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WHO Pharmaceuticals NEWSLETTER

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WHO Vision for Medicines Safety
No country left behind:
worldwide pharmacovigilance
for safer medicines, safer patients

The aim of the Newsletter is to disseminate regulatory information on the safety of pharmaceutical 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:

Safety and Vigilance: Medicines,

EMP-HIS,
World Health Organization,
1211 Geneva 27, Switzerland,
E-mail address: pvsupport@who.int

This Newsletter is also available at:
http://www.who.int/medicines

The WHO Pharmaceuticals Newsletter provides you with the latest information on the safety of medicines and legal actions taken by regulatory authorities around the world. It also provides signals based on information derived from the WHO global database of individual case safety reports, VigiBase.

In addition, this edition of the Newsletter includes a summary of discussions and key recommendations of Advisory Committee on Safety of Medicinal Products (ACSoMP) Seventeenth meeting.

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Signal

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Alemtuzumab

Risk of cardiac toxicity, hepatotoxicity and hematological toxicity

Malaysia. The National Pharmaceutical Regulatory Agency (NPRA) has announced that the approved indication of alemtuzumab (Lemtrada®) has been revised, to include restrictions for use due to the risk of myocardial ischemia, myocardial infarction, autoimmune hepatitis, haemorrhagic stroke and thrombocytopenia.

Alemtuzumab is indicated to treat active relapsing remitting multiple sclerosis.

Alemtuzumab is now restricted for use in patients with at least one disease modifying therapy, including those with highly active disease despite a full and adequate course of treatment.

Additionally alemtuzumab is contraindicated in patients with uncontrolled hypertension and with a history of stroke, including those with severe active infection.

Additional risk minimization measures have been implemented regarding initiation, infusion and post infusion monitoring.

Reference:
Safety Alerts, NPRA, 20 January 2021 (www.npra.gov.my/)

(See also WHO Pharmaceuticals Newsletter No.2, 2020: Updated restrictions and strengthened monitoring in UK; No.6, 2019: Risk of cardiovascular disorders and immune-related disorders in EU)

Bacitracin (injection)

Potential risk of nephrotoxicity and anaphylactic reactions

Canada. Health Canada has requested the manufacturers of bacitracin injection products (Bacitracin USP® and BaciJect®) should include the risk of nephrotoxicity and anaphylactic reactions in the product safety information.

Bacitracin injection (to the muscle) is indicated to treat infants with pneumonia and accumulation of pus in the chest (empyema) caused by staphylococci.

Health Canada reviewed the available information on the potential risks of nephrotoxicity and anaphylactic reactions with the use of bacitracin injection products. This included 10 published international studies for nephrotoxicity and 14 articles published for anaphylactic reactions. There were no cases of nephrotoxicity linked to the use of bacitracin and there was one case of an anaphylactic reaction in which the patient was taking other medications that could have contributed to the anaphylactic reaction. Health Canada's review concluded that there may be a link between bacitracin products for injection and the risks of nephrotoxicity and anaphylactic reactions.

Reference:
Summary Safety Review, Health Canada, 2 December 2020 (www.hc-sc.gc.ca)

Bupropion

Increased risk of serotonin syndrome: drug interaction with other serotonergic drugs

United Kingdom. The Medicines and Healthcare Products Regulatory Agency (MHRA) has announced that the product information for bupropion has been updated to include information on post-marketing reports of serotonin syndrome when bupropion (Zyban®) is co-administered with serotonergic agents such as selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs).

Bupropion is indicated as an aid for smoking cessation and for management of weight in adults (in combination with naltrexone, Mysimba®).

A recent European review of the safety data for bupropion identified at least eight cases of serotonin syndrome, where a possible interaction between bupropion and a serotonergic drug was thought to have led to serotonin syndrome.

If bupropion is prescribed with other serotonergic medicines, the recommended dose should not be exceeded, and health-care professionals should remind patients of the milder symptoms of serotonin syndrome at initiation of treatment and advise to seek medical advice if they occur.

Reference:
Drug Safety Update, MHRA, 16 November 2020 (www.gov.uk/mhra)

(See also WHO Pharmaceuticals Newsletter No.5, 2019: Risk of dizziness and somnolence in UK)

Carboplatin

Potential risk of posterior reversible encephalopathy syndrome (PRES)

Canada. Health Canada has announced that it will work with the manufacturers of carboplatin containing products to update the product safety information to include the risk of posterior reversible encephalopathy syndrome (PRES).

Carboplatin containing products are used to treat ovarian cancer.

Health Canada reviewed information from the Canada vigilance database and the scientific literature for the risk of PRES with the use of carboplatin containing products. Health Canada had not received Canadian reports, and the review focused on 19 international case reports of

PRES with the use of carboplatin containing products.

Health Canada's review concluded that there may be a link between the use of carboplatin containing products and the risk of PRES.

Reference:
Summary Safety Review, Health Canada, 16 December 2020 *(www.hc-sc.gc.ca)*

Chloroquine, Hydroxychloroquine

Risk of psychiatric disorders

Europe. The European Medicines Agency (EMA) has announced that the Pharmacovigilance Risk Assessment Committee (PRAC) has recommended updating the product information for chloroquine and hydroxychloroquine containing medicines to include the risk of psychiatric disorders and suicidal behaviour.

Chloroquine and hydroxychloroquine are indicated for the treatment of certain autoimmune diseases such as rheumatoid arthritis and lupus, as well as for prophylaxis and treatment of malaria. They are not authorised for the treatment of COVID-19, but both medicines have been used as off-label treatments in patients with the disease.

In view of the use during the COVID-19 pandemic, the EMA had reminded health-care professionals of the risks in 2020. It is already known that chloroquine and hydroxychloroquine can cause a broad range of psychiatric disorders, even if used in approved doses for authorized indications.

A review was triggered by reports received by the Spanish regulatory authority of psychiatric disorders in patients with COVID-19 who were given hydroxychloroquine. The review confirmed that psychiatric disorders have occurred and may be serious, both in patients with and without prior mental health problems.

The PRAC recommends updating the product information for chloroquine and hydroxychloroquine to provide better information to health-care professionals and patients on the risk. Patients using chloroquine or hydroxychloroquine who experience mental health problems should contact a health-care professional.

Reference:
EMA, 27 November 2020 *(www.ema.europa.eu)*

Clobazam

Potential risk of drug reaction with eosinophilia and systemic symptoms (DRESS)

Canada. Health Canada has announced that it will work with the manufacturers to update the safety information for clobazam containing products to include the risk of drug reaction with eosinophilia and systemic symptoms (DRESS).

Clobazam is used as an add-on therapy in patients whose epilepsy is not well controlled with their current antiepileptic drug therapy.

Health Canada reviewed information including clinical study data, the Canadian vigilance database and published literature for the potential risk of DRESS with clobazam use. Additionally, the review focused on two Canadian cases and 18 international cases of DRESS with clobazam.

Health Canada's review concluded that there may be a link between the use of clobazam and the potential risk of DRESS.

Reference:
Summary Safety Review, Health Canada, 9 December 2020 *(www.hc-sc.gc.ca)*

(See also WHO Pharmaceuticals Newsletter No.1, 2014: Risk of serious skin reactions in USA)

Dimethyl fumarate

Risk of progressive multifocal leukoencephalopathy (PML) associated with mild lymphopenia

United Kingdom. The MHRA has announced that the risk of progressive multifocal leukoencephalopathy (PML) has been added to the product information for dimethyl fumarate (Tecfidera®), alongside a new contraindication for suspected or confirmed PML.

Dimethyl fumarate is indicated to treat adults with relapsing-remitting multiple sclerosis. The MHRA informed health-care professionals of the risk of PML associated with prolonged moderate to severe lymphopenia caused by dimethyl fumarate in March 2015.

A recent European review identified 11 cases of PML with lymphopenia associated with dimethyl fumarate treatment.

Although the MHRA have not received UK reports of confirmed PML cases associated with dimethyl fumarate, it asks health-care professionals to continue to be vigilant for suspected adverse drug reactions in UK patients.

In patients with severe lymphopenia the treatment with dimethyl fumarate should not be started, and patients with low lymphocyte counts should be investigated for underlying causes of this before initiation of the treatment.

Also, all patients should have a lymphocyte count at least every three months and should be closely monitored during the treatment. The treatment should be stopped in patients who have prolonged severe lymphopenia for longer than six months.

Reference:
Drug Safety Update, MHRA, 7 January 2021 *(www.gov.uk/mhra)*

(See also WHO Pharmaceuticals Newsletter No.3, 2015: Fatal PML in an MS patient with severe, prolonged lymphopenia in UK; No.1, 2015 for Case of progressive multifocal leukoencephalopathy with the use of dimethyl fumarate reported in the US)

Direct-acting antiviral products containing a protease inhibitor

Potential risk of hepatic decompensation and hepatic failure

Canada. Health Canada has announced that it has requested the manufacturers of direct-acting antiviral products containing a protease inhibitor such as Maviret® (glecaprevir/pibrentasvir), Vosevi® (sofosbuvir/velpatasvir/voxilaprevir) and Zepatier® (grazoprevir/elbasvir) to include the risk of hepatic decompensation and hepatic failure.

Direct-acting antiviral products containing a protease inhibitor are indicated to treat chronic hepatitis C virus infection.

Health Canada reviewed the risk of worsening liver function and liver failure with the use of direct-acting antiviral products containing a protease inhibitor. At the time of the review, Health Canada reviewed 53 cases of worsening liver function and/or liver failure with the use of Maviret® (one Canadian), 23 for Vosevi® (six Canadian) and 18 for Zepatier® (one Canadian)

Health Canada's review concluded that there may be a link between the use of direct-acting antiviral products containing a protease inhibitor and the risk of worsening liver function and liver failure in some patients with pre-existing significant liver disease.

Reference:
Summary Safety Review, Health Canada, 2 December 2020 *(www.hc-sc.gc.ca)*

(See also WHO Pharmaceuticals Newsletter No.5, 2020: Risk of hepatic toxicity in New Zealand; No.2, 2019: Risk of hepatic impairment and jaundice in Japan)

Eculizumab (genetical recombination)

Risk of serious infections

Japan. The Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA) have announced that the package inserts for eculizumab (Soliris®) should be revised to include serious infection as an adverse drug reaction.

Eculizumab is indicated for reduction of haemolysis in paroxysmal nocturnal haemoglobinuria, inhibition of thrombotic microangiopathy in atypical haemolytic uremic syndrome, generalized myasthenia gravis and prevention of relapse of neuromyelitis optica spectrum disorder.

Although the risks of infection due to the primary disease and concomitant drugs prescribed in the course of treatment could not be ruled out, a total of 122 cases of infections have been reported in Japan during the previous three years. Also, a total of 11 patient mortalities have been reported.

As a result of a review of ravulizumab (Ultomiris®), it was decided to add a cautionary statement for infection as an adverse drug reaction in the package insert. Because eculizumab targets the same epitope as ravulizumab, the revision of the package insert for eculizumab was also necessary.

Reference:
Revision of Precautions, MHLW/PMDA, 8 December 2020 *(www.pmda.go.jp/english/)*

Erythromycin

1. Risk of infantile hypertrophic pyloric stenosis updated

United Kingdom. The MHRA has announced that the magnitude of the risk of infantile hypertrophic pyloric stenosis following exposure to erythromycin in infancy has been reflected in the product information.

Erythromycin is a macrolide antibiotic, active against gram-positive cocci and gram-positive bacilli, some gram-negative cocci and some gram-negative bacilli. It is widely used to treat chest infections such as pneumonia, skin problems and sexually transmitted diseases.

A recent European review of safety data assessed published literature studies that support an association between exposure to erythromycin in infants and the risk of infantile hypertrophic pyloric stenosis.

Although this risk was already included in the Summary of Product Characteristics (SmPC) for erythromycin medicines, the review recommended that information on the magnitude of the increased risk should be added.

Health-care professionals should advise parents to seek advice from their doctor if vomiting or irritability with feeding occurs in infants during treatment with erythromycin.

Reference:
Drug Safety Update, MHRA, 17 December 2020

(www.gov.uk/mhra)

2. Risk of cardiac failure and drug-drug interaction with rivaroxaban

United Kingdom. The MHRA has announced that the product information for erythromycin will be updated to include warnings regarding the risk of QT interval prolongation, fatal arrhythmia; and risk of bleeding due to a drug interaction with rivaroxaban.

A recent European review of safety data has highlighted an increased risk of cardiotoxicity with macrolide antibiotics, particularly erythromycin. A new contraindication has been added for those with risk factors for QT interval prolongation and arrhythmia.

Erythromycin should not be given to patients with a history of QT interval prolongation or ventricular cardiac arrhythmia or those with electrolyte disturbances. Health-care professionals should direct patients to the information leaflet and remind patients at-risk of the importance of seeking medical attention if they develop signs or symptoms of a cardiac event.

Also, erythromycin as well as clarithromycin inhibit CYP3A4 and can lead to an increase in the blood concentration of rivaroxaban, increasing the risk of bleeding in high-risk patients, especially in those with mild or moderate renal impairment. Therefore, this interaction should be considered when prescribing antibiotics and health-care professionals should follow precautions in the product information if concomitant use is necessary.

Reference:
Drug Safety Update, MHRA, 17 December 2020 *(www.gov.uk/mhra)*

(See also WHO Pharmaceuticals Newsletter No.6, 2020: Risk of cardiovascular event and infantile hypertrophic pyloric stenosis (IHPS) in Ireland)

Ferric carboxymaltose

Risk of symptomatic hypophosphatemia leading to osteomalacia and fractures

United Kingdom. The MHRA has announced that the risk of hypophosphatemic osteomalacia is included in the product information for ferric carboxymaltose (Ferinject®).

