World Health Organization

WHO Pharmaceuticals NEWSLETTER

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

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

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

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This Newsletter is also available at:
https://www.who.int/teams/regulation-prequalification

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

In addition, this edition includes summaries of discussions and key recommendations of Advisory Committee on Safety of Medicinal Products (ACSoMP) Eighteenth meeting and Global Advisory Committee on Vaccine Safety (GACVS) meetings held in 2021.

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Features

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

Amoxicillin

Potential risk of aseptic meningitis

Canada. Health Canada has announced that the product safety information for amoxicillin-containing products will be updated to include the potential risk of aseptic meningitis.

Amoxicillin is an antibiotic indicated for the treatment or prevention of certain bacterial infections. Products may contain amoxicillin alone or in combination with other antibiotics.

Health Canada reviewed the available information by searching national and international databases, and the published literature. Twenty-one case reports of aseptic meningitis in adult patients receiving amoxicillin-containing products were obtained and all of them were found to be possibly or probably linked with the use of the amoxicillin-containing products. The review concluded that there may be a link between amoxicillin-containing products and the risk of aseptic meningitis.

Reference:
Summary Safety Review, Health Canada, 10 December 2021 *(link to the source within www.hc-sc.gc.ca)*

Antiepileptic drugs

Risk of major congenital malformations and neurodevelopmental disorders in children exposed in-utero

Ireland. The Health Products Regulatory Authority (HPRA) has announced that the product information for antiepileptic drugs (AEDs) (including phenytoin, phenobarbital, carbamazepine, pregabalin and valproate) are to be updated based on the latest evidence of risks associated with in-utero exposure to AEDs. For some medicines in this class, use during pregnancy has been associated with major congenital malformations (MCMs) and neurodevelopmental disorders in children exposed in-utero.

AEDs are indicated for the treatment of various forms of epilepsy with some having additional indications in other therapeutic areas such as psychiatry.

A summary of the recent review includes:

- Phenytoin, phenobarbital and carbamazepine have an approximate 2-3 fold risk of MCMs compared to the general population. Study findings on the risk of neurodevelopmental disorders are contradictory and a risk cannot be excluded based on available evidence at this time.
- Pregabalin monotherapy: available data show that if used in the first trimester, it is associated with a slightly higher risk of MCMs compared to women not using pregabalin, or those using lamotrigine or duloxetine.
- Valproate: epidemiological data have demonstrated that use of valproate monotherapy during pregnancy is associated with an approximate 11% (4-5 fold) risk of MCMs and up to 30-40% for risk of neurodevelopmental disorders in children exposed in-utero.

When prescribing AEDs for a woman of childbearing potential for any indication, health-care professionals should fully consider and discuss what is known about the potential risks associated with in-utero exposure, as well as any recommendations concerning contraception and pregnancy planning, including actions to take in the event of a suspected or confirmed pregnancy.

Reference:
Newsletters and Reports, HPRA, 11 February 2022 *(link to the source within www.hpra.ie)*

(See also WHO Pharmaceuticals Newsletter No.1, 2021: Updated advice for the risk of congenital malformations and neurodevelopmental disorders and delay in UK)

Blonanserin or suvorexant, and posaconazole

Contraindication for co-administration

Japan. The Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA) have announced that the product information for blonanserin (Lonasen®), suvorexant (Belsomra®), and posaconazole (Noxafil®) should be revised to include the contraindication for concomitant use of blonanserin or suvorexant with posaconazole.

Blonanserin (available as an oral dosage form and as a patch) is used to treat schizophrenia; suvorexant is used for insomnia; and posaconazole (oral dosage form and intravenous injection) is indicated for fungal infections.

Posaconazole is an azole and strongly inhibits CYP3A4. Based on the prediction using a model with parameters obtained from in vivo data, it was estimated that the plasma exposure of blonanserin or suvorexant would increase to a level that causes safety concerns when either of them are co-administered with posaconazole. The risks are considered to outweigh the benefits with the increased plasma levels.

