healthcare professionals should review and follow the updated information in the labelling to dilute promethazine hydrochloride injection and administer by intravenous infusion to reduce the risk of severe tissue injury.

FDA has required that manufacturers update their prescribing information for promethazine hydrochloride injection to include new safety information and update the carton labelling and container labels with the corresponding information.

Reference:
Drug safety and availability, US FDA, 27 December 2023 (link to the source within www.fda.gov)

Valproate

Potential increased risk of neurodevelopmental disorders in children

1. Europe. The PRAC of EMA is recommending precautionary measures for the treatment of male patients with valproate medicines. These measures are to address a potential increased risk of neurodevelopmental disorders in children born to men treated with valproate during the 3 months before conception. Neurodevelopmental disorders are problems with development that begin in early childhood, such as autism spectrum disorders, intellectual disability, communication disorders, attention deficit/hyperactivity disorders and movement disorders.

Valproate medicines are used to treat epilepsy, bipolar disorders and, in some EU countries, migraine.

The PRAC recommends that valproate treatment in male patients is started and supervised by a specialist in the management of epilepsy, bipolar disorder or migraine. Doctors should inform male patients who are taking valproate about the possible risk and discuss the need to consider effective contraception, for both the patient and their female partner. Valproate treatment of male patients should be reviewed regularly to consider whether it remains the most suitable treatment, particularly when the patient is planning to conceive a child.

In reaching its conclusion, the PRAC reviewed data from a retrospective observational study carried out by companies that market valproate and data from other sources, including non-clinical (laboratory) studies and scientific literature, and consulted patients and clinical experts.

The retrospective observational study used data from multiple registry databases in Denmark, Norway and Sweden and focused on birth outcomes in children born to men who were taking valproate or taking lamotrigine or levetiracetam (other medicines to treat conditions similar to those treated with valproate) around the time of conception. The results of the study suggest there may be an increased risk of neurodevelopmental disorders in children born to men taking valproate in the 3 months before conception.

The data showed that around 5 out of 100 children had a neurodevelopmental disorder when born to fathers treated with valproate compared with around 3 out of 100 when born to fathers treated with lamotrigine or levetiracetam. The study did not investigate the risk in children born to men who stopped using valproate more than 3 months before conception.

The possible risk in children born to men treated with valproate in the 3 months before conception is lower than the previously confirmed risk in children born to women treated with valproate during pregnancy. It is estimated that up to 30 to 40 out of 100 preschool children whose mothers took valproate during pregnancy may have problems with...
early childhood development, such as being slow to walk and talk, being intellectually less able than other children, and having difficulty with language and memory.

The potential risk of neurodevelopmental disorders and the precautionary measures will be reflected in updates to the product information and educational material for valproate medicines.

Reference:
News, EMA, 12 January 2024 (link to the source within www.ema.europa.eu)
(See also WHO Pharmaceuticals Newsletter No.4, 2023: Valproate and New study on potential risk of neurodevelopmental disorders (NDDs) in children after paternal exposure, No.3, 2023: Valproic acid and risks of birth defects and developmental disorders in children. No.1, 2023: Valproate and risks in pregnancy and potential risks in male patients in UK, and No.2, 2023: summary of AC SoMP meeting on 14 December 2022)

2. United Kingdom. The MHRA has introduced new safety and educational materials for men and women and healthcare professionals to reduce the harms from valproate, including the significant risk of serious harm to the baby if taken during pregnancy and the risk of impaired fertility in males.

Health-care professionals are advised that valproate must not be started in new patients (male or female) younger than 55 years, unless two specialists independently consider and document that there is no other effective or tolerated treatment, or there are compelling reasons that the reproductive risks do not apply. For the majority of patients, other effective treatment options are available.

Exposure to valproate in pregnancy is associated with physical birth defects in 11% of babies and neurodevelopmental disorders in up to 30-40% of children, which may lead to permanent disability. Since 2018, valproate has been contraindicated in women of childbearing potential unless the conditions of the Pregnancy Prevention Programme (PPP) are followed.

Reference:
Drug safety updates, MHRA, 22 January 2024 (link to the source within www.gov.uk)

Venlafaxine

Risk of overdose and severe poisoning

Ireland. The HPRA has updated warning and advice on complex cases involving overdose and severe poisoning for patients treated with venlafaxine. Overdose with venlafaxine, including cases with fatal outcomes, have been reported predominantly in combination with alcohol and/or other medicinal products.