Ferric carboxymaltose is indicated for the treatment of iron deficiency. It has been associated with common cases of hypophosphatemia.

A recent European review concluded that ferric carboxymaltose is associated with hypophosphatemic osteomalacia. The review considered 36 spontaneous cases worldwide in patients with concurrent hypophosphatemia associated with the use of ferric carboxymaltose. In the UK (up to 22 October 2020), the MHRA received 28 reports of hypophosphatemia, two of which reported the use of ferric carboxymaltose. These UK cases were considered as part of the EU review.

Health-care professionals should monitor serum phosphate levels in patients on long-term treatment with ferric carboxymaltose or with pre-existing risk factors for hypophosphatemia including vitamin D deficiency, calcium and phosphate malabsorption and osteoporosis. Also, health-care professionals should advise patients to seek medical advice if they experience symptoms indicative of hypophosphatemia.

Reference:
Drug Safety Update, MHRA, 16 November 2020 *(www.gov.uk/mhra)*

(See also WHO Pharmaceuticals Newsletter No.2, 2020: Risk of hypophosphataemia in Australia)

Fingolimod

Risk of serious liver injury and herpes meningoencephalitis

United Kingdom. The MHRA has announced that the product information for fingolimod will be revised to include an update on advice for health-care professionals and patients on the risks of serious liver injury, herpes meningoencephalitis and cryptococcal meningitis.

A recent European review identified seven cases of clinically significant liver injuries. Although the MHRA has not received reports of serious liver injury considered causally related to fingolimod treatment, the MHRA asks health-care professionals to continue to be vigilant for this suspected adverse drug reactions.

Health-care professionals should monitor liver function tests routinely before, during and after the treatment. Also, in patients without signs and symptoms of liver injury, liver function tests should be monitored more frequently if elevation of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels exceed three times the upper limit. Fingolimod should be discontinued if ALT or AST levels exceed five times.

In patients with symptoms or signs of hepatic dysfunction, health-care professionals should check liver function tests urgently and discontinue fingolimod if significant hepatic injury is confirmed.

Reference:
Drug Safety Update, MHRA, 7 January 2021 *(www.gov.uk/mhra)*

Fluoroquinolones (systemic, inhaled)

Risk of heart valve regurgitation

United Kingdom. The MHRA has announced that the risk of heart valve regurgitation has been added to the product information for fluoroquinolones.

Fluoroquinolones (such as ciprofloxacin, levofloxacin, moxifloxacin and ofloxacin) are antibiotics used for serious, life-threatening bacterial infections.

Fluoroquinolones have previously been associated with a small increased risk of aortic aneurysm and dissection, and serious musculoskeletal and nervous system related adverse effects

A recent European review has considered data from epidemiological and non-clinical studies indicating an increased risk of heart valve regurgitation after use of fluoroquinolones.

Fluoroquinolones should only be used after a careful benefit-risk assessment is conducted and after consideration of other therapeutic options in patients at risk such as those with congenital heart valve disease and those diagnosed with connective tissue disorders.

Also, health-care professionals should advise patients of the importance of seeking immediate medical attention if they experience a rapid onset of shortness of breath, swelling of the ankles, feet or abdomen and new-onset heart palpitations.

Reference:
Drug Safety Update, MHRA, 17 December 2020 (www.gov.uk/mhra)

(See also WHO Pharmaceuticals Newsletter No.2, 2020: Risk of aortic aneurysm and dissection in Australia; No.6, 2019: Risk of tendon disorders, peripheral neuropathy and psychiatric symptoms in Japan; No.3, 2019)

Lidocaine/Adrenaline

Contraindication for ears and digits removed

Japan. The MHLW and the PMDA have announced that the package inserts for lidocaine/adrenaline injections (Xylocaine®) should be revised to remove the contraindication for the administration of injection to ears and digits (fingers and toes) for local anesthesia.

Lidocaine/adrenaline injections are indicated for epidural anaesthesia, conduction anaesthesia and infiltration anaesthesia.

The PMDA conducted an investigation on the text of package inserts for lidocaine/adrenaline injections in other countries, relevant guidelines, published literature and adverse reactions reported in Japan. Based on the results, the PMDA concluded that injection to ears and digits may be removed from the contraindications. One of the reasons for this is that injection of adrenaline containing anaesthetics to ears and digits is recommended or indicated as an anaesthetic approach in the textbooks in Japan and other countries as well as the US guidelines.

However, a certain level of precaution should be used regarding ears and digits because a decrease in local blood flow is pharmacologically anticipated and a small number of adverse reactions have been reported in Japan and the published literature including digital necrosis.

Reference:
Revision of Precautions, MHLW/PMDA, 21 December 2020 (www.pmda.go.jp/english/)

Modafinil

Increased risk of congenital malformations if used during pregnancy

United Kingdom. The MHRA has announced that the product information for modafinil (Provigil® and generics) has been updated to include the increased risk of congenital malformations.

Modafinil is indicated in adults for the treatment of excessive sleepiness associated with narcolepsy with or without cataplexy.

A recent European review concluded that there was a possible increased risk of congenital malformations in the children of women treated with modafinil during pregnancy.

Women of childbearing potential must use effective contraception during treatment and for two months after stopping modafinil. Modafinil may reduce the effectiveness of steroidal contraceptives through the induction of CYP3A4/5, and therefore alternative or concomitant methods of contraception are required.

Health-care professionals should ensure that all female patients of childbearing potential taking modafinil are informed and fully understand the risk and the importance of the contraception.

Reference:
Drug Safety Update, MHRA, 16 November 2020 (www.gov.uk/mhra)

(See also WHO Pharmaceuticals Newsletter No.1, 2020: Potential risk of congenital malformations in New Zealand; No.6, 2019: Potential risk of congenital malformations in Ireland)

Montelukast

Risk of psychiatric effects

Singapore. The Health Sciences Authority (HSA) has announced that they are working with the product registrants of montelukast containing products to update

the local package inserts to include the risk of neuropsychiatric adverse effects.

Montelukast is indicated to treat allergic rhinitis.

In response to the regulatory actions taken by the US FDA to include a boxed warning on serious behaviour and mood-related changes with montelukast, the HSA initiated a safety review of montelukast in March 2020. The review took into consideration local safety data, current international guidelines and international regulatory actions.

The HSA has received a small number of reports of neuropsychiatric events associated with the use of montelukast since 1998. The reports include aggressive behaviour, agitation, depression, tremor, hallucination, hyperactivity, somnolence, insomnia and nightmares.

The HSA concluded that the benefit-risk profile of montelukast remains favourable for its approved indication if additional precautionary measures are put in place to mitigate the risk. Such measures include restricting the use of montelukast in the treatment of allergic rhinitis to patients who have inadequate response or are intolerant to alternative therapies, and the strengthening of existing warnings on neuropsychiatric risks in the package inserts.

Health-care professionals are advised to consider the benefits of treatment and risks of neuropsychiatric effects before prescribing montelukast.

Reference:
Product Safety Alerts, HSA, 10 December 2020 (www.hsa.gov.sg/)

(See also WHO Pharmaceuticals Newsletter No.2, 2020: Boxed warning strengthened for serious behaviour and mood-related changes in USA; No.6, 2019: Risk of neuropsychiatric reactions in UK; No.3, 2013: Neuropsychiatric risks in Australia)

Pirfenidone

Risk of serious liver injury

1. United Kingdom. The MHRA has announced that existing warnings of hepatotoxicity in the product information for pirfenidone (Esbriet®) will be strengthened to include the risk of clinically relevant drug-induced liver injury.

Pirfenidone is an anti-fibrotic and anti-inflammatory agent indicated for the treatment of idiopathic pulmonary fibrosis. Pirfenidone is known to commonly cause elevation of ALT and AST.

A recent European review of safety data identified post market reports of severe cases of drug-induced liver injury associated with pirfenidone use.

Health-care professionals should measure ALT, AST and bilirubin levels before starting pirfenidone treatment, monthly for the first six months, and then every three months. Health-care professionals should advise patients to seek medical help immediately if they have signs and symptoms that may indicate liver injury such as fatigue, anorexia, right upper abdominal discomfort and jaundice.

Health-care professionals should monitor closely for signs of toxicity with the use of concomitant medicines that are inhibitors of CYP isozymes in the metabolism of pirfenidone such as fluvoxamine (CYP1A2), chloramphenicol (CYP2C19) and fluoxetine (CYP2D6).

Reference:
Drug Safety Update, MHRA, 16 November 2020 (www.gov.uk/mhra)

2. Singapore. The HSA has announced that the local package insert for pirfenidone (Esbriet®) has been strengthened to highlight the risk of clinically relevant drug-induced liver injury (DILI). Additionally recommendations on monitoring liver function, signs and symptoms of liver injury have been added.

Pirfenidone has been known to be associated with transient and clinically silent elevation of liver enzymes. However, fatal outcomes were reported in overseas cases of DILI. The HSA has not received any local reports of DILI.

Health-care professionals are advised to perform liver function tests prior to treatment initiation with pirfenidone.

Reference:
Product Safety Alerts, HSA, 10 December 2020 (www.hsa.gov.sg/)

Posaconazole, Venetoclax

Co-administration contraindicated due to drug-drug interaction

Japan. The MHLW and the PMDA have announced that the package inserts for posaconazole (Noxafil®) and venetoclax (Venclexta®) should be revised to include a contraindication for co-administration due to increased risk of tumor lysis syndrome/or adverse events due to elevated blood concentrations of venetoclax.

Posaconazole is indicated for prophylaxis of deep mycosis in haematopoietic stem cell transplant patients and for treatment of fungal infections including fusariosis, mucormycosis and coccidioidomycosis. Venetoclax is indicated for relapsed or refractory chronic lymphocytic leukemia.

Posaconazole is a CYP3A inhibitor, and in a study investigating the co-administration of posaconazole and venetoclax, increased blood concentrations of venetoclax were observed

compared to when venetoclax was administered alone.

Although no cases of co-administration of posaconazole and venetoclax have been reported in the previous three years, it was concluded that the revision of the package insert was necessary considering the possibility of the risk of tumor lysis syndrome due to elevated blood concentrations of venetoclax.

Reference:
Revision of Precautions, MHLW/PMDA, 8 December 2020 (*www.pmda.go.jp/english/*)

Serotonin reuptake inhibitors (SSRIs), Serotonin norepinephrine reuptake inhibitors (SNRIs)

1. Potential risk of sexual dysfunction despite treatment discontinuation

Canada. Health Canada has announced that it will work with manufacturers to update the product safety information for all SSRIs and SNRIs to recommend that health-care professionals inform patients about the potential risk of long lasting sexual dysfunction despite discontinuation of SSRIs or SNRIs.

SSRIs and SNRIs are indicated to treat depression. Certain SSIRs and SNRIs are also used in other conditions such as anxiety disorders and pain. SSRIs authorized in Canada include citalopram, escitalopram and fluoxetine and SNRIs include desvenlafaxine, duloxetine and levomilnacipran.

Health Canada reviewed the potential risk of persistent worsening sexual dysfunction, as well as the appearance of new symptoms of sexual dysfunction after stopping SSRI or SNRI treatment. The review included 58 case reports of sexual dysfunction, of which 43 cases (16 Canadian, 27 international) of persistent sexual dysfunction were considered possibly linked to the use of a SSRI or a SNRI.

Health Canada's review could not confirm nor exclude a causal link between stopping SSRI or SNRI treatment and persistent sexual dysfunction, but rare cases of long lasting sexual symptoms persisting after stopping SSRI or SNRI treatment were found.

Reference:
Summary Safety Review, Health Canada, 6 January 2021 (www.hc-sc.gc.ca)

(See also WHO Pharmaceuticals Newsletter No.3, 2020: Potential risk of sexual dysfunction in Ireland)

2. Increased risk of postpartum haemorrhage

United Kingdom. The MHRA has announced that warnings are being added to the product information for SSRIs and SNRIs to include information on the increased risk of postpartum haemorrhage.

The SSRIs include citalopram, escitalopram and fluoxetine and the SNRIs include desvenlafaxine, milnacipran and venlafaxine. It has been known for some time that these medicines increase the general risk of bleeding.

A recent EU review concluded that the data suggested a slightly increased risk of postpartum bleeding with use of SSRIs and SNRIs during the month before delivery.

In the UK, the MHRA has received a very small number of reports of postpartum haemorrhage in association with antidepressant medicines.

Health-care professionals should consider the benefits and risks for use of antidepressants during pregnancy, and the risks of untreated depression in pregnancy. Also, health-care professionals should continue to enquire about the use of antidepressant medicines, particularly in women in the later stages of pregnancy.

Anticoagulant medication in women at high risk of thrombotic events should not be stopped in response to this information, but women should be made aware of the risk.

Reference:
Drug Safety Update, MHRA, 7 January 2021 (*www.gov.uk/mhra*)

Tramadol

Potential risk of hallucinations

Canada. Health Canada has announced that it will work with manufacturers to update the product safety information for tramadol containing products to include the risk of visual and auditory hallucinations.

Tramadol is indicated to treat moderate to moderately severe pain in adults who require treatment for several days or more.

Health Canada reviewed the risk of hallucinations with the use of tramadol containing products using information from the Canada vigilance database, international databases and scientific literature. Also, Health Canada reviewed 24 serious case reports (two Canadian, 22 international) of hallucinations with the use of tramadol containing products.

Health Canada's review of the available information has established a link between the use of tramadol containing products at normal doses and the risk of visual and auditory hallucinations, particularly in patients over 65 years of age.

