World Health Organization

WHO Pharmaceuticals NEWSLETTER

2022 No. 1

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 of the Newsletter includes a short article on the recent Advisory Committee on Safety of Medicinal Products (ACSoMP) meeting.

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Safety of medicines

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

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Bisphosphonates, denosumab and romosozumab

Risk of atypical fracture in non-femur sites

Japan. The Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA) have announced that the product information for bisphosphonates, denosumab (Ranmark®) and romosozumab (Evenity®) should be revised to include the risk of atypical fracture in non-femur sites.

Bisphosphonates (including alendronate, ibandronate, etidronate, zoledronic, pamidronate, minodronic acid and risedronate), denosumab and romosozumab are indicated for the treatment of osteoporosis.

The MHLW and the PMDA reviewed reports of atypical fracture in non-femur sites (such as ulna or tibia) following administration of those products.

Reference:
Revision of Precautions, MHLW/PMDA, 20 June 2021 *(link to the source within www.pmda.go.jp/english/)*

(See WHO Pharmaceuticals Newsletter No.3, 2019: Risk of hypercalcaemia and multiple vertebral fractures for denosumab in UK)

Cefoperazone and sulbactam

Risk of acute coronary syndrome accompanying allergic reaction

Japan. The MHLW and the PMDA have announced that the product information for the products containing both cefoperazone and sulbactam (Sulperazon®) should be revised to include the risk of acute coronary syndrome accompanying allergic reaction.

Cefoperazone and sulbactam are indicated for the treatment of infectious diseases which are strains of genus susceptible to the substances.

The MHLW and the PMDA reviewed two cases of acute coronary syndrome accompanying allergic reaction in patients treated with the products reported in Japan.

Reference:
Revision of Precautions, MHLW/PMDA, 12 October 2021 *(link to the source within www.pmda.go.jp/english/)*

Chloral hydrate, cloral betaine

Restriction of paediatric indication

United Kingdom. The Medicines and Healthcare Products Regulatory Agency (MHRA) has announced that the paediatric indication for chloral hydrate (for children aged two years and older) and cloral betaine (children aged 12 years and older) has been restricted to short-term treatment (maximum two weeks) of severe insomnia only when the child or adolescent has a suspected or definite neurodevelopmental disorder and when the insomnia is interfering with normal daily life after treatment failure with other therapies (behavioural and pharmacological). The product information is being amended to clarify the restricted use.

Chloral hydrate (Welldorm Elixir®) and cloral betaine (Welldorm®) are indicated for severe insomnia that is interfering with normal daily life and where other therapies have failed, as an adjunct to non-pharmacological therapies. Chloral hydrate is licensed for use in adults and in children aged two years and older. Cloral betaine tablets are licensed for use in adults and adolescents aged 12 years and older.

The MHRA conducted a review of safety and efficacy data and sought independent expert advice including for paediatric sleep disorders. No new safety concerns were identified; however, in view of the carcinogenicity data in animals and the lack of long-term studies, a risk in humans for long-term use was not excluded. As such, the above restriction was recommended where the benefits of short-term use outweigh any potential risk, reflecting current clinical practice.

In addition, the maximum treatment period for these medicines in all patients has now been defined as two weeks in the product information because their prolonged use is associated with tolerance and the risks of dependence and abuse. Repeated courses are not recommended and can only be administered following medical specialist re-assessment. Following prolonged treatment, the dose should be slowly tapered before discontinuation

to avoid delirium.

Reference:
Drug Safety Update, MHRA, 6 October 2021 *(link to the source within www.gov.uk/mhra)*

COVID-19 vaccine NRVV Ad (ChAdOx1 nCoV-19)

Risk of immune thrombocytopenia (ITP)

Europe. The Pharmacovigilance Risk Assessment Committee (PRAC) has recommended a change to the product information for COVID-19 vaccine NRVV Ad (ChAdOx1 nCoV-19) (Vaxzevria®) to include a warning on immune thrombocytopenia (ITP) as an adverse reaction with an unknown frequency. ITP is a condition in which the immune system mistakenly targets platelets in blood.

COVID-19 vaccine NRVV Ad (ChAdOx1 nCoV-19) is a vaccine for preventing COVID-19.