Venlafaxine is a dual-acting serotonin (5-HT) and norepinephrine (NE) reuptake inhibitor (SNRI). It is authorized for the treatment of depression, prevention of relapse and prevention of recurrence of depression, and treatment of anxiety and panic-related disorders.

Following a periodic safety review of available data from the literature and spontaneous reports, the PRAC of EMA has recommended an update to product information to expand advice and warnings regarding the established risk for serious outcomes due to suicide attempts, misuse, overdoses, and severe poisoning.

Health-care professionals are advised to prescribe venlafaxine for the smallest quantity consistent with good patient management, to reduce the risk of overdose. Patients should be advised not to use alcohol, considering its central nervous system (CNS) effects and potential of clinical worsening of psychiatric conditions, and the potential for adverse interactions with venlafaxine including CNS depressant effects.

Reference:
HPRA drug safety newsletter, HPRA, 21 December 2023 (link to the source within www.hpra.ie)
**Aripiprazole**

**Risk of pathological gambling**

**United Kingdom.** The MHRA is reminding health-care professionals of the risk of addictive gambling and other impulse control disorders with the use of aripiprazole.

Aripiprazole is a medicine that helps with the management of schizophrenia and bipolar disorder.

From 30 June 2009 to 28 August 2023, the MHRA received 69 Yellow Card reports citing aripiprazole as a suspect medicine for side effects of gambling or gambling disorder. Across the 69 reports of gambling and gambling disorder, most reports concerned people aged 20 to 40 years, although there were reports in patients up to 60 years of age. In many cases the patients had no previous history of gambling behaviour. In the majority of cases, cessation of aripiprazole led to a marked reduction or total loss of impulses to gamble.

Reference:
Drug safety update, MHRA, 18 December 2023 (link to the source within www.gov.uk)

**Chimeric Antigen Receptor (CAR) T cell Immunotherapies**

**Risk of T-cell malignancy**

1. **United States.** US FDA is investigating serious risk of T-cell malignancy following BCMA-directed or CD19-directed autologous Chimeric Antigen Receptor (CAR) T cell immunotherapies.

CAR T cell immunotherapies are human gene therapy products in which the T cell specificity is genetically modified to enable recognition of a desired target antigen for therapeutic purposes.

US FDA has received reports of T-cell malignancies, including chimeric antigen receptor CAR-positive lymphoma, in patients who received treatment with BCMA- or CD19-directed autologous CAR T cell immunotherapies. Reports were received from clinical trials and/or post marketing adverse event (AE) data sources. US FDA has determined that the risk of T-cell malignancies is applicable to all currently approved BCMA-directed and CD19-directed genetically modified autologous CAR T cell immunotherapies.

Although the overall benefits of these products continue to outweigh their potential risks for their approved uses, US FDA is investigating the identified risk of T cell malignancy with serious outcomes, including hospitalization and death, and is evaluating the need for regulatory action.

Patients and clinical trial participants receiving treatment with these products should be monitored life-long for new malignancies. In the event that a new malignancy occurs following treatment with these products, contact the manufacturer to report the event and obtain instructions on collection of patient samples for testing for the presence of the Chimeric Antigen Receptor (CAR) transgene.

Reference:
Safety & Availability (Biologics), US FDA, 28 November 2023 (link to the source within www.fda.gov)

2. **Saudi Arabia.** The Saudi Food & Drug Authority (SFDA) has notified health-care professionals about the potential risk of T-cell malignancy associated with the use of chimeric antigen receptor (CAR) T cell Immunotherapies.

SFDA has reviewed the current evidence, including published literature and post-marketing data to assess the association between the potential risk of T-cell malignancies with CAR T-cell immunotherapy, and found one clinical trial and two published case reports suggesting a possible association between secondary T-cell malignancy with CAR T-cell immunotherapy. In addition, SFDA identified 10 serious spontaneous case reports of T-cell malignancies in VigiBase with tisagenlecleucel (KYMRIAH®) and
Modafinil and armodafinil

Risk of severe cutaneous adverse reactions (SCARs)

Singapore. The Health Sciences Authority (HSA) has alerted the public on the severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS), with the use of modafinil and armodafinil. Modafinil and armodafinil are used for the treatment of conditions that involve excessive somnolence such as narcolepsy and obstructive sleep apnoea.

As at 31 October 2023, HSA has received nine adverse event reports with modafinil and armodafinil. Seven reports were dermatological/cutaneous reactions, and of these three reports were SJS. The remaining two reports described increased paranoia and giddiness.