Reference:

Summary Safety Review, Health Canada, 29 December 2020 *(www.hc-sc.gc.ca)*

Aminoglycosides

Increased risk of ototoxicity

United Kingdom. The MHRA has announced that aminoglycoside use can result in rare cases of ototoxicity in patients with mitochondrial mutations.

Aminoglycosides are broad-spectrum bactericidal antibiotics, which includes gentamicin, amikacin, tobramycin and neomycin. Aminoglycosides have a narrow therapeutic window and use can result in toxicity, including nephrotoxicity and ototoxicity. The effect is exacerbated by renal or hepatic impairment.

In 2020, the MHRA conducted a safety review and identified several published epidemiological studies showing an increased risk of deafness in patients with mitochondrial mutation who were given aminoglycosides. The evidence from key epidemiological studies is supported by a plausible biological mechanism where mutated mitochondrial ribosomes more closely resemble bacterial ribosomes, providing a binding site for aminoglycosides.

Health-care professionals should consider the need for genetic testing particularly in those requiring recurrent or long-term treatment with aminoglycosides, but should not delay urgent treatment in order to test. Also, when making prescribing decisions in patients with a susceptible mutation, available alternative options should be considered versus the need for aminoglycoside treatment.

Furthermore, in order to minimize the risks of adverse events including ototoxicity, continuous monitoring of renal function and auditory function is recommended for all patients. Patients with known mitochondrial mutations or a family history of ototoxicity are advised to inform their doctor or pharmacist before they take an aminoglycoside.

Reference:
Drug Safety Update, MHRA, 7 January 2021
(*www.gov.uk/mhra*)

Antibiotics, Antifungals, Calcium channel blockers, Carbamazepine, Paracetamol

Risk of acute generalized exanthematous pustulosis (AGEP)

New Zealand. The Medsafe has announced that over 90 percent of cases of acute generalized exanthematous pustulosis (AGEP) are caused by medicines, most commonly antibiotics.

AGEP is a rare type of severe cutaneous type IV (T-cell mediated) hypersensitivity reaction. AGEP is characterized by pustules starting on the face and skin flexures. Over 90 percent of cases of AGEP are provoked by medicines.

Antibiotics such as penicillin, cephalosporin and tetracyclines are among the most commonly implicated medicines. Other medicines associated with AGEP include terbinafine, diltiazem, carbamazepine and paracetamol. The CARM has received 25 case reports of AGEP, of which five reports included more than one suspect medicine.

Reference:
Prescriber Update, Medsafe, December 2020
(www.medsafe.govt.nz/)

(See also WHO Pharmaceuticals Newsletter No.6, 2019: Risk of acute generalized exanthematous pustulosis (AGEP) in Republic of Korea)

Antiepileptic drugs

Updated advice for the risk of congenital malformations and neurodevelopmental disorders and delay

United Kingdom. The MHRA has published the results of its safety review of antiepileptic drugs and the risk of congenital malformations, neurodevelopmental disorders and delay. The review studied carbamazepine, gabapentin, lamotrigine, oxcarbazepine, phenobarbital, phenytoin, pregabalin, topiramate and zonisamide.

Antiepileptic drugs are indicated to control seizures and other epilepsy symptoms. Use of the antiepileptic drugs during pregnancy has been associated with a range of harmful effects to the baby.

In particular, valproate is highly teratogenic and evidence supports the risk of congenital malformations and neurodevelopmental disorders. Valproate is contraindicated in women of childbearing potential unless a pregnancy prevention programme is in place.

In this context, the Commission on Human Medicines (CHM) reviewed available safety data relating to the use of antiepileptic drugs in pregnancy and the risk of major congenital malformations, neurodevelopmental disorders and delay.

For the risk of major congenital malformations, data for lamotrigine and levetiracetam do not suggest an increased risk, but data for carbamazepine, phenobarbital, phenytoin and topiramate are associated with an increased risk.

For the risk of neurodevelopmental disorders and delay, data for carbamazepine, lamotrigine and levetiracetam do not suggest an increased risk, but data for phenobarbital and

phenytoin show the possibility of a risk.

It is recommended that monotherapy treatment is used for treatment of epilepsy at the lowest effective dose where possible. Also, prescribers should consult advice from the SmPC and relevant clinical guidance for dosing and monitoring recommendations for use of antiepileptic drugs during pregnancy.

Reference:
Drug Safety Update, MHRA, 7 January 2021 (www.gov.uk/mhra)

(See also WHO Pharmaceuticals Newsletter No.5, 2020: Sodium valproate (Information note); No.5, 2019: New measures to avoid valproate exposure in pregnancy (Information note))

Carbamazepine

Risk of severe cutaneous adverse reactions

Singapore. The HSA has reminded health-care professionals to verify the HLA-B*1502 status before starting carbamazepine treatment in new patients of Asian ancestry, due to the risk of severe cutaneous adverse reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS/TEN).

Carbamazepine is an anticonvulsant dug indicated for treatment of epilepsy, diabetic neuropathy, trigeminal neuralgia and bipolar disorders.

Patients with HLA-B*1502 genotype are at a risk of developing carbamazepine induced SJS/TEN. The use of carbamazepine should be avoided and alternative treatments are strongly recommended in patients who are found to be positive for HLA-B*1502.

Reference:
Product Safety Alerts, HSA, 10 December 2020 (www.hsa.gov.sg/)

(See also WHO Pharmaceuticals Newsletter No.3, 2018: Risk of DRESS in India; No.1, 2017: HLA-B 1502 genotyping to minimize carbamazepine-induced severe cutaneous adverse reactions in Singapore)

Ceftriaxone

Increased risk of hypokalaemia

Saudi Arabia. The Saudi Food & Drug Authority (SFDA) has released a safety signal concerning hypokalaemia associated with the use of ceftriaxone.

Ceftriaxone is a broad-spectrum cephalosporin antibiotic indicated for the treatment of infections.

In 2020, the SFDA reviewed all the evidence available on the association between ceftriaxone and hypokalaemia following an individual case safety report (ICSR) sent to Saudi national pharmacovigilance centre.

The SFDA's investigation concluded that the current available evidence from assessment of the ICSRs might support a relationship between ceftriaxone and hypokalaemia. This signal needs further investigation to confirm the risk, and health-care professionals should be aware of this potential adverse reaction.

Reference:
Safety Alerts, SFDA, 2020 (www.sfda.gov.sa)

Fingolimod

Increased risk of molluscum contagiosum viral infection

Saudi Arabia. The SFDA has released a safety signal concerning the risk of molluscum contagiosum viral infection associated with the use of fingolimod.

Fingolimod is a sphingosine 1-phosphate receptor modulator and is indicated to treat relapsing-remitting multiple sclerosis patients.

In 2019, the SFDA reviewed all the evidence available on the association between fingolimod and molluscum contagiosum following ICSRs reported to Saudi national pharmacovigilance centre.

The SFDA investigation concluded that the current available evidence might support a relationship between fingolimod and molluscum contagiosum. This signal requires further investigation to confirm the risk, and health-care professionals should be aware of this potential adverse reaction.

Reference:
Safety Alerts, SFDA, 2020 (www.sfda.gov.sa)

Fluconazole

Potential risk of spontaneous abortion and cardiac septal closure anomalies

New Zealand. The Medsafe has announced that use of oral fluconazole during early pregnancy may increase the risk of spontaneous abortion and that doses higher than 150 mg during the first trimester may increase the risk of cardiac septal closure anomalies.

Fluconazole is an oral treatment for vulvovaginal candidiasis and indicated for the treatment of fungal infections.

Triggered by results of a study, the MARC reviewed the data on fluconazole and its use in pregnancy in June 2020.

Topical treatment remains an effective first-line therapy for most pregnant women. Questions around the possibility of pregnancy should be included in routine patient

counselling.

Reference:
Prescriber Update, Medsafe, December 2020 (www.medsafe.govt.nz/)

(See also WHO Pharmaceuticals Newsletter No.3, 2017: Reminder not to use during pregnancy in Ireland and Malaysia; No.3, 2016: Risk of miscarriage in pregnancy: under investigation in the USA)

Hydrocortisone

Risk of acute adrenal insufficiency when switching oral formulations

Europe. The EMA has announced that the PRAC recommended actions to minimize the risk of acute adrenal insufficiency in children when switching from conventional oral tablets of hydrocortisone to hydrocortisone granules Alkindi®.

Hydrocortisone (Alkindi®) is indicated for children whose adrenal glands cannot make enough of a hormone called cortisol.

The PRAC evaluated the risk of acute adrenal insufficiency, triggered by a case report of a baby developing severe adrenal insufficiency after switching from hydrocortisone tablets to Alkindi® granules.

Following the evaluation, the PRAC recommend that doctors should carefully observe the child for symptoms of adrenal insufficiency such as tiredness, headache, unstable temperature and vomiting during the first week after switching to Alkindi®, and that doctors should advise carers to increase the doses of Alkindi® if the child develops symptoms of adrenal insufficiency.

Reference:
EMA, 15 January 2021 (www.ema.europa.eu)

(See also WHO Pharmaceuticals Newsletter No.1, 2019: Risk of insufficient cortisol absorption and life-threatening adrenal crisis in UK)

Ibrutinib

Increased risk of cardiac failure

Saudi Arabia. The SFDA has released a new signal communication describing the potential risk of cardiac failure associated with the use of ibrutinib.

Ibrutinib is a Bruton's tyrosine kinase inhibitor that is indicated to treat certain type of cancers such as mantle cell lymphoma (MCL) and chronic lymphocytic leukaemia (CLL) particularly for patients with relapsed conditions.

The signal detection team at the SFDA has reviewed the local and global databases to find and assess the related case reports of ibrutinib associated cardiac failure. Among more than half of the 35 cases that were selected for assessment of causality, a supportive association (4 probable and 15 possible cases) of cardiac failure with the use of ibrutinib was found.

In conclusion, the weighted cumulative evidence identified from causality assessment of the reported cases and data mining are sufficient to support a causal association between ibrutinib and cardiac failure.

Health regulators and health-care professionals are advised to be aware of this potential risk and should monitor any signs or symptoms in patients treated with ibrutinib.

Reference:
Safety Alerts, SFDA, 2020 (www.sfda.gov.sa)

(See also WHO Pharmaceuticals Newsletter No.4, 2018: Potential risk of ventricular tachyarrhythmia in Canada; No.6, 2017: Risk of ventricular tachyarrhythmia, hepatitis B reactivation and infection in Australia; No.5, 2017)

Methotrexate

Potential risk of skin cancer

Saudi Arabia. The SFDA has released a new signal communication describing the potential risk of skin cancer associated with the use of methotrexate (MTX).

MTX is an antimetabolite used to treat multiple conditions, including neoplastic diseases, severe psoriasis and rheumatoid arthritis.

The SFDA has searched the local and global databases to find any reported cases, alongside with literature screening to retrieve related information for assessing the causality between skin cancer and MTX.

In SFDA has concluded that the weighted cumulative evidence are sufficient to support a causal association. Therefore, health-care professionals should be aware of this potential risk and may consider monitoring any signs or symptoms of skin cancer in patients treated with MTX.

Reference:
Safety Alerts, SFDA, 2020 (www.sfda.gov.sa)

Oseltamivir

Potential risk of haemorrhage

Canada. Health Canada has announced that there may be a link between the use of oseltamivir (Tamiflu® and generics) and the risk of lower gastrointestinal bleeding.

Oseltamivir is indicated to treat or prevent the onset of flu. The Canadian product safety information for oseltamivir includes the risk of gastrointestinal bleeding based on experience with its use after marketing.

Triggered by the PMDA, Health Canada reviewed the potential risk of bleeding in general with the use of oseltamivir with the Canadian vigilance database, international databases and published literature. Also, Health Canada reviewed 59 case (four Canadian and 55

international) of bleeding in patients receiving oseltamivir. Of the 59 case reports, 42 reports showed a possible link between oseltamivir use and haemorrhage.

The information reviewed was inconclusive regarding the risk of bleeding in general, but the review concluded that there may be a link between the use of oseltamivir and the risk of lower gastrointestinal bleeding.

Given that the product safety information for oseltamivir already includes the risk of gastrointestinal bleeding, no updates are required at this time.

Reference:
Summary Safety Review, Health Canada, 8 January 2021 (www.hc-sc.gc.ca)

(See also WHO Pharmaceuticals Newsletter No.2, 2019: Risk of bleeding in Japan)

Pembrolizumab

Increased risk of rhabdomyolysis

Saudi Arabia. The SFDA has released a communication on a safety signal concerning rhabdomyolysis associated with the use of pembrolizumab.

Pembrolizumab is a programmed death receptor-1 (PD-1) blocking antibody and inhibits the immune response of T-cells, including an anti-tumor response.

In March 2020, the SFDA reviewed all available evidence on the association between pembrolizumab and rhabdomyolysis. The investigation was based on ICSRs reported to Saudi national pharmacovigilance centre.

The SFDA's investigation concluded that the current available evidence might support a relationship between pembrolizumab and rhabdomyolysis. Therefore, this signal needs to be investigated further to confirm the risk ,and health-care professionals should be aware of this potential adverse reaction.

Reference:
Safety Alerts, SFDA, 2020 (www.sfda.gov.sa)

Tumor necrosis factor alpha (TNFα) inhibitors

Risk of Kaposi's sarcoma

Malaysia. The NPRA has announced that Tumor necrosis factor alpha (TNFα) inhibitors may lead to an increased risk of severe infections or malignancies.

TNFα inhibitors are indicated to treat chronic inflammatory diseases such as rheumatoid arthritis and Crohn's disease.