Reference:
Revision of Precautions, MHLW/PMDA, 17 December 2021 *(link 1 and link 2 to the source within www.pmda.go.jp/english/)*

Brolucizumab

Risk of intraocular inflammation and retinal vascular occlusion

United Kingdom. The Medicines and Healthcare Products Regulatory Agency (MHRA) has announced that the product information for brolucizumab (Beovu®) will be updated to include advice on dosage intervals to reduce the risk of intraocular inflammation and retinal vascular occlusion. The maintenance dose of brolucizumab (after the first three doses) should not be given at intervals of less than eight weeks apart.

Brolucizumab is monoclonal antibody indicated for the treatment of neovascular (wet) age-related macular degeneration (AMD) by intravitreal injection. Intraocular inflammation, including retinal vasculitis, and retinal vascular occlusion are adverse drug reactions known to be associated with brolucizumab.

A review was conducted on new data from a randomised study, where brolucizumab administered every four weeks was compared with aflibercept administered with the same time interval between doses. More frequent reports of intraocular inflammation, including retinal vasculitis, occurred in the brolucizumab group compared to the aflibercept group (9.3% versus 4.5%, respectively). Also in another study, the frequency of reports in the brolucizumab group with a four week dosage interval was higher than brolucizumab dosage intervals of 8 and 12 weeks.

Based on observational studies, retinal vasculitis and retinal vascular occlusion after brolucizumab treatment appear to be more frequent in female patients and in patients of Japanese ancestry.

Health-care professionals are advised to closely monitor patients treated with brolucizumab and who have a medical history of intraocular inflammation or retinal vascular occlusion.

Reference:
Drug Safety Update, MHRA, 18 January 2022 *(link to the source within www.gov.uk/mhra)*

Ceftriaxone

Potential risk of hepatitis and encephalopathy

Australia. The Therapeutic Goods Administration (TGA) has announced that the product information for ceftriaxone has been updated to include a warning about hepatitis and encephalopathy as potential adverse events.

Ceftriaxone is a broad-spectrum cephalosporin antibiotic indicated for the treatment of pneumonia, skin, urinary tract, and other infections.

The TGA reviewed evidence published in the literature and international and national post-market adverse event data. There were 52 reports of hepatitis and related symptoms and three reports of encephalopathy for patients treated with ceftriaxone. Health-care professionals should be aware of reports of encephalopathy particularly in the elderly with severe renal impairment or central nervous system disorders. Suspension of treatment with ceftriaxone should be considered if encephalopathy is suspected.

Reference:
Medicines Safety Update, TGA, 15 December 2021 *(link to the source within www.tga.gov.au)*

Chloramphenicol

Recommended dose considering risk of reproductive toxicity

New Zealand. The Medsafe has announced that the

product information for chloramphenicol eye drops will be updated to include dosing recommendations for children aged under two years. The recommended dose is one drop in the affected eye(s) four times daily for five days.

Chloramphenicol eye drops are indicated for the treatment of infections of the eye. Some products contain boron in the excipients (boric acid and borates), which could be associated with reproductive toxicity (based on animal studies).

The Medicines Adverse Reactions Committee considered that the relevance of the animal data to humans is uncertain. Although human studies have not shown reproductive toxicity, they were not sufficiently robust to rule out this risk. The paediatric dose, reflecting the conventional dosing regimen for children, is associated with a boron exposure below the threshold of concern for reproductive toxicity.

Reference:
Prescriber Update, Medsafe, December 2021 *(link to the source within www.medsafe.govt.nz/)*

Cladribine

Risk of serious liver injury

Europe. The European Medicines Agency (EMA) announced that the product information for cladribine (Mavenclad®) will be updated to include liver injury as an adverse drug reaction. A direct health-care professional communication (DHPC) will be issued on new recommendations for monitoring liver function.