Health-care professionals are advised to consider the possibility of SCARs in patients presenting with prodromal symptoms such as flu-like symptoms, mouth ulcers, sore throat and ditto conjunctivitis.

Reference:
SFDA safety communication, SFDA, 27 February 2024 (link to the source within www.sfda.gov.sa)

Nirmatrelvir/ritonavir

Risk of serious and potentially fatal adverse reactions

Europe. The PRAC of EMA has reminded health-care professionals of the risk of serious and potentially fatal adverse reactions with nirmatrelvir/ritonavir (Paxlovid®) when used in combination with certain immunosuppressants that have a narrow safe dosage range (where small changes in the dose can lead to serious adverse reactions), due to drug-drug interactions reducing the body’s ability to eliminate these medicines.

Nirmatrelvir/ritonavir is a medicine used for treating COVID-19 in adults who do not require supplemental oxygen and who are at increased risk of the disease becoming severe. The immunosuppressants concerned are called calcineurin inhibitors (tacrolimus, ciclosporin) and mTOR inhibitors (everolimus, sirolimus), which reduce the activity of the immune system. They are used for treating certain autoimmune disorders or for preventing the body from rejecting transplanted organs.

Nirmatrelvir/ritonavir should only be given with tacrolimus, ciclosporin, everolimus or sirolimus if close and regular monitoring of their blood levels is possible, to reduce the risk of drug-drug interactions causing serious reactions. Health-care professionals need to consult with a multidisciplinary group of specialists to manage the complexity of taking these medicines together.

The PRAC reviewed all available evidence, including reports of serious adverse reactions, some of which were fatal, resulting from drug-drug interactions between nirmatrelvir/ritonavir and these immunosuppressants. In several cases, blood levels of these immunosuppressants increased rapidly to toxic levels resulting in life-threatening conditions. Therefore, the PRAC agreed on a direct health-care professional communication (DHPC) to remind health-care professionals of the risk of these interactions, which is known and already described in the product information for this medicine.

Reference:
News, EMA, 9 February 2024 (link to the source within www.ema.europa.eu)
(See also WHO Pharmaceuticals Newsletter No.3, 2023: Nirmatrelvir/ritonavir and immunosuppressants and risk of adverse events from drug-drug interaction)
Omega-3-acid ethyl esters

Risk of atrial fibrillation

Europe. The EMA is reminding health-care professionals by issuing a Direct Health-care Professional Communication (DHPC) that a dose-dependent increased risk of atrial fibrillation (AF) in patients with established cardiovascular diseases or cardiovascular risk factors who were treated with omega-3-acid ethyl ester medicines compared to those treated with placebo. The observed risk was found to be highest with a dose of 4 g/day.

Medicinal products containing omega-3 ethyl esters are indicated for the reduction of triglyceride levels (hypertriglyceridemia) when the response to diet and other non-pharmacological measures has proved inadequate.

The PRAC assessed data from several systematic reviews and meta-analyses of large randomised controlled trials (RCTs) that overall enrolled more than 80,000 patients mostly with cardiovascular diseases or cardiovascular risk factors and investigated omega-3 fatty acid treatment on cardiovascular outcomes compared with placebo.

Health-care professionals should advise patients to seek medical attention in case of symptoms of atrial fibrillation such as light-headedness, asthenia, palpitations or shortness of breath. If atrial fibrillation develops, treatment should be permanently discontinued.

Reference:
Direct healthcare professional communication, EMA, 1 December 2023 (link to the source within www.ema.europa.eu)
(See also WHO Pharmaceuticals Newsletter No.2, 2024: Omega-3-acid ethyl esters and risk of atrial fibrillation)

Paracetamol

Risk of hepatotoxicity

Ireland. The HPRA has reminded health-care professionals that hepatotoxicity in association with paracetamol may occur even at doses within the normal therapeutic range in patients who are at increased risk. It is important to maintain awareness of any emerging or changing risk factors during treatment with paracetamol.

Paracetamol is recommended for the short-term treatment of the mild to moderate pain such as headache, toothache, musculoskeletal disorders and menstrual pain and for fever associated with cold and flu.

Patients at an increased risk of hepatotoxicity include those who are underweight, of low body mass index, malnourished, dehydrated, chronic alcoholism or with co-existing renal or hepatic impairment. Those with conditions that may predispose to glutathione deficiency or depletion and those concomitantly taking hepatotoxic drugs are also considered at risk.