In August 2020, the NPRA received information from the EMA on the risk of Kaposi's sarcoma associated with TNFα inhibitors.

Although the NPRA has received 314 adverse drug reaction reports, no event related to Kaposi's sarcoma has been reported locally for all TNFα inhibitors.

Health-care professionals should be alert on the risk of Kaposi's sarcoma with the use of TNFα inhibitors.

Reference:
Safety Alerts, NPRA, 20 January 2021 (www.npra.gov.my/)

Vascular endothelial growth factor (VEGF) inhibitors

Risk of aneurysms and artery dissections

New Zealand. The Medsafe has announced that systemic vascular endothelial growth factor (VEGF) inhibitors increase the risk of aneurysms and artery dissections.

Systemic VEGF inhibitors are used to treat a variety of cancers. Approved systemic VEGF inhibitors in New Zealand include axitinib (Inlyta®), bevacizumab (Avastin®), sorafenib (Nexavar®) and sunitinib (Sutent®).

Although no cases have been reported in New Zealand, an association between the use of VEGF inhibitors and the risk of aneurysms and artery dissections has been identified. The mechanism by which VEGF inhibitors can cause aneurysms and artery dissections is unclear but may include aggravation of pre-existing hypertension and changes in the structure of the vascular endothelium.

Also, hypertension, smoking and high cholesterol are modifiable risk factors for aneurysms and artery dissections. Non-modifiable risk factors include increasing age and a family history of aneurysm and artery dissection.

To minimize the risk, patients should be regularly monitored for blood pressure during treatment. Antihypertensive therapies should be initiated according to blood pressure treatment guidelines. Also, smokers should be referred to a smoking cessation service.

Reference:
Prescriber Update, Medsafe, December 2020 (www.medsafe.govt.nz/)

(See also WHO Pharmaceuticals Newsletter No.6, 2020: Risk of aneurysm and artery dissection in Ireland; No.1, 2019: Risk of artery dissections and artery aneurysms in Canada; No.1, 2015: Thrombotic microangiopathy in Canada)

A signal is defined by WHO as reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously. Usually more than a single report is required to generate a signal, depending upon the seriousness of the event and the quality of the information. A signal is a hypothesis together with data and arguments and it is important to note that a signal is not only uncertain but also preliminary in nature.

The signals in this Newsletter are based on information derived from reports of suspected adverse drug reactions available in the WHO global database of individual case safety reports (ICSRs), VigiBase. The database contains over 24 million reports of suspected adverse drug reactions, submitted by National Pharmacovigilance Centres participating in the WHO Programme for International Drug Monitoring. VigiBase is, on behalf of the WHO, maintained by the Uppsala Monitoring Centre (UMC) and periodic analysis of VigiBase data is performed in accordance with UMC's current routine signal detection process. International pharmaceutical companies, when identified as uniquely responsible for the drug concerned, are invited to comment on the signal text. Signals are thereafter communicated to National Pharmacovigilance Centres, before being published in this Newsletter. Signal texts from UMC might be edited to some extent by WHO and may differ from the original version. More information regarding the ICSRs, their limitations and proper use, is provided in the UMC Caveat document available at the end of Signal (page 33). For information on the UMC Measures of Disproportionate reporting please refer to WHO Pharmaceuticals Newsletter Issue No. 1, 2012.

UMC, a WHO Collaborating Centre, is an independent foundation and a centre for international service and scientific research within the field of pharmacovigilance. For more information, on the UMC Measures of Disproportionate Reporting etc., visit www.who-umc.org. To leave a comment regarding the signals in this Newsletter, please contact: the Uppsala Monitoring Centre, Box 1051, SE-751 40 Uppsala, Sweden. E-mail: signals@who-umc.org.

Loperamide and acute pancreatitis in patients with a history of cholecystectomy: signal strengthening

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Summary

Loperamide is an over-the counter antidiarrhoeal with opioid receptor affinity. By virtue of their excitatory effects on the Sphincter of Oddi, opioids could increase the pressure of the pancreatic duct and lead to acute pancreatitis. In the wake of communications of acute pancreatitis induced by eluxadoline in patients without a gallbladder, some international medicines agencies have considered a mechanistically similar over the counter antidiarrhoeal, loperamide, as a potential factor in the onset of the same condition in patients with a similar clinical history. VigiBase, the WHO global individual case safety reports database, held 35 deduplicated case reports of loperamide and loperamide;simeticone with the MedDRA Preferred Terms "Pancreatitis" and "Pancreatitis acute" as of 26 January 2020. Of this patient sample, those without clear confounders (gallstones, infections, alcoholism) were mostly female, while eight of the 35 had a history of cholecystectomy; the time to onset ranged between one and five days (except an episode of two months) and there were at least 10 positive dechallenges. Of the patients with cholecystectomy, four had already been recorded in the published literature. This communication adds more information on the suspected relationship between loperamide and acute pancreatitis, and may be useful in the interim before scheduled PSURs emerge, or where relevant preceding regulatory decisions might be reconsidered in light of recent data. Precautionary measures may be necessary, as loperamide is an easily accessible alternative for patients who have experienced adverse effects to eluxadoline.

Introduction

Loperamide is an over the counter agonist of μ-, κ-opioid receptors, with higher affinity for μ receptors, and an antagonist of δ-opioid receptors.[1, 2] It was originally approved in the United States in 1976[3] and was considered non-addictive, without evident clinical signs of long-term tolerance or interactions with barbiturates and alcohol.[4] Later analyses of spontaneous reports from the US Food and Drug Administration (FDA) database of adverse effects (FAERS) have suggested QT-prolonging effects in the context of abuse[5] that have resulted in the apposition of a boxed warning on the FDA's labels.[6] Loperamide's indications, as reported on the European Summary of Products Characteristics (SmPC) and FDA's drug labels, encompass short-term symptomatic relief of diarrhoea in patients above 12 years of age and extends to that induced by irritable bowel syndrome.[7, 8]

Cholecystectomy is a surgical procedure typically performed as an early response to acute cholecystitis (inflammation of the gallbladder), whether or not it is complicated by gallstones. A systematic review and meta-analysis of prospective randomised/non-randomised clinical trials and

retrospective trials (10 studies in total) suggests laparoscopic are preferable over open procedures in terms of morbidity, mortality, post-operative length of stay and intra-operative blood loss.[9]

Acute pancreatitis is a transient inflammation of the pancreas and is distinct from its recurring counterpart: chronic pancreatitis. It is described as a common cause for hospitalisation, with an incidence of 14-45 cases per 100,000 persons, primarily induced by gallstones and alcohol abuse.[10] Specifically, biliary duct obstruction in the presence of gallstones is the aetiological explanation for acute pancreatitis, though formations of smaller biliary crystals (microlithiasis) without obstruction can also contribute to the onset of acute pancreatitis.[11]

Drug-induced pancreatitis is a complicated adverse effect difficult to ascertain; the mechanism varies according to the therapeutic class of the triggering drug, its dose, and the underlying conditions of the patient, and also varies in its time to onset: it may range from hours, to days, or even months.[12] There is at least one compendium of drugs "definitely" known to induce acute pancreatitis, primarily based on rechallenge information and time to onset.[12]

Finally, Oddi's Sphincter dysfunction has been described as a potential mechanistic explanation of (drug-induced) acute pancreatitis. This sphincter regulates the flow of pancreatic and biliary digestive secretions into the small intestines. In animal models and in humans its spasms may produce a reflux of secretions into the pancreas leading initially to increased ductal pressure and then to pancreatitis, though there may be idiosyncratic competing causes for the onset of acute pancreatitis.[13]

Reports in VigiBase

As of 26 January 2020, there were 39 case reports of loperamide, loperamide;simeticone and the MedDRA Preferred Terms (PT) "Pancreatitis" and "Pancreatitis acute" in VigiBase, the WHO global individual case safety reports database. The SMQ "Acute pancreatitis (narrow)" did not reveal additional case reports. Four case reports were identified as duplicates, leaving 35 in total. The cases were from France (13), Germany (4), United States (5), Spain (3), Canada (2), Italy (2), Switzerland (2), United Kingdom (2), Australia (1), Portugal (1). None of the drugs-adverse event combinations were disproportional.

The 16 cases that suggest a plausible relationship between the medicinal product and adverse event are summarised below and included in Table 1.

These case reports came from seven countries: France (8), United Kingdom (2), Italy (2), Canada, Switzerland, Germany and Portugal (1 each). Pancreatitis was diagnosed either by imaging (patients 1, 2, 3, 4, 5, 12) or blood amylase and lipase (6, 7, 10, 14). A positive dechallenge was recorded in ten case reports (patients 1, 4, 6, 7, 9, 10, 12, 13, 14, 15) with one positive rechallenge (patient 14) and one instance of recurrent pancreatitis on loperamide. Where reported, the time to onset was short: one to five days, except an outlier of two months. Eight patients had a history of cholecystectomy (patients 1-7, and 16). Of those who did not, one (patient 9) had a family history of pancreatitis. Females were far more prevalent (14 patients) than males (2) in the case series. Indication for use was diarrhoea of unclear aetiology where specified. Only one patient (number 16) had potential confounders, of Crohn's disease and a 'likely history of gallstones'. Since the latter was not ascertained, we saw fit to include this patient in this group.

The 19 cases that do not necessarily suggest a relationship between the medicinal product and adverse event are summarised below.

These case reports came from seven countries and are available upon reasonable request.

The time to onset was short but on the whole longer than those in the previous series; it ranged from 5 to 15 days, with 1 day, 2 days, and 1 month as outliers. Fewer case reports contained this information compared to the 16 case reports commented on above. Dechallenge and rechallenge fields were either incomplete or the role of other co-reported medicines could not be excluded. Where sex was reported, there were at least 8 male and 10 female patients. Imaging and other laboratory values were not specified to the same extent as in the previous group of reports.

Literature and labelling

Literature

There are six published literature cases for loperamide and pancreatitis or pancreatitis acute in patients who underwent cholecystectomy, with an additional one from a clinical trial whose cholecystectomy status is unknown.

Electronic databases

Four case reports in VigiBase were from the literature, and are summarised in Table 1.[14-16] Two additional case reports were found in PubMed and Embase when searching for "loperamide" AND "pancreatitis" in title and abstract.[17, 18] Both are discussed below:

Howaizi and colleagues describe a 57-year-old woman with concomitant dosulepine, alprazolam who experienced acute pancreatitis after two hours of loperamide intake, who had a positive history of cholecystectomy (21 years prior). Coproculture did not reveal pathogens. The patient had experienced four previous episodes in five years that rapidly improved and were described as "similar" by the patient. The two previous episodes coincided with intake of codeine;paracetamol fixed-dose combination, but for the other two episodes the

cause was unclear.[17] This literature report presents strong similarities (dates of treatment and onset, patient age and gender) with case 5 in the table below. A 58-year-old woman with a history of hypertension, hypothyroidism, and cholecystectomy started taking loperamide due to diarrhoea, along with daily thyroxin, hydrochlorothiazide, and atenolol for her underlying conditions. She experienced abdominal pain, nausea, and vomiting after two days of loperamide, which went on for seven days before visiting the emergency room. She denied alcohol consumption or smoking. Her lipase, amylase, white blood cell-count and c-reactive protein were elevated. A CT scan showed post-cholecystectomy status and acute pancreatitis. Magnetic resonance cholangio-pancreatography confirmed post-cholecystectomy status, a common bile duct of 5 mm, and no signs of gallstones.[18]

Clinical trials

Consultation of the clinical trials registers in the United States (US) revealed one randomised controlled trial, later published as "Controlling faecal incontinence in women by performing anal exercises with biofeedback or loperamide: a randomised clinical trial", with one patient in the treated arm who experienced pancreatitis (PT). The comparison was placebo with or without biofeedback.[19, 20]

Labelling

Summaries of Product Characteristics

Pancreatitis is not labelled in the European SmPC available at the Electronic Medicines Compendium, nor on the US FDA's label.[3, 7]

Regulatory proceedings

Loperamide-induced pancreatitis was discussed by the Pharmacovigilance Risk Assessment Committee (PRAC) in January 2019, and the manufacturer was asked to review all the relevant cases of loperamide, and loperamide;simeticone, with pancreatitis in a PSUR (deadline: 28 August 2021).[21, 22] The same suspected adverse drug reaction has been partially touched upon by the Australian Therapeutic Goods Administration.[23] In 2011, FDA deemed that information available at that time on loperamide and pancreatitis was insufficient to take action.[24]

Discussion

Of the 35 case reports, 16 may present evidence of pancreatitis-inducing effects of loperamide; the diagnosis of pancreatitis was based on medical history, upper abdominal pain, and laboratory analyses in several patients. Eight in particular had a history of cholecystectomy, which raises the possibility that the surgical removal of the gallbladder may predispose patients taking loperamide to pancreatitis. In support of this hypothesis is the reported failure to detect cholelithiasis in patients with a history of cholecystectomy, a main cause of pancreatitis. Micro-crystalline formations at the common bile duct were ruled out in one case report (patient 5). Ten case reports suggested a positive dechallenge, with one positive rechallenge (though confounded by total colectomy). Other causes of pancreatitis were specifically excluded, for example history of alcohol abuse. Consistent with the literature, case reports in Table 1 have a time to onset compatible with the relatively short latency of drug-induced pancreatitis (e.g. in literature case reports describing patients on codeine and with a history of cholecystectomy).[12]

Another emerging finding is that women more frequently reported suspected pancreatitis with loperamide. Cholelithiasis is more common in women, which may explain the prevalence of female patients and, in particular, the original cause for cholecystectomy – for which the clinical rationale was never provided in the case reports.