The PRAC assessed cases of ITP reported following vaccination and evidence from the scientific literature.

Healthcare professionals should consider the risk of developing low platelet levels prior to administering the vaccine if an individual has a history of ITP and are recommended to monitor platelet levels following vaccination in individuals with a history of ITP.

Reference:
Patients and carers, EMA, 1 October 2021 *(link to the source within www.ema.europa.eu)*

COVID-19 vaccine NRVV Ad26 (JNJ 78436735)

1. Risk of venous thromboembolism (VTE)

Europe. The PRAC has recommended that thromboembolism (VTE) should be listed as a rare side effect in the product information for COVID-19 vaccine NRVV Ad26 (JNJ 78436735) (COVID-19 vaccine Janssen®). VTE is a condition in which a blood clot forms in a deep vein, usually in a leg, arm or groin, and may travel to the lungs causing a blockage of the blood supply, with possible life-threatening consequences.

COVID-19 vaccine NRVV Ad26 (JNJ 78436735) is indicated for preventing COVID-19.

The PRAC reviewed data form two large clinical studies and post marketing surveillance and concluded that there is a possible link to rare cases of VTE with COVID-19 vaccine NRVV Ad26 (JNJ 78436735).

The PRAC has also recommended to provide a warning to raise awareness among healthcare professionals and people taking the vaccine, especially those who may have an increased risk of VTE, and to assess a potential diagnosis of thrombosis with thrombocytopenia syndrome (TTS) when signs are present within three weeks after vaccination.

Reference:
Patients and carers, EMA, 1 October 2021 *(link to the source within www.ema.europa.eu)*

2. Risk of immune thrombocytopenia (ITP)

Europe. The PRAC has recommended a change to the product information for COVID-19 vaccine NRVV Ad26 (JNJ 78436735) (COVID-19 vaccine Janssen®) to include a warning on immune thrombocytopenia (ITP) as an adverse reaction with an unknown frequency. ITP is a condition in which the immune system mistakenly targets platelets in blood.

The PRAC assessed cases of ITP reported following vaccination and evidence from the scientific literature.

Healthcare professionals should consider the risk of developing low platelet levels prior to administering the vaccine if an individual has a history of ITP. They are recommended to monitor platelet levels following vaccination in individuals with a history of ITP.

Reference:
Patients and carers, EMA, 1 October 2021 *(link to the source within www.ema.europa.eu)*

3. Risk of dizziness and tinnitus

Europe. The PRAC has recommended that dizziness and tinnitus should be listed as adverse reactions in the product information of COVID-19 vaccine NRVV Ad26 (JNJ 78436735) (COVID-19 vaccine Janssen®). Tinnitus is ringing or other noises in one or both ears.

The PRAC assessed the available evidence including

cases of dizziness identified in spontaneous reports and cases of tinnitus identified in clinical trials and spontaneous reports and concluded that cases of dizziness and tinnitus are linked to the administration of COVID-19 vaccine NRVV Ad26 (JNJ 78436735).

Reference:
Patients and carers, EMA, 6 August 2021 *(link to the source within www.ema.europa.eu)*

Eperisone

Risk of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)

Republic of Korea. The Ministry of Food and Drug Safety (MFDS) has updated the product information for eperisone products (oral) to include the risk of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).

Eperisone is a centrally-acting muscle relaxant used for relieving painful muscle spasms or rigidity in musculoskeletal and neuromuscular disorders.

The Korea institute of Drug safety and Risk Management (KIDS) reviewed one report, which suggested a causal link between oral eperisone and SJS/TEN, and information from a foreign regulatory authority and a medical database.

Healthcare professionals should be aware of the signs and symptoms of SJS and TEN to allow early diagnosis and prompt treatment. Patients are advised to seek immediate medical attention if they experience these severe cutaneous symptoms.

Reference:
Based on the communication from MFDS and KIDS, November 2021

Erenumab

Risk of hypertension

Australia. The Therapeutic Goods Administration (TGA) has announced that the product information for erenumab (Aimovig®) has been updated with a warning statement about a potential causal relationship between the drug and hypertension.

Erenumab is indicated for prophylaxis of migraine in adults.