Cladribine is indicated for the treatment of relapsing forms (repeated flare-ups of the symptoms) of multiple sclerosis in adults.

Liver injury, including serious cases and cases leading to discontinuation of treatment, has been reported in patients treated with cladribine. A recent review of available safety data has concluded that there is an increased risk of liver injury following treatment with cladribine.

Health-care professionals are advised to perform a detailed review of history of underlying liver disorders or episodes of liver injury with other medicines before initiating treatment in patients. During treatment, liver function tests should be conducted, and repeated as necessary. In case a patient develops liver injury, treatment with cladribine should be interrupted or discontinued, as appropriate.

Reference:
Patients and carers, EMA, 14 January 2022 *(link to the source within www.ema.europa.eu)*

Clindamycin

Potential risk of acute kidney injury

Australia. The TGA has announced that the product information for clindamycin capsules and injections have been updated to include a warning about the potential risk of acute kidney injury.

Clindamycin products are indicated for the treatment of serious infections caused by susceptible strains of streptococci, pneumococci, staphylococci and anaerobic bacteria. Product information for topical clindamycin products will not be updated.

The TGA reviewed five reports of renal impairment and five cases of acute kidney injury associated with systemic clindamycin.

Health-care professionals are advised to monitor the renal function during clindamycin therapy in patients with pre-existing renal dysfunction or patients taking concomitant nephrotoxic drugs. Renal function should be monitored if therapy with clindamycin is prolonged.

Reference:
Medicines Safety Update, TGA, 3 February 2022 *(link to the source within www.tga.gov.au)*

COVID-19 vaccine Astrazeneca (ChAdOx1-S) and COVID-19 vaccine Janssen (Ad26.COV2-S)

Potential risk of transverse myelitis (TM)

Europe. The Pharmacovigilance Risk Assessment Committee (PRAC) has recommended that the product information for COVID-19 vaccine Astrazeneca (ChAdOx1-S, Vaxzevria®) and COVID-19 vaccine Janssen (Ad26.COV2-S, COVID-19 vaccine Janssen®) should be updated to include a warning of the potential risk of very rare

cases of transverse myelitis (TM) reported following vaccination.

TM is a rare neurological condition characterised by an inflammation of one or both sides of the spinal cord.

The PRAC has reviewed available information on cases reported globally which include cases in the European database for suspected adverse events and data from the scientific literature. The PRAC has concluded that there is a reasonable possibility of a causal relationship between the vaccines and transverse myelitis. The benefit-risk profile of the vaccines remains unchanged.
Health-care professionals should be alert to signs and symptoms of TM, allowing early diagnosis, supportive care and treatment. People receiving either of these vaccines are advised to seek immediate medical attention if they develop symptoms of the condition.

Reference:
Patients and carers, EMA, 14 January 2022 *(link to the source within www.ema.europa.eu)*

COVID-19 vaccine Janssen (Ad26.COV2-S)

Risk of small vessel vasculitis

Europe. The PRAC has recommended that product information for COVID-19 vaccine Janssen (Ad26.COV2-S) should be updated to include small vessel vasculitis with cutaneous manifestations as a possible adverse event of unknown frequency.

The PRAC has reviewed a total of 21 international cases provided by the latest summary safety report. Ten cases reported single organ cutaneous vasculitis (vasculitis affecting a single organ). For most of these 10 cases, other causal explanations could not be identified and in eight of the cases, the reaction occurred soon after the administration of the vaccine.

Reference:
Patients and carers, EMA, 11 March 2022 *(link to the source within www.ema.europa.eu)*

COVID-19 vaccine Moderna (Elasomeran)

1. Potential risk of flare-ups of capillary leak syndrome (CLS)

Europe. The PRAC has recommended that the product information for COVID-19 vaccine Moderna (elasomeran, Spikevax®) should be revised to include a warning about flare-ups of capillary leak syndrome (CLS).