Painful contractions of the Sphincter of Oddi in patients without gallbladder have been described as early as 1936, with morphine,[25] and later, following codeine, in 1941.[26] A recent claims-based nested case-control study of patients who had undergone laparoscopic cholecystectomy has found a four-fold risk of hospitalisation due to pancreatitis within the first 15 days of treatment with codeine.[27] In line with these findings, before the suspected pancreatitis due to loperamide, patient 5 had been hospitalised for pancreatitis due to codeine.

A substance similar to loperamide for its mixed agonist/antagonist-effect on μ-, κ-, and δ-opioid receptors, is eluxadoline[28]; it displays higher affinity for μ-receptors than for κ-receptors (although the affinity for κ-receptors was only determined in animal models).[29] Eluxadoline is indicated to treat diarrhoea due to irritable bowel syndrome, and has recently been under investigation by regulatory agencies, namely the FDA[30] and the Australian Therapeutic Goods Administration.[23] Among the 120 case reports in FAERS of eluxadoline and pancreatitis, 68 patients reported a gallbladder status and 56 had undergone cholecystectomy.

Both agencies concluded that plausible explanations for the causes of pancreatitis could include effects on the Sphincter of Oddi. This conclusion is warranted: sub-analgesic doses of morphine have been reported to have excitatory effects ('spasms') on Oddi's Sphincter by an increase in the frequency of its phasic pressure waves, phasic wave amplitude and basal pressure. The effects on the frequency of phasic pressure waves and basal pressure have been shown to be competitively antagonised by naloxone, which increases the possibility that Oddi's Sphincter could be partially regulated by opioids.[31] Indeed, morphine is a full agonist of μ-, κ- and δ-opioid receptors and naloxone a full antagonist, however, eluxadoline and loperamide are mixed agonists of μ-, κ-receptors but antagonists of δ-receptors. As mixed agonists/antagonists, eluxadoline and loperamide may have both excitatory and depressive effects on the Sphincter of Oddi mediated by their anti-δ-opioid receptor

activity. A key distinction lies in their binding affinities for the δ-opioid receptors. Loperamide's inhibitory constant (Ki) is nearly ten times lower (meaning nearly ten times higher affinity) than eluxadoline's (48 nM[1] vs 430 nM[29]). A higher affinity for δ-receptors may suggest a higher inhibitory activity of loperamide's own excitatory potential when compared to eluxadoline.

Patient 9 was reported to have had a family history of pancreatitis. Howaizi and colleagues[17] suggest that Sphincter of Oddi's spasms caused by morphine derivatives could be explained by an individual's hereditary susceptibility. They support this claim with a reference to a series of three patients, one mother and her two children, who all experienced episodes of "biliary colic" after ethylmorphine or codeine phosphate for cough suppression. As negative controls, two other siblings had never had any episode of biliary colic but at the same time did not recall taking any opioid-based cough suppressant. Notably, the mother had experienced biliary spasms before undergoing cholecystectomy, and 13 years after the surgery.[32] These observations may suggest that family history may be a predisposing factor, rather than a confounding one.

There are limitations to this assessment. First, a history of cholecystectomy was not given for most patients. Requests for original reports from national centres and corresponding authors revealed more information on gallbladder status and dates of surgery. Requests for additional information for the patient involved in the clinical trial of loperamide and biofeedback for faecal incontinence were unsuccessful, so the dates of cholecystectomy were unknown for some patients without a gallbladder. These may have been useful in minimising confounding by "post-cholecystectomy syndrome".[34] Information on the surgical technique used to remove the gallbladder was not always given but would have been useful in understanding the individual risk of pancreatitis.[35]

The case reports that suggested a plausible relationship were more complete and had compatible times to onset, but they should be viewed together with the ones that did not. Moreover, the former cases were not without co-reported drugs (patients 1, 5, 7, 10, 13, 14) or underlying disorders (patient 16) that may have played a role in the onset of pancreatitis. Other case reports clearly indicated misuse of loperamide and overdoses in suicide attempts (these data are not shown, but available upon reasonable request), although there are two published case reports of pancreatitis following loperamide overdose.[36, 37]

Conclusion

The present communication strengthens earlier signals of loperamide-induced pancreatitis by providing evidence from case reports of, a) a subset of eight patients without a gallbladder, suggesting an at-risk-group; b) a time to onset compatible with drug-induced pancreatitis; c) ten instances of positive dechallenge and one positive rechallenge with minor significance (as it may have referred to the sporadic use of loperamide without diagnosis of pancreatitis). A further strength was that the same observations were consistent across seven countries (or 10, if one includes the reports that did not necessarily suggest a relationship).

With several published case reports, this association has already been discussed by different regulatory agencies, however, FDA's latest public update is from 2011 and the EU PSUR is due in 2021. This signal may prove sufficient to re-open previous decisions, or as an interim update before due PSUR dates. Finally, a loperamide-induced pancreatitis may suggest the need for action in view of the drug's over-the-counter availability and its status as proposed alternative for patients without gallbladder who have been treated with eluxadoline and experienced pancreatitis.

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Table 1. Cases of pancreatitis and pancreatitis acute that suggest a plausible relationship with loperamide

Case	Age/ Sex	Other suspected (S), interacting (I) or concomitant (C) drugs	Reactions (MedDRA Preferred Term)	Time to onset	Action taken with drug (dechallenge and rechallenge)	Outcome	Comment
1	77/ M	Metopimazine (S) Clopidogrel*, Rosuvastatin*, Serenoa repens, Lorazepam, Lansoprazole*, Sodium alginate, Paracetamol*, Verapamil, Glyceryl trinitrate, Macrogol (all C)	Pancreatitis	Within 1 day	Drug withdrawn/ Reaction abated	Recovered	Cholecystectomy 15 years before the event of pancreatitis Habitual treatment with concomitant drugs Lab values compatible with pancreatitis CT scan did not reveal cholelithiasis; alcoholic aetiology discarded
2	77/F	-	Pancreatitis	1 day	-	-	Literature case Peserico et al. 2017[16] History of remote cholecystectomy, at least 40 years before the date of the case report (personal communication) No alcohol consumption, smoking, or family history of pancreatitis Lab values compatible with pancreatitis Magnetic resonance-cholangio-pancreatography showed a well-defined pancreas without acute inflammation pancreatitis; common bile duct lithiasis excluded
3	46/F	-	Pancreatitis, Sphincter of Oddi dysfunction	1 day	-	-	Literature case Peserico et al. 2017[16] History of laparoscopic cholecystectomy confirmed by abdominal ultrasound, at least 10

Case	Age/ Sex	Other suspected (S), interacting (I) or concomitant (C) drugs	Reactions (MedDRA Preferred Term)	Time to onset	Action taken with drug (dechallenge and rechallenge)	Outcome	Comment
							years before the date of the case report (personal communication) Hepatic steatosis No fever, smoking, or alcohol consumption Magnetic resonance-cholangio-pancreatography: no inflammation of pancreas; no gallstones
4	65/F	-	Pancreatitis acute	-	Drug withdrawn/ Reaction abated	Recovered	Literature case Labgaa et al 2015[15] Loperamide taken for 2 days, 6 mg/day History of laparoscopic cholecystectomy confirmed by abdominal ultrasound Recurrent pancreatitis after loperamide (previous occurrence 4 months before this report) Denies alcohol consumption, no family history for pancreatitis Lab values compatible with pancreatitis CT-scan (during prior admission): well-defined pancreas without interstitial or peripancreatic oedema Magnetic resonance-cholangio-pancreatography excluded inflammation of pancreas and common bile duct lithiasis Follow-up of 16 months, without loperamide and no recurrence of pancreatitis
5	57/F	Codeine* (S)	Oedematous pancreatitis, Product use in unapproved indication, Pancreatitis acute	-	-	Recovered	Literature case Hastier et al. 2000[14] presents strong similarities to literature report by Howaizi and colleagues[17] History of cholecystectomy 23 years before Denies "excessive" alcohol consumption, or risk factors for pancreatitis Recurrent "similar" abdominal pain after administration of loperamide and codeine, accompanied by "significant elevation of serum amylase on each occasion" Lab values compatible with pancreatitis Abdominal CT-scan: oedematous acute pancreatitis and normal common bile duct Biliary crystals not detected
6	85/F	Lomefloxacin, Ibuprofen (all S) Levothyroxine, Metformin, Esomeprazole, Fenofibrate*, Irbesartan (all C)	Pancreatitis acute	5 days (15 days, 5 days for lomefloxacin and ibuprofen)	Drug withdrawn/ Reaction abated	Recovered	History of cholecystectomy Lab values compatible with pancreatitis. Negative for *C. difficile* Urinary infection treated with lomefloxacin, 10 days before onset of pancreatitis. Ibuprofen concomitant to start of therapy with loperamide Gout, urinary infection, sigmoid diverticulosis, hypertension arterial, gastritis, dyslipidaemia, hypothyroidism, type II diabetes mellitus
7	68/ M	Tramadol*, Omeprazole (all S)	Pancreatitis acute	-	Drug withdrawn/	Recovering	History of cholecystectomy and pancreatitis Prostate cancer

Case	Age/ Sex	Other suspected (S), interacting (I) or concomitant (C) drugs	Reactions (MedDRA Preferred Term)	Time to onset	Action taken with drug (dechallenge and rechallenge)	Outcome	Comment
		Tamsulosin, Phloroglucinol, Trimethylphlorog-lucinol, Degarelix, Docetaxel, Parecetamol*, Tinzaparin (all C)			Reaction abated		Lab values compatible with pancreatitis
8	-/F	-	Pancreatitis acute	Within 1 day	-	-	-
9	23/F	-	Pancreatitis acute	Within 1 day	Drug withdrawn/ Reaction abated	Recovered	Lab values compatible with pancreatitis Family history of pancreatitis (grandmother) Viral load undetected No visible lithiasis "Occasional" alcohol intake
10	78/F	Paracetamol; Tramadol* (all S)	Pancreatitis acute	2 days (1 month for paracetamol; tramadol)	Drug withdrawn/ Reaction abated	Recovered	Lab values compatible with pancreatitis Hypertension arterial, diabetes No findings of dilation or obstacles of biliary ducts Paracetamol; tramadol reintroduced without recurrence of pancreatitis
11	30/F	Budesonide, Formoterol (all C)	Pancreatitis	1 day	-	Not recovered	Non-infectious gastroenteritis and colitis
12	73/F	-	Pancreatitis acute	2 days	Drug withdrawn/ Reaction abated	Recovered	Lab values compatible with pancreatitis Abdominal scan without injection: intrahepatic tract aerobilia, slightly oedematous pancreas Abdominal scan with injection: G-lobe aerobilia, tumefied pancreatic tail Abdominal echography: Heterogeneous hepatic parenchyma without focal lesions, aerobilia
13	17/F	Ketoprofen*, Paracetamol*, Colchicine, Thiocolchicoside, Lansoprazole* (all S)	Pancreatitis	5 days	Drug withdrawn/ Reaction abated	Recovered	Lab values compatible with pancreatitis
14	50/F	Sulindac (C)*	Pancreatitis, Abdominal pain upper, Nausea, Vomiting	< 2 months	Drug withdrawn/ Reaction abated Rechallenge/ Reaction recurred	Recovered	Lab values compatible with pancreatitis, confirmed by echography Total colectomy due to familial polyposis Intermittent use of loperamide for the previous 2 years
15	50/F	Omeprazole, Ondansetron, Salbutamol (all C)	Pancreatitis	Within 1 day	Drug withdrawn/ Reaction abated	Recovering	-
16	53/F	-	Pancreatitis	-	-	-	History of cholecystectomy age 19

Case	Age/ Sex	Other suspected (S), interacting (I) or concomitant (C) drugs	Reactions (MedDRA Preferred Term)	Time to onset	Action taken with drug (dechallenge and rechallenge)	Outcome	Comment
							History of C. difficile infection (2 years before date of report) Concurrent conditions: hypothyroidism, fibromyalgia Hysterectomy (7 years prior to date of report) Potential confounders: Crohn's disease, 'likely history of gallstones'

* Known to be associated with pancreatitis on EU SmPC

Tramadol and Hyponatraemia – new aspects of an old signal

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Summary

Tramadol is an opioid analgesic for treatment of moderate to severe pain. Hyponatraemia is an electrolyte disturbance especially common among elderly and hospitalised patients. In 2016, the Pharmacovigilance Risk Assessment Committee (PRAC) at the European Medicines Agency reviewed a signal of hyponatraemia and the syndrome of inappropriate anti-diuretic hormone secretion (SIADH) with tramadol, but causality was not established. The aim of our review was to investigate if VigiBase, the WHO global database of individual case safety reports, included cases suggestive of causality. VigiBase data up to 4 February 2018 for the broad MedDRA SMQ 'Hyponatraemia/SIADH' included 278 unique cases. A subset of 118 cases was reviewed case by case. In these 118 patients, the ages ranged between 20 and 106 years (median 77), with 35 patients younger than 65. Time-to-onset distribution was: within one day (21 cases), 2-7 days (56), 8-14 days (15), 15 days to 1 month (8) and >1 month (6). Seventy-nine patients recovered after tramadol withdrawal and one well-described positive rechallenge was identified. Tramadol was the sole suspect in 63 cases, and in 26 it was the sole reported drug. Potentially confounding conditions were described in a quarter of the cases. In another quarter, older diagnosed conditions were mentioned which were more likely to be risk factors than confounders. Fifty-five patients were co-treated with drugs known to cause hyponatraemia. In 19 cases these were reported as long-term drugs which had been taken for many months or years, and the reaction occurred only after tramadol was added. In five cases, tramadol was reported as being suspected of having interacted with the co-medications. VigiBase cases that support causality between tramadol and hyponatraemia were found. The key cases usually concerned elderly and predisposed patients, but young individuals were also identified. Causality was supported by the time-to-onset pattern and by cases with positive de- and re-challenge. The results were also strengthened by hypothesised mechanisms of actions, and findings in the literature.

