World Health Organization

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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,

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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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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

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

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

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