CLS is an extremely rare, serious condition that causes fluid leakage from small blood vessels (capillaries), resulting in rapid swelling of the arms and legs, sudden weight gain, feeling faint, thickening of the blood, low blood levels of albumin, and low blood pressure.

The PRAC assessed all the available data as well as all the cases of CLS reported in the Eudravigilance database after the administration of Moderna and Pfizer COVID-19 vaccines (tozinameran, Comirnaty®).

The PRAC concluded that there was insufficient evidence to establish a causal association between the two vaccines and the onset of new cases of CLS.

However, the PRAC recommended that a warning in the product information for COVID-19 vaccine Moderna should be included as some of the flare-up cases pointed towards an association with COVID-19 vaccine Moderna. Such an association was not supported in cases reported after vaccination with Pfizer COVID-19 vaccines.

Health-care professionals should be aware of the signs and symptoms of CLS and of a possible risk of a flare-up in people with a history of CLS. Vaccinated individuals with a history of CLS should consult their treating physician when planning their vaccination.

Reference:
Patients and carers, EMA, 11 March 2022 *(link to the source within www.ema.europa.eu)*

2. Risk of paraesthesia

Europe. The PRAC has recommended that the product information for COVID-19 vaccine Moderna should be updated to include paraesthesia as an adverse event. The frequency of this paraesthesia was estimated to be rare (i.e. occurring in less than 1 in 1,000 vaccinated persons). Hypoesthesia is already included as an adverse event in the current product information.

The PRAC assessed 1,425 international reports of

paraesthesia which were considered to be unrelated to anxiety, and possibly caused by vaccination. Additionally, results of clinical trials were reviewed, and a higher number of paraesthesia cases were reported in people who received the vaccine (2 cases) compared to those who received placebo (0 cases).

Reference:
COVID-19 vaccines safety update, EMA, 20 January 2022 *(link to the source within www.ema.europa.eu)*

Dexmedetomidine

Risk of mortality in patients aged 65 years and less

Europe. The EMA has requested that the product information for dexmedetomidine is updated to include a warning of increased risk of mortality when used in patients that are in intensive care unit (ICU).

Dexmedetomidine is indicated for light sedation (a state of calm or feeling sleepy) of adult patients in ICU, to allow the patient to stay awake and respond to verbal stimulation during diagnostic or surgical procedures.

The PRAC reviewed the result alternative sedatives.

Reference:
Patients and carers, EMA, 11 March 2022 *(link to the source within www.ema.europa.eu)*

Donepezil

Risk of cardiac conduction disorders

Australia. The TGA has announced that the product information for donepezil has been updated to include a caution for use in patients with known QTc prolongation or a family history of this condition.

Additionally, caution is advised in patients receiving other medicines that affect the QTc interval, or who have certain types of cardiac disease or electrolyte disturbances.

Donepezil is a cholinesterase inhibitor and indicated for the treatment of mild, moderate and severe Alzheimer's disease.

The TGA reviewed evidence published in the literature and from international and national post-market adverse event data. There were 18 cases of atrioventricular block (complete, second degree) bundle branch block, bifascicular block or Torsades monitored for cardiac function.

Reference:
Medicines Safety Update, TGA, 28 February 2022 *(link to the source within www.tga.gov.au)*

(See also WHO Pharmaceuticals Newsletter No.3, 2021 Potential risk of QT prolongation in Saudi Arabia)

Dupilumab

Potential risk of psoriasis

Saudi Arabia. The Saudi Food & Drug Authority (SFDA) has announced that the product information for dupilumab (Dupixent®) will be updated to include the potential risk of psoriasis.

Psoriasis is an immune-mediated disease that causes inflammation on the skin and is associated with visible signs of the inflammation such as raised plaques and scales on the skin.

Dupilumab is a monoclonal antibody for interleukin 4 and interleukin 13 and is indicated for the treatment of moderate-to-severe atopic dermatitis, severe asthma and chronic rhinosinusitis.

The SFDA reviewed the literature and post-marketing databases. A review of identified cases suggested a