Introduction

Tramadol is an opioid analgesic for treatment of moderate to severe pain. It is a non-selective pure agonist at μ-, δ- and κ-opioid receptors with a higher affinity for the μ-receptor. Other mechanisms for its analgesic effect involve inhibition of serotonin- and noradrenaline reuptake.[1] To exert full analgesic effect tramadol must be converted by CYP2D6 to its main metabolite O-desmethyltramadol (M1) which has a several-fold higher affinity for μ-opioid receptors than the parent drug. Tramadol is also converted by CYP3A4 and CYP2B6 to an inactive metabolite.[2] The inhibition of CYP3A4 and CYP2D6 may affect the plasma concentration of tramadol or M1.[3] Tramadol and its metabolites are almost completely excreted via the kidneys. An elimination half-life of up to three times longer than normal has been observed in patients with renal insufficiency.[4]

Hyponatraemia (HN) is characterised by serum sodium <135 mmol/L and is considered severe at <125 mmol/L. It is especially common among elderly and hospitalised patients with comorbidities and who are taking many drugs. Symptoms may include nausea, headache, decreased level of consciousness, seizures, impaired mental status,

brain oedema and coma.[5] Chronic HN develops over a longer time (>48 hours) and is often asymptomatic. Acute HN has an onset of symptoms within 48 hours, with a higher risk of neurologic symptoms and death.[6] HN is usually classified according to volume status, i.e. hypovolaemic HN (caused by vomiting, diarrhoea, renal losses and diuretics, especially thiazides), euvolaemic HN (caused by hypothyroidism, stress, surgery, pain, the syndrome of inappropriate anti-diuretic hormone secretion (SIADH), and various drugs such as antiepileptics, antipsychotics, antidepressants, proton pump inhibitors (PPIs), ACE-inhibitors, angiotensin II antagonists and diuretics), or hypervolaemic HN (caused by cirrhosis, heart failure, nephrotic syndrome and excessive fluid intake).[7] Drug-induced HN commonly emerges within the first few weeks of treatment.[8]

In 2016, the Pharmacovigilance Risk Assessment Committee (PRAC), at the European Medicines Agency, undertook a signal review of the association of '*Tramadol – Hyponatraemia and SIADH'*. The PRAC concluded that the data did not suggest a causal association since the number of cases was very low in view of the extensive post-authorisation exposure, and that many cases occurred in elderly patients and were confounded by concomitant therapy or other factors.[9] However, tramadol-induced HN could be a very rare adverse drug reaction (ADR), which might explain the relatively low number of cases. HN has many causes, and the diagnosis of drug-induced HN can easily be overlooked.[8] Lastly, as HN is largely predominant in the elderly population and is a symptom of various spontaneous or drug-induced conditions, it is inevitable that the reports mainly concern these patients. With these considerations in mind and because of additional reports in VigiBase, the WHO global database of individual case safety reports, a causality assessment of the VigiBase reports of tramadol and HN was conducted by UMC.

Reports in VigiBase

As of 4 February 2018, there were 340 reports for tramadol and the broad MedDRA SMQ 'Hyponatraemia/SIADH'. Sixty-two duplicates were identified, leaving the number of unique cases as 278. The reports came from 24 countries, and the top five reporting countries were France (100 reports), United States (92), Australia (42), United Kingdom (21) and India (14). The IC/IC_{025} values were -0.1/-0.3 for HN and 1.1/0.7 for SIADH (September 2019).

To identify key cases our analysis focused on those with a time-to-onset available for tramadol, or where tramadol was the only reported drug in the structured data. For additional reports, with a potential of being key cases (e.g. where there was a start date for tramadol but no onset of reaction date), the narrative texts were further reviewed for time-to-onset information. Original reports were requested from national centres when possible and where thought to be of additional value. Cases with potentially confounding drugs (i.e. drugs with HN and/or SIADH listed as ADRs in their Summary of Products Characteristics (SmPCs)[10], and other opioids) reported as started within two months before or after tramadol start, were excluded. The remaining 118 cases were reviewed case by case. Twenty-eight were considered to be key cases. A selection of those are set out in the text or in Tables 3 and 4.

Case by case review of 118 cases

Age was available in 111 cases and ranged from 20 to 106 years old, with a median value of 77 years. The age group distribution was 18-44 years (18 cases), 45-64 years (17), 65-74 years (14) and 75 years or older (62). Patient sex was 83 females and 34 males and was not reported for one.

Sixty-three cases were reported as serious, 11 reported convulsions and five were fatal. In four of the fatal cases the reported SMQ term was 'brain oedema' and HN was not mentioned. Two of these were overdoses and two were strongly confounded by existing condition. Only one fatal case clearly implicated HN:

- A 27-year-old woman suffered a pelvic fracture after a motor vehicle accident. No other injuries were identified, and her serum sodium was normal. Pain relief was achieved with the maximum daily doses of paracetamol and tramadol. From the 5th day she showed symptoms of HN and became a lot worse over the next days. Severe HN was detected (97 mmol/L) on the 9th day and she was transferred to intensive care. The corrective treatments of HN led to the development of osmotic demyelination syndrome, and the patient died.

Potentially confounding conditions, including those that had recently appeared and were of an acute nature, e.g. major surgery, head trauma and recently worsened renal insufficiency, were given in approximately a quarter of the cases. Another quarter described conditions that the patients had had in the past or for a long time, such as chronic obstructive pulmonary disease (COPD), diabetes and hypothyroidism, which were more likely to be risk factors than confounders. One example is the case below (also a conference abstract by Farouk and Uribarri).

- A 44-year-old male with a past medical history of hypothyroidism started with tramadol for leg pain. Within two weeks he presented to the emergency department with nausea and leg pain. He was euvolaemic and had severe HN (109 mmol/L) and SIADH. Thyroid secreting hormone was within normal limits. The patient had no obvious source of SIADH other than tramadol. Tramadol was discontinued and fluid was restricted. By day 3, the patient was improving.

The reference sodium values prior to taking tramadol were provided for nine patients among the key cases. In seven of these, the sodium levels were within the normal range but close to the lower limit for HN, while in one case the patient already had a slightly low sodium value when tramadol was initiated (the rechallenge case below).

The time-to-onset for tramadol was reported in 106 cases, see Table 1.

Table 1. Time-to-onset for tramadol and hyponatraemia

Time-to-onset	No. cases
0-1 day	21
2 to 7 days	56
8 to 14 days	15
15 days to 1 month	8
>1 month to 2 months	4
>2 months	2

Tramadol was withdrawn in 89 cases. The patient recovered after drug withdrawal in 79 cases, but 39 of these were also treated by either fluid restriction, saline infusion or sodium orally, and in 11 cases there was at least one other drug withdrawn. In 34 cases positive dechallenge was reported for tramadol without mentioning any other corrections or dechallenge of other drugs.

There was one well-described case with a positive rechallenge (also a publication by Udy et al).

- A 79-year-old female was treated with tramadol for post-operative pain after knee replacement surgery on two occasions with a six months gap in between. Her regular medication included indapamide and valsartan, both known to cause HN. Fentanyl (another opiate) was administered pre-operative. Her pre-operative serum sodium was 131 mmol/L. The day after surgery her sodium levels dropped rapidly to 115 mmol/L. Tramadol was stopped and HN was corrected with fluid restriction. The same happened after the second operation. The major confounding drug, indapamide, was only taken at the time of the first operation and had been discontinued at the time of the second. Surgery itself is a confounder. The case was very complex and the cause of HN was probably multifactorial.

Another three cases also gave indications of positive rechallenge but the reports were not very informative. They described patients who had developed HN during tramadol treatment in the past, and that tramadol was the suspected cause.

- A 47-year-old female presented three times with SIADH and severe HN, and each time she was treated with tramadol. Her sodium level was normalised after tramadol was stopped.

Tramadol was the sole suspected drug in 63 of the selected cases and was the only reported drug in 26 of these. A majority of the 63 cases were sparsely documented or confounded by other conditions.

Fifty-five cases had co-suspected or concomitant drugs with HN and/or SIADH listed as ADRs in their UK SmPCs, see Table 2.

Table 2. Co-suspected or concomitant drugs with HN and/or SIADH listed as ADRs in UK SmPCs

Drug groups	No. cases
Thiazide and thiazide-like diuretics	19
Proton pump inhibitors	18
Angiotensin II antagonists	16
ACE-inhibitors	15
Antidepressants	10
Loop diuretics	7
Spironolactone	6
Antiepileptics	5
Antipsychotics	3
Benzodiazepines	3
Antiarrhythmics	2
Osmotically acting laxatives	2

In 19 of the 55 cases these were clear long-term drugs, and HN occurred only after tramadol initiation; In 10 there were full dates, showing that treatment with the HN risk drugs had been ongoing for a period of between 2.5 months and 19 years before tramadol was started. Six of these were among the key cases and are further described in Table 3. Two were sparsely documented and two were confounded. In nine cases there were no exact dates for the HN risk drugs, but they were described as long-term treatment. Four of these are listed in Table 4. In one case, all drugs except tramadol (including valpromide) had been taken for several years (case 8). In two cases, the patients were taking selective serotonin reuptake inhibitors (SSRIs) as long-term treatment when tramadol was started for back pain (cases 10, 12). In another example (case 11), the patient was taking a thiazide diuretic, an angiotensin II antagonist and a PPI long term when tramadol was initiated.

In five cases, tramadol was reported as suspected of having interacted with the co-medications. One example is described below:

- A 56-year-old female received tramadol drops for chronic back pain. The patient was also treated with venlafaxine, zolpidem, lorazepam and quetiapine, whose doses had not recently been modified. Tramadol abuse was suspected but the dose unknown. She was hospitalised the next day with acute HN, renal failure, rhabdomyolysis, inflammation and respiratory acidosis. The symptoms were suspected to be a result of serotonin syndrome or neuroleptic syndrome, from an interaction or an overdose. Tramadol and venlafaxine (an SSRI) were reported as interacting.

Literature and Labelling

Abadie et al published a review describing all serious adverse drug reactions (SADRs) with tramadol notified to the French pharmacovigilance centres and pharmaceutical companies between 2010 and 2011,[11] and a similar study described all reported SADRs in the French national pharmacovigilance database between 2011 and 2015.[12] In both analyses, HN was highlighted as an unexpected SADR but causality assessments were not done. Buon et al suggested that co-treatment with PPIs and tramadol potentiates the risk of HN.[13] In a population-based study it was suggested that the use of tramadol, compared to use of codeine, was associated with an increased risk of HN requiring hospitalization.[14] But according to Chevalier et al codeine is not an appropriate comparator to tramadol, because of their differing therapeutic traditions.[15]

Seven published case reports from between 2004 and 2018 were found in the literature[16-22], of which five were included in the dataset of 340 reports in VigiBase.[16-20] Two consisted of more than one case:[16,21] 1) In Hunter from 2004, a 76-year-old woman developed HN nine days after tramadol was added to regular treatment including perindopril, an ACE-inhibitor, and other concomitant drugs. HN did not resolve after fluid restriction but only after tramadol cessation.[16] The author also mentioned other elderly patients who had taken tramadol for pain control after fractures and developed HN, which was corrected on cessation of tramadol. One of these cases occurred when tramadol was given to a patient already on citalopram, an SSRI. He recommended that "*Sodium concentrations should be monitored when prescribing tramadol particularly in the elderly and those taking other medications, such as SSRIs and diuretics, which also predispose to HN.*" 2) In Yong and Khow from 2018, two similar cases are described, of women aged 70 and 86 who received tramadol for fracture pain. They both had perindopril, an ACE-inhibitor, in their regular medication, for which HN is a known ADR. The 86-year old was also taking omeprazole. Both had diabetes type 2. After one week and three days respectively, their sodium levels had dropped to 123 and 121 mmol/L. They were euvolaemic and SIADH was indicated. Tramadol was stopped and replaced with oxycodone, and they had fluid restriction. Both recovered within a few days after cessation of tramadol.[21] Three additional case reports published in conference abstracts were found during the assessment of the VigiBase reports.[23-25] Five of the above case reports were published after the PRAC's 2016 review.[21-24]

Neither HN nor SIADH are acknowledged ADRs for tramadol in the EU and US.[1,8,26] Only one of 16 Marketing Authorisation Holders with SmPCs for tramadol in the UK Electronic Medicines Compendium has listed HN as an ADR (and then only for the drops formulation, and not in their tablet SmPCs).[4] In Canada, HN is described in tramadol's product monographs.[27] In Australia and New Zealand, both HN and SIADH are included in the product information.[28,29]

CYP2D6 and CYP3A4 inhibitors (such as some SSRIs, SNRIs, quetiapine and haloperidol) and CYP3A4 inducers (such as carbamazepine) may alter the plasma concentration of tramadol and its metabolites. Antidepressants (such as SSRIs and mirtazapine) in combination with tramadol increase the risk of serotonin syndrome and convulsions.[1,26] In the EU, US, Australian and New Zealand sources there is no information stating that interactions could lead to an increased risk of HN. The monographs from Health Canada state that the use of tramadol with drugs that can decrease electrolyte levels (including loop- and thiazide diuretics, laxatives and enemas, high-dose corticosteroids and PPIs) should be avoided as far as possible.[27]

It has been hypothesized that tramadol-induced HN may involve both its serotonin and opioid pathways, leading to anti-diuresis.[20] Opioids are involved in very complex regulatory mechanisms, including vasopressin and the renin-angiotensin-aldosterone system, and they also have diuretic properties.[30,31] A third pathway that may be involved is tramadol's inhibition of noradrenaline reuptake; noradrenaline also regulates vasopressin and has been attributed to both anti-diuretic and diuretic effects.[32-34]

Discussion

Cases in VigiBase that support causality between tramadol and HN were identified. The key cases usually concerned elderly and predisposed patients. There were also suggestive cases in the younger age groups, even though they were few in comparison.