Health-care professionals should take into consideration any emerging or changing risk factors (e.g. malnourishment, weight loss, dehydration) and maintain awareness over the course of treatment to any dose adjustment that may be warranted when prescribing or administering paracetamol.

For some patients considered to be at higher risk of hepatotoxicity, a lower starting dose, a reduction in dose and/or a reduced frequency of dosing may be appropriate.

Reference:
HPRA drug safety newsletter, HPRA, 21 December 2023 (link to the source within www.hpra.ie)
(See also WHO Pharmaceuticals Newsletter No.5, 2019: Paracetamol and dangerous when not used correctly)

Pseudoephedrine

Risks of posterior reversible encephalopathy syndrome (PRES) and reversible cerebral vasoconstriction syndrome (RCVS)

Europe. The EMA is reminding health-care professionals by issuing a Direct Health-care Professional Communication (DHPC)
that cases of posterior reversible encephalopathy syndrome (PRES) and reversible cerebral vasoconstriction syndrome (RCVS), which are serious conditions affecting the cerebral blood vessels, have been reported in patients taking pseudoephedrine-containing medicines. Most reported cases resolved following discontinuation and appropriate treatment. No fatal cases of PRES or RCVS have been reported.

Pseudoephedrine is authorized, alone or in combination with other substances, for short-term symptomatic relief of nasal or sinus congestion caused by the common cold or allergic rhinitis, vasomotor rhinitis, and aerotitis.

Following an EU-wide review of reported cases and other available data to evaluate the risks of PRES and RCVS with pseudoephedrine-containing medicines, it has been concluded that pseudoephedrine is associated with risks of PRES and RCVS and that the product information should be updated to include information on these adverse reactions and measures to reduce the risks.

Reference:
Direct healthcare professional communication, EMA, 8 February 2024 (link to the source within www.ema.europa.eu)

(See also WHO Pharmaceuticals Newsletter No. 2, 2024: Pseudoephedrine and risks of posterior reversible encephalopathy syndrome (PRES) and reversible cerebral vasoconstriction syndrome (RCVS))

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**Valaciclovir and aciclovir**

**Risk of drug reaction with eosinophilia and systemic symptoms (DRESS)**

**South Africa.** The South African Health Products Regulatory Authority (SAHPRA) has reminded health-care professionals about the risk of DRESS associated with the use of valaciclovir/aciclovir-containing medicines. DRESS is a rare, but serious, and potentially life-threatening fatal drug reaction that includes fever, severe skin rash or peeling of the skin over large areas of the body, swollen face, elevated white blood cell count (including eosinophils), and can affect one or more organs (commonly liver).

Valaciclovir and aciclovir are indicated to treat various conditions including herpes simplex and herpes zoster.

The SAHPRA has advised health-care professionals that at the time of prescription, patients should be advised of the signs and symptoms of DRESS; and monitored for skin reactions.

Reference:
Communication to health care professionals, SAHPRA, 19 January 2024

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**Vitamin B12**

**(hydroxocobalamin, cyanocobalamin)**

**Risk of cobalt sensitivity reactions**

**United Kingdom.** The MHRA is reminding health-care professionals the risk of cobalt sensitivity reactions in patients being treated for vitamin B12 deficiency. Cobalt sensitivity reactions typically present with cutaneous symptoms of chronic or subacute allergic contact dermatitis.

Hydroxocobalamin and cyanocobalamin are oral and injectable forms of vitamin B12 that are used to treat vitamin B12 deficiency. Endogenous vitamin B12 and these medicines contain a cobalt component.

There is evidence within the literature of cobalt sensitivity reactions occurring following administration of vitamin B12. Additionally, the MHRA received three Yellow Card reports, which report vitamin B12 as a suspect drug and possible allergic reactions to cobalt. Following the MHRA’s review, it was considered appropriate to improve awareness that hydroxocobalamin and cyanocobalamin medicines...
Contain cobalt.

**Reference:**
Drug safety update, MHRA, 18 December 2023 ([link](http://www.gov.uk)) to the source within [www.gov.uk](http://www.gov.uk)

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**Call for Submissions**

We are very keen to make this newsletter even more useful to all our readers. We are calling out to all national medical products regulatory authorities to send us the latest information on safety and regulatory actions on medicinal products from their countries.

We also welcome short reports on any recent events or achievements in pharmacovigilance in your country.

All submissions will be reviewed for relevance and subject to the WHO internal selection, editorial review, and clearance process.

Please send your submissions or questions to: pvsupport@who.int