The TGA reviewed cases of the development of hypertension and worsening of pre-existing hypertension reported following use of the drug in the postmarketing setting internationally. Hypertension can occur at any time during treatment, but it was most frequently reported within seven days of dose administration. In the majority of cases, the onset or worsening of hypertension was reported after the first dose of erenumab.
Healthcare professionals should monitor patients treated with erenumab for new-onset hypertension or worsening of pre-existing hypertension. If hypertension is observed and evaluation fails to establish an alternative etiology, they should consider whether discontinuation of erenumab is warranted.

Reference:
Medicines Safety Update, TGA, 9 September 2021 *(link to the source within www.tga.gov.au)*

Fingolimod

Risk of liver injury

New Zealand. The Medsafe has announced that the product information for fingolimod (Gilenya®) has been updated to include the risk of liver injury, to require liver function monitoring during and after treatment, and to include criteria for stopping treatment to prevent serious drug-induced liver injury.

Fingolimod is an immunomodulating drug indicated for the treatment of relapsing multiple sclerosis.

Clinically significant liver injury and cases of acute liver failure requiring liver transplant have been reported in patients treated with fingolimod and the Centre for Adverse Reactions Monitoring (CARM) received four adverse reaction reports of increased hepatic enzymes where fingolimod was the suspected medicine.
Healthcare professionals are advised to check recent transaminase and bilirubin levels before initiation of treatment, to promptly measure transaminase and bilirubin levels if the patient treated with fingolimod reports signs and symptoms of liver injury, and not to resume the treatment unless a plausible alternative aetiology for the signs and symptoms of liver injury can be established.

Reference:
Prescriber Update, Medsafe, September 2021 *(link to the source within*

www.medsafe.govt.nz/)

(See WHO Pharmaceuticals Newsletter No.1, 2021: Risk of serious liver injury and herpes meningoencephalitis in UK)

Gadolinium-based contrast agents

Potential risk of stillbirth and neonatal death

Canada. Health Canada announced that it will work with the manufacturers of gadolinium-based contrast agents (GBCAs) to include the potential risks of stillbirth and neonatal death in their Canadian Product Monographs (CPMs) to raise awareness among healthcare professionals and encourage reporting of these potential safety issues.

GBCAs are used to make certain body tissues easier to see during a magnetic resonance imaging (MRI) or a magnetic resonance angiography (MRA) scan. Gadopentetate dimeglumine, gadobenate dimeglumine, gadodiamide, gadoxetate disodium, gadoterate meglumine, gadobutrol and gadoteridol are authorized as GBCAs.

Health Canada reviewed information from databases harm to fetuses and infants.

In the review process, case reports of congenital anomalies with the use of GBCAs were also assessed but no link was found between the use of GBCAs during pregnancy and the risk of congenital anomalies.

Reference:
Summary Safety Review, Health Canada, 22 September 2021 *(link to the source within www.hc-sc.gc.ca)*

Hydrocortisone

Risk of hypertrophic cardiomyopathy in neonates and infants

Japan. The MHLW and the PMDA have announced that the product information for hydrocortisone preparations (oral and injectable dosage forms) should be revised to include the risk of hypertrophic cardiomyopathy in neonates and infants.

Hydrocortisone preparations are used for various indications including endocrine and allergic diseases.

The MHLW and the PMDA reviewed cases of hypertrophic cardiomyopathy reported in neonates and infants treated

Ivermectin

1. Risk of disturbed consciousness

Japan. The MHLW and the PMDA have announced that the product information for ivermectin (Stromectol®) should be revised to include the risk of disturbed consciousness.

Ivermectin is indicated for the treatment of intestinal strongyloidiasis and scabies.

The MHLW and the PMDA reviewed four cases of disturbed consciousness reported in patients treated with ivermectin in Japan and other countries.

Reference:
Revision of Precautions, MHLW/PMDA, 12 October 2021 *(link to the source within www.pmda.go.jp/english/)*

2. Potential risk of encephalopathy

Saudi Arabia. The Saudi Food & Drug Authority (SFDA) has announced that healthcare professionals should be aware of the potential risk of encephalopathy associated with the use of ivermectin and to monitor any signs or symptoms in treated patients.