The evidence for causality included consistent temporal relationships between tramadol initiation and the onset of reaction; in more than half of the cases with onset dates reported, the time-to-onset ranged between 2 to 7 days. In a notable proportion of the cases, HN developed with a time-to-onset less than 2 days. This is unusual for drug-induced HN and suggests that additional or other causes were involved. Many patients were clearly in an at-risk group and they may already have been close to the border of low sodium levels when tramadol was started.

There were 79 cases with a reported positive dechallenge, and one well documented case of a positive rechallenge. In 34 of these cases there were no other corrective treatments of HN (e.g. fluid restriction or dechallenge of other drugs) reported.

There are several possible mechanisms of actions for tramadol-induced HN, involving the opioid, serotonin and noradrenaline pathways. But these neurotransmitters are all active in very complex regulatory mechanisms and their functions are sometimes contradictory; e.g. opioids and noradrenaline may have both diuretic and anti-

diuretic properties. Therefore the exact mechanisms for tramadol-induced HN may be difficult to fully understand, and tramadol's ability to cause HN may be very unpredictable.

In many of the key cases and the published literature cases, HN developed only after tramadol was added to regular treatment of drugs with the potential of causing HN or SIADH. The most frequent drug groups were: PPIs, SSRIs and other antidepressants, diuretics, angiotensin II antagonists and ACE-inhibitors. The temporal pattern in these cases indicates that these co-reported drugs are risk-factors for tramadol-induced HN.

For some of these risk-drug groups there are possible pharmacokinetic mechanisms for drug-drug interactions with tramadol. Inhibitors of CYP2D6 and CYP3A4, and inducers of CYP3A4, may influence the metabolism of tramadol.[1,26] In the case with the 56-year-old woman, a drug interaction was suspected between the SNRI venlafaxine, a CYP2D6 inhibitor, and tramadol. The same patient was also treated with quetiapine, another inhibitor of both CYP2D6 and CYP3A4, which could also have affected the plasma levels of tramadol and its metabolites. Diuretics, angiotensin II antagonists and ACE-inhibitors have the potential to cause renal insufficiency, and renal insufficiency may prolong the elimination half-life of tramadol. But such drug-drug interactions are not described in the UK SmPC or the US product label for tramadol.[1,26]

Patients and healthcare professionals should be aware of the risk of tramadol-induced HN, particularly in cases concerning elderly and predisposed patients, and when there is co-treatment with other drugs known to cause HN. The risk may be highly unpredictable due to tramadol's complex mechanisms of actions.

Conclusions

VigiBase cases and published case reports that support causality between tramadol and HN were found. The key cases usually concerned elderly and predisposed patients, but young individuals were also identified. Causality was supported by the time-to-onset pattern, cases with positive dechallenge and one positive rechallenge. Co-treatment with drugs with the potential to cause HN seem to be risk-factors of tramadol-induced HN, and in some cases pharmacokinetic drug-drug interactions may have occurred. These findings are supported by hypothesised mechanisms of actions.

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Table 3. Key cases with clear start dates for the hyponatraemia risk drugs

Case	Age/ Sex	Medical history	Suspected (S), interacting (I) or concomitant (C) drugs Underline = HN risk drugs	Time to onset	Actions taken/ Outcome	Case summary
1	88/F	-	Indapamide, tramadol (S) Clopidogrel, felodipine, paracetamol, risedronic acid, dorzolamide/timolol, latanoprost (C)	5 days	Drug withdrawn/ Reaction abated	An 88-year-old female with indapamide for 3 years started tramadol for sciatic (ichias) pain. After 5 days she was diagnosed with very low sodium levels (104 mmol/L) and hypokalaemia. Her sodium reference value was 135-145 mmol/L. Treatment of reaction was cessation of therapy.

Case	Age/ Sex	Medical history	Suspected (S), interacting (I) or concomitant (C) drugs Underline = HN risk drugs	Time to onset	Actions taken/ Outcome	Case summary
2	81/F	Breast cancer, COPD, hypertension	Hydrochlorothiazide/valsartan, tramadol (S) Budesonide/formoterol, ramipril, verapamil (C)	1 day	Drug withdrawn/ Unknown Oral potassium and sodium, and fluid replacement	An 81-year-old female was taking hydrochlorothiazide, valsartan and ramipril for 3 years. She took tramadol for pain after tooth extraction, after which she had repeated vomiting (4-5 times). The next day she was admitted to hospital for deterioration of general condition. HN and hypokalaemia were found and she was hospitalized for 3 days. Tramadol and hydrochlorothiazide were discontinued on the first day and vomiting stopped. Valsartan was continued.
3	73/F	Hypertension, back pain, thrombo-embolic accident	Calcitonin, tramadol, losartan, furosemide, paracetamol (S) Enoxaparin (C)	13 days	Drug withdrawn/ Reaction abated Sodium correction	A 73-year-old female had been taking furosemide and losartan for 3 years, paracetamol and enoxaparin for an unknown period, and calcitonin for a week when tramadol was introduced for back pain. After 13 days she had asthenia, nausea, vomiting, depressive state and increased back pain. Codeine, amitriptyline, tetrazepam and lactulose were added. Severe HN (114 mmol/L) and hypokalemia was found 2 days later, and she was very confused. At hospital all medications except enoxaparin were stopped, and sodium chloride was administered. A week later she was recovering and losartan reintroduced. *Note: Amitriptyline may cause HN but was started after the first symptoms.*
4	75/F	Hypertension, atrial fibrillation	Captopril/hydrochlorothiazide, tramadol (S) Paracetamol (C)	12 days	Drug withdrawn/ Reaction abated	A 75-year-old female patient, who had been taking captopril, hydrochlorothiazide and paracetamol since the year before (>7 months), started tramadol treatment for unspecified pain. After 12 days SIADH was reported. Eight days later all drugs except paracetamol were stopped. The patient recovered.
5	88/F	Trigeminal neuralgia	Atenolol, carbamazepine, losartan, tramadol (I) Alprazolam (C)	11 days	Drug withdrawn/ Reaction abated	An 88-year-old female had been treated with carbamazepine for trigeminal neuralgia for 1.5 years, atenolol 1.5 years, and losartan 1 year when she started tramadol treatment. After 11 days HN was diagnosed. An interaction was reported between tramadol, carbamazepine, atenolol and losartan. The first three were discontinued, and the losartan dose was increased.
6	96/F	Hypertension arterial, thyroid cancer, thrombosis venous deep, osteoporosis	Indapamide/perindopril, Tramadol (S) Levothyroxine, warfarin, calcium carbonate/ colecalciferol, risedronic acid, ginkgo biloba, zopiclone (C)	7 days	Drug withdrawn/ Reaction abated Fluid restriction	A 96-year-old female suffered from hip pain after a fall. She had been on indapamide and perindopril for 19 years and concomitant drugs for an unknown time. She was prescribed tramadol. A week later she was extremely tired and was vomiting. Her sodium level was 128 mmol/L and her TSH higher than normal (medicated for hypothyroidism since unknown). Two days later she was hospitalized, tramadol was stopped and fluid was restricted. The following week she recovered.

Table 4. A selection from the additional key cases

Case	Age/ Sex	Medical history	Suspected (S), interacting (I) or concomitant (C) drugs Underscore/ = HN risk drugs	Time to onset	Actions taken/ Outcome	Case summary
7	84/F	Alzheimer's disease, ulcer gastroduodenal	Tramadol (S) Calcium, cetornan, vitamine D3, metoclopramide (C)	3 days	Drug withdrawn/ Reaction abated Fluid restriction	An 84-year-old female was hospitalised for back pain from a spine fracture. At admission her sodium level was normal at 136 mmol/L. She received tramadol for the pain. Three days later, severe HN at 121 was found. She improved after stopping tramadol and fluid restriction.
8	45/ M	Diabetes type 2, psychosis	Fluphenazine, tramadol, valpromide (S) Acarbose, calcium carbonate, clonazepam, glucophage loxapine, trihexyphenidyl, pravastatin, risedronate (C)	4 days	Drug withdrawn/ Unknown	A 45-year-old male received tramadol for hip dislocation on two occasions. Four days after the first occasion, HN with a sodium level at 134 mmol/L (ref. 137 mmol/L) appeared, which further decreased to 130 over the next 6 days. Tramadol was stopped a week later, and her sodium level rose to 133. All drugs except tramadol had been taken for several years.
9	43/F	Psychosis manic-depressive, convulsions, chronic alcohol abuse	Escitalopram, haloperidol, olanzapine, tramadol (S) Nicotinamide, oxazepam, pyridoxine, thiamine, zopiclone (C)	2 days	Drug withdrawn/ Reaction abated Fluid restriction	A 43-year-old female was taking escitalopram for 2 months, olanzapine for more than a year, and haloperidol and oxazepam for an unknown period. She started tramadol for tooth pain. After 2 days she was hospitalised after a seizure with loss of consciousness and severe HN (120 mmol/L). HN was corrected with fluid restriction, tramadol and escitalopram were stopped and the patient recovered.
10	63/ M	Epilepsy, hypertension	Escitalopram, tramadol (S) Lamotrigine, manidipine (C)	A few days	Drug withdrawn/ Reaction abated	A 63-year-old male was taking escitalopram as a long-term treatment and tramadol for a few days for back pain. His medical history included epilepsy but the patient had been free from

Case	Age/ Sex	Medical history	Suspected (S), interacting (I) or concomitant (C) drugs Underscore/ = HN risk drugs	Time to onset	Actions taken/ Outcome	Case summary
		arterial, mental retardation				convulsion for a year. He was hospitalized for convulsions and severe HN (121 mmol/L), and lab values indicated SIADH. Escitalopram and tramadol were suspected drugs. The patient recovered after dechallenge of tramadol while escitalopram was switched to citalopram.
11	70/F	Cholecystectomy, hypertension arterial,	Hydrochlorothiazide/ olmesartan, Paracetamol/tramadol, Tramadol (S) Acetylsalicylic acid, manidipine, nadolol, pantoprazole, zolpidem (C)	7 days	Drug withdrawn/ Reaction abated	A 70-year-old female with hip pain was treated with paracetamol and tramadol. Seven days later she was hospitalised for decreased consciousness and convulsions. Severe HN at 118 mmol/L was found (normal levels two months earlier) with indication of SIADH. Hydrochlorothiazide, olmesartan and all concomitants were being taken long-term. Hydrochlorothiazide, olmesartan, paracetamol and tramadol were stopped and sodium normalised.
12	79/F	Depression, psychosis	Tramadol (S) Citalopram, olanzapine, valproic acid (C)	20 days	Drug withdrawn/ Reaction abated Fluid restriction	A 79-year-old female developed acute HN (121 mmol/L) after recent (20 days) tramadol treatment start. All other drugs were reported as "long-term". The indication for tramadol was back pain. The sodium level went back to normal after cessation of tramadol only and fluid restriction.
13	86/F	-	Tramadol (S) Alendronic acid, codeine, enalapril, mirtazapine, paracetamol (C)	2 days	Drug withdrawn/ Reaction abated	An 86-year-old female was hospitalised due to back pain. She had been taking ongoing medications since an unknown date. Her sodium was 137 mmol/L at admission. Tramadol was initiated. Two days later her sodium had fallen to 122 mmol/L, and again to 119 after another two days. Tramadol was suspected and treatment stopped on day 4. On day 5 the sodium increased again and was back to normal on day 7.
14	75/F	-	Candesartan/ hydrochlorothiazide, dextropropoxyphene/ paracetamol, tramadol (S) Celecoxib, esomeprazole, trihexyphenidyl (C)	8 days	Drug withdrawn/ Reaction abated Fluid restriction	A 75-year-old female took tramadol for back pain. After 8 days she had HN at 118 mmol/L (reference 140), which resulted in admission to hospital. SIADH was diagnosed. She had candesartan, hydrochlorothiazide taken "long-term" an esomeprazole since an unknown date. She recovered after fluid restriction and cessation of all three suspected drugs.
15	90/F	Hypothyroidism, cholecystitis, osteoporosis, fracture, recurring falls, dehydration, depression, cognitive problems, hypertension, acute pancreatitis	Mirtazapine, spironolactone, tramadol, tetrazepam (I) Alendronic acid, paracetamol, calcium, levothyroxine, pantoprazole (C)	3 days	Drug withdrawn/ Reaction abated	A 90-year-old female was being treated with mirtazapine and spironolactone since unknown. Her concomitants were long-term. She had a fall and contusion of chest wall with intense pain, and were treated with tramadol, paracetamol and tetrazepam. Three days later she was nauseous, confused and vomited. On the 4th day she was hospitalized and profound HN (112 mmol/L) was found. Her TSH levels were normal. No renal or hepatic insufficiency, ECG abnormalities or infections were found. Orthostatic hypotension investigation was negative. There was a positive dechallenge for tramadol, mirtazapine, spironolactone and tetrazepam. The sodium levels and confusion improved after 48 hours and she had recovered 10 days later (Na 137 mmol/L).

CAVEAT DOCUMENT

Statement of reservations, limitations and conditions relating to data released from VigiBase, the WHO global database of individual case safety reports (ICSRs).
Understanding and accepting the content of this document are formal conditions for the use of VigiBase data.

Uppsala Monitoring Centre (UMC) in its role as the World Health Organization (WHO) Collaborating Centre for International Drug Monitoring receives reports of suspected adverse reactions to medicinal products from National Centres in countries participating in the WHO Programme for International Drug Monitoring. The information is stored in VigiBase, the WHO global database of individual case safety reports (ICSRs). It is important to understand the limitations and qualifications that apply to this information and its use.

Tentative and variable nature of the data

Uncertainty: The reports submitted to UMC generally describe no more than suspicions which have arisen from observation of an unexpected or unwanted event. In most instances it cannot be proven that a specific medicinal product is the cause of an event, rather than, for example, underlying illness or other concomitant medication.

Variability of source: Reports submitted to national centres come from both regulated and voluntary sources. Practice varies: some national centres accept reports only from medical practitioners; others from a broader range of reporters, including patients, some include reports from pharmaceutical companies.

Contingent influences: The volume of reports for a particular medicinal product may be influenced by the extent of use of the product, publicity, the nature of the adverse effects and other factors.

No prevalence data: No information is provided on the number of patients exposed to the product, and only a small part of the reactions occurring are reported.

Time to VigiBase: Some national centres make an assessment of the likelihood that a medicinal product caused the suspected reaction, while others do not. Time from receipt of an ICSR by a national centre until submission to UMC varies from country to country. Information obtained from UMC may therefore differ from that obtained directly from national centres.

For these reasons, interpretations of adverse effect data, and particularly those based on comparisons between medicinal products, may be misleading. The data comes from a variety of sources and the likelihood of a causal relationship varies across reports. Any use of VigiBase data must take these significant variables into account.

Prohibited use of VigiBase Data includes, but is not limited to:

- patient identification or patient targeting
- identification, profiling or targeting of general practitioners or practice

Any publication, in whole or in part, of information obtained from VigiBase must include a statement:

(i) recording 'VigiBase, the WHO global database of individual case safety reports (ICSRs)' as the source of the information

(ii) explaining that the information comes from a variety of sources, and the probability that the suspected adverse effect is drug-related is not the same in all cases

(iii) affirming that the information does not represent the opinion of the UMC or the World Health Organization.

Omission of this statement may exclude the responsible person or organization from receiving further information from VigiBase.
UMC may, in its sole discretion, provide further instructions to the user, responsible person and/or organization in addition to those specified in this statement and the user, responsible person and/or organization undertakes to comply with all such instructions.

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Advisory Committee on Safety of Medicinal Products (ACSoMP) Seventeenth meeting

World Health Organization, Geneva (Virtual Meeting) 27 – 29 October 2020

The WHO Advisory Committee on Safety of Medicinal Products (ACSoMP) was established in 2003, to provide advice to WHO, including its Collaborating Centre for International Drug Monitoring (the UMC), and through it, to the Member States of WHO, on safety issues relating to medicinal products.

A summary of discussions and key recommendations from the 17th meeting of ACSoMP is provided below.

WHO 5-year Strategic Plan to improve Global Regulatory Systems (2019-2023)

The WHO Strategy provides the framework for all activities across the entire regulatory spectrum for medicines, vaccines, diagnostics, etc. Pharmacovigilance (PV) activities span across the four priorities of the strategy. The following activities are proposed for the biennium (2020-2021):

- **Strengthen Country and Regional Regulatory Systems**.
  The goals are to strengthen safety surveillance, to support and safeguard the uptake of newly manufactured products and to support regulatory convergence through the convening power of WHO.
- **Improve regulatory preparedness for public health emergencies (PHEs) and health product shortages**
  The goal is to increase the number of countries that have adapted their regulatory preparedness for PHEs.
- **Strengthen and expand WHO's prequalification (PQ) service**
  To expand the range of products eligible for PQ.
- **Increase the scope and impact of WHO's regulatory support activities**
  To enhance monitoring of WHO's impact on regulation and access to health products.

WHO Collaborating Centre for International Drug Monitoring (Uppsala Monitoring Centre, UMC)

Much of UMC's efforts in 2020 were devoted to Covid-19 work, and a task force was established to undertake these new activities. The top priority is signal detection and analysis related to Covid-19 treatments and vaccines as they become available. This involves providing summary reports of VigiBase data and developing syndromic detection methods to identify any emerging harm to patients. It is important to ensure that the data reaching VigiBase is timely and relevant, which means adapting the tools to accommodate the data and working with WHO to establish a flow of data from public health programmes. VigiFlow developments intend to improve support for vaccines in PV data entry and for immunization programme reporting and feedback, in order to facilitate geographical analysis and efficient global sharing of data.

The core of UMC is signal detection and capacity building. Since individual case safety reports are the absolute core, it is critically important that UMC receives the data that it needs. Structured data facilitate signal detection.

Access to Covid-19 Tools Accelerator (ACT A)

The aim of the ACT A strategy is to accelerate global access to tools that reduce the risk of severe disease, thereby ending the acute phase of the Covid-19 pandemic and restoring societal and economic health. Access to these tools, as well as their allocation, needs to be equitable otherwise they will just be used in high-income countries.

The vaccines component or pillar is led by CEPI (Coalition for Epidemic Preparedness Innovations) and GAVI (The Vaccine Alliance), whereas the therapeutic pillar is led by the Wellcome Trust and UNITAID. ACT A was launched in late April by WHO, the European Commission and France. WHO is responsible for overall

coordination and ensuring that norms and standards relating to PQ policy and technical guidance remain in place.

GAVI is hosting the "Risk Pooling" mechanism in collaboration with WHO and CEPI, which should ensure that once a vaccine proves to be safe and effective there is a good chance that countries worldwide will be able to access it. Some countries will be self-financing but others will receive vaccines via the GAVI mechanism.

At the moment, there are still no strong therapeutic candidates for dealing with severe cases. There are currently 1700 ongoing therapeutic trials, which can be grouped into five categories according to treatment use: pre-exposure prophylaxis, post-exposure prophylaxis, mild cases, moderate cases and severe/critical cases. Studies with monoclonal antibodies are showing very promising results, but the ability to deliver at scale is very small.

WHO COVAX Regulatory Update on Covid-19

As part of the support to COVAX activities, WHO has been looking to see how regulatory preparedness can be improved across the product streams on all the Access to Covid-19 Tools (ACT) pillars, for instance, by ensuring that regulators are informed and involved, initially in the research and development activities, but now more importantly in preparedness activities. Mechanisms have been set up to collaborate with regulators across the world to allow the rapid exchange of information on Covid-19 developments. The overall aim is to promote regulatory alignment in order to facilitate rapid access to quality, safe and effective products.

WHO is working closely with the International Coalition of Medicines Regulatory Authorities (ICMRA) in order to avoid duplication and to leverage developments within the ICMRA countries. It is also working with the regional regulatory groups to ensure that they are aligned on the specific PV preparedness regarding the expected adverse events following immunization. A roadmap has been produced to help align the assessment process and facilitate in-country approval. This applies to all Covid-19 vaccines, not merely those that come within the scope of the COVAX facility, but focusing on those at the most advanced stage.

One of the greatest challenges identified in the roll-out of vaccines is, given the speed of developments, making sure that there are appropriate feedback mechanisms in order to be able to monitor and identify any risks and update as necessary. By aiming to have the best possible Global Monitoring System, the challenge of how different processes are aligned can be addressed (e.g. information coming through both public health systems and regulatory authorities).

One big concern is the communication of risks to the general population and the media. The best way to counter misinformation is to direct countries to websites with correct information. There is a need for a Vaccine Adverse Event response plan functioning at three levels: on the ground, between countries and at the global level.

There is a real need for pro-active communication in the context of the roll out of vaccines. WHO has communication experts who are examining this from a pro-active perspective, taking into account the different national situations.

There is a need for a coordinated approach to making the data accessible from different data sources, e.g. aggregate AEFI data that arrive through the WHO/UNICEF joint reporting form. The WHO standard reporting form used for collecting case-based AEFI data is being incorporated into VigiFlow (a national PV data management system developed and offered to countries by WHO/UMC), which will help immunization programmes to collect data from the district level up to the national level, where data will be shared between the regulators and the EPI programme.

Review and analysis of safety data for new TB medicines and regimens

Safety data in the active TB Drug Safety Monitoring (aDSM) database was evaluated by WHO in order to better understand the benefit and risk profiles of bedaquiline, delaminid, clofazimine and linezolid in the treatment of multidrug-resistant tuberculosis (MDR-TB). The aim was to identify for these four TB drugs any new potential "signal" and to review any new emerging characteristics with known safety concerns. A review was also made of the data quality and minimum data fields that support meaningful data analysis and causality assessments.

Signal detection exercise carried out on aDSM data reconfirmed the listed safety adverse event profiles for these four TB drugs, and provided a level of reassurance that known events were being reported to the aDSM database. The committee recommended that systematic reviews such as this one should be performed on the safety of all new WHO-recommended products in public health programmes. Systems such as aDSM can be used to identify potential signals for further in-depth review and analysis. In addition, as not all adverse events are reported to traditional databases, such as VigiBase, the time needed to identify potential signals of rare adverse events could potentially be decreased by using aDSM data.

Sodium valproate

Valproate has been on the WHO Essential Medicines List for 40 years, having first been listed as an anti-epileptic in 1979. It is also on the list for bipolar disorder but only for the treatment of adults. Thus, the listing of valproate on the model Essential Medicines List (EML) is in full alignment with the current recommendations in the WHO guidelines for use in epilepsy and bipolar disorder. The first WHO guidelines for epilepsy were issued in 2009/10 as part of WHO's mental health Gap Action Programme (mhGAP) guidelines. They were updated in 2015/16, and work on a further update started in 2020.

The risk of anti-epileptic medications to women of childbearing age applies during the preconception phase, pregnancy and breastfeeding. WHO's position on the use of valproate has been clearly stated in the WHO Pharmaceuticals Newsletter (2020) that:

- medicines containing valproate (e.g. sodium valproate, valproic acid, divalproex) should be avoided in pregnant women or in females of child-bearing potential, unless alternative treatments are ineffective or not tolerated, because of the high risk of birth defects (such as spina bifida, facial, skull, limb and heart malformations) and developmental disorders in infants who are exposed to valproate in the womb.
- When alternative treatments are not available or appropriate, female patients prescribed valproate medicines should be made aware of the risk and use effective contraception methods.

WHO guidelines have made a strong recommendation, since 2009, that valproate should be avoided for women of childbearing age, both for epilepsy and bipolar disorder, the challenge is to ensure better implementation. Therefore, in addition to updating the guidelines, resource materials and tools are now available for implementing the recommendations at country level. These include mhGAP intervention guide, training manuals for trainers, as well as for health-care providers, and care has been taken to make this information accessible to both specialists and non-specialists.

Investigational drugs used for treatment of Covid-19: remdesivir (Veklury)

Marketing authorization in the European Union for remdesivir was granted in July 2020. This was a conditional approval, the indication being the treatment of adults and adolescents (aged 12 years and older and with body weight at least 40 kg) with pneumonia requiring supplemental oxygen. There is a risk management plan (RMP) and, an expedited summary safety review. This medicine is subject to additional monitoring. The full report for remdesivir is available on the European Medicines Agency (EMA) website.

A new signal of acute renal injury was detected and validated by EMA and confirmed by its Pharmacovigilance and Risk Assessment Committee (PRAC) in September 2020. The causal relationship is yet to be determined and warrants further investigation. Although the known safety profile of remdesivir is currently limited, more than half of reported adverse events (from the compassionate use programme, the expanded access programme and spontaneous cases) belong to the unexpected adverse reactions.

Interim results from the WHO Solidarity trial published in October 2020 indicate that remdesivir, along with some other Covid-19 drugs, seems to have little or no effect on 28-day mortality or the in-hospital course of Covid-19 among hospitalized patients. The WHO prequalification listing of the drug will be reviewed following the recommendation from the WHO Guidelines Review Panel or following a review of the conditional approval by EMA.

Dolutegravir

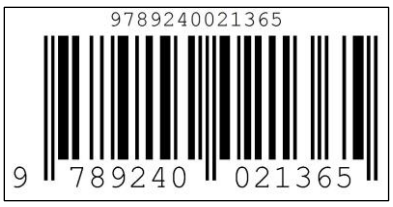
Dolutegravir (DTG) is an antiviral medication used, together with other medications, to treat HIV/AIDS. In May 2018 a potential association between DTG use and an increased risk of neural tube defect (NTD) in infants born to women who were taking DTG at the time of conception was reported in a large observational study of birth outcomes that started in 2014 in Botswana. In August 2018, ACSoMP set up a subcommittee on DTG to review all available evidence, to confirm or refute this signal of NTD.

DTG is one of the first cases where ACSoMP has undertaken a very careful and detailed analysis of accumulating evidence. After a period of decline since the original safety signal, the prevalence of NTDs among infants born to women on DTG at preconception appears to be stabilizing at a low prevalence level of 0.19%. This is no longer significantly higher than for preconception non-DTG ART, although it remains statistically significantly higher than preconception EFV and in HIV-uninfected women.

The Meeting of Global Advisory Committee on Vaccine Safety (GACVS) 1 – 3 December 2020

The meeting of Global Advisory Committee on Vaccine Safety (GACVS) was held on 1 to 3 December 2020. The report of the meeting is published in the weekly epidemiological record (WER) available online at:

https://apps.who.int/iris/bitstream/handle/10665/338770/WER9603-eng-fre.pdf.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