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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.

This newsletter includes two brief reports, on the Pharmacovigilance Workshop held in Seoul for APEC countries and the workshop on ATC/DDD and drug utilization research held in Rabat.

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Atypical antipsychotics

Potential risk of sleep walking and sleep-related eating disorder

Canada. Health Canada recommends that the product safety information for all atypical antipsychotics should be updated to include risks of sleep walking (SW) and sleep-related eating disorder (SRED).

Atypical antipsychotics are used to treat mental disorders such as schizophrenia, bipolar disorder and depression. Health Canada reviewed the potential risk of SW and SRED with the use of atypical antipsychotics, following the publication of a case report which described these events in a patient treated with ziprasidone.

At the time of the review, Health Canada had received a total of 13 unique Canadian reports of SW and SRED suspected to be linked to the use of atypical antipsychotics. In the review it was suggested that of these 13 reports, two cases of sleep disorder were likely to be linked to atypical antipsychotics use. The patients recovered when they stopped the treatment. Six reports, out of 13, were found to have a possible link. Other risk factors such as pre-existing conditions, history of sleep disorders or use of other medications could have contributed to the events; however, a link could not be ruled out. The five remaining reports could not be assessed due to insufficient information.

This safety review evaluated information from 413 international reports of SW and SRED suspected to be associated with the use of atypical antipsychotics, but these reports provided limited additional information.

In addition, Health Canada found 23 published case reports of SW and SRED suspected to be associated with the use of atypical antipsychotics. In the majority of these reports, patients recovered when they stopped the treatment and in some cases, the events returned when patients resumed the treatment. The drug was taken as recommended and the events appeared to happen more often with higher doses. Overall, the review of these case reports suggested a link between the use of atypical antipsychotics and SW or SRED.

Reference:
Summary Safety Review, Health Canada, 21 September 2017 (*www.hc-sc.gc.ca*)

Azithromycin

Risk of acute generalized exanthematous pustulosis

Japan. The Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA) have announced that the package insert for azithromycin (Zithromax®) has been updated to include the risk of acute generalized exanthematous pustulosis as a clinically significant adverse reaction.

Azithromycin is an antimicrobial used for a number of bacterial infections caused by strains of genus *Staphylococcus*, *Streptococcus*, *Pneumococcus*, Neisseria gonorrhoeae, *Moraxella (Branhamella) catarrhalis*, *Haemophilus influenzae*, *Legionella pneumophila*, *Peptostreptococcus*, *Prevotella*, *Chlamydia*, and *Mycoplasma.*

One case of acute generalised exanthematous pustulosis has been reported in Japan. A causal relationship could not be excluded in this case. In addition, the company core datasheet (CCDS) has been updated.

Reference:
Revision of Precautions, MHLW/PMDA, 8 August 2017 *(www.pmda.go.jp/english/)*

(See WHO Pharmaceuticals Newsletter No.5, 2016: Risk of acute generalized exanthematous pustulosis in India)

Combined use of buprenorphine or methadone with benzodiazepines or CNS depressants

Medication management can reduce risks of serious adverse effects

USA. The US Food and Drug Administration (FDA) has required that drug labels for buprenorphine and methadone medicines (medication assisted treatment, MAT) are updated to include detailed recommendations for minimizing the use of MAT medicines and benzodiazepines together.

Medicines containing buprenorphine or methadone as the active ingredient are FDA-approved to treat opioid addiction and dependency. MAT should not be withheld from patients taking benzodiazepines or other drugs that depress the central nervous system (CNS), despite the risk of serious adverse effects, as harm caused by untreated opioid addiction usually outweighs risks.

Careful medication management by health-care professionals can reduce these risks.

The FDA recommended that health-care professionals should take several actions and precautions and develop a treatment plan when buprenorphine or methadone is used in combination with benzodiazepines or other CNS depressants.

Reference:
Drug Safety Communication, US FDA, 6 September 2017 *(www.fda.gov)*

Dabigatran

Risk of acute hepatic failure, hepatic function disorder, and jaundice

Japan. The MHLW and the PMDA have announced that the package insert for dabigatran (Prazaxa®) has been updated to include the risks of acute hepatic failure, hepatic function disorder and jaundice as clinically significant adverse reactions.

Dabigatran is used to reduce the risk of ischemic stroke and systemic embolism in patients with nonvalvular atrial fibrillation.

A total of five cases associated with acute hepatic failure, hepatic function disorder and jaundice have been reported in Japan. Of these, a causal relationship could not be excluded in one case.

Reference:
Revision of Precautions, MHLW/PMDA, 12 September 2017 *(www.pmda.go.jp/english/)*

Doxycycline

Risk of fixed drug eruptions

Saudi Arabia. The Saudi Food and Drug Authority (SFDA) has updated the summary of product characteristics and patient information leaflet for doxycycline to include the risk of fixed drug eruptions (FDE).

Doxycycline is a tetracycline broad-spectrum antibiotic with bacteriostatic characteristics. It is used as treatment or prophylaxis against a wide range of susceptible strains of gram-negative and gram-positive bacteria and other microorganisms.

The SFDA initiated the investigation based on a signal observed in a published case report examining potential associations between doxycycline and risk of FDE. As a result, the SFDA reviewed the available evidence related to this safety issue including screening of the WHO global database of Individual Case Safety Reports, VigiBase. In addition, a literature review was conducted.

The SFDA concluded that the available evidence suggests a probable association between doxycycline and FDE.

Reference:
Based on the communication from Saudi Food and Drug Authority, December 2016

Gadolinium based contrast agents for MRI

Retention of gadolinium in the brain

New Zealand. The Medicines and Medical Devices Safety Authority (Medsafe) has updated the data sheet for gadolinium based contrast agents (GBCAs) with information about the retention of gadolinium in the brain. Medsafe has stated that although GBCAs enter the brain, and so far no harm has been identified due to retention, use should be restricted.

GBCAs are used to enhance magnetic resonance (MR) images.

Medsafe and the Medicines Adverse Reactions Committee (MARC) recently conducted a safety review of GBCAs. It was concluded that the use of GBCAs should be restricted to situations where they are expected to provide additional information so that the patient's condition is diagnosed or monitored correctly.

Medsafe will continue to monitor the safety of GBCAs, provide more information and take further action if necessary.

Reference:
Safety Information, Medsafe, 21 August 2017 (*www.medsafe.govt.nz/*)

(See WHO Pharmaceuticals Newsletters No.4, 2017: Restrictions on use in EU, No harmful effects identified with brain retention in the US and No.5, 2015: Possible risk of brain deposits with repeated use in the US)

Hyoscine butylbromide ampoule

Caution of use in patients with pre-existing cardiac conditions

Australia. The Therapeutic Goods Administration (TGA) has updated product information for hyoscine butylbromide (Buscopan®) to include a caution regarding the use of hyoscine ampoules in patients with pre-existing cardiac conditions (for example cardiac failure, coronary heart disease). The Australian product information for hyoscine butylbromide already lists tachycardia, decreased blood pressure and anaphylaxis as potential adverse effects, but the product information has been updated to include a stronger warning in the precautions section because these adverse events can be more serious in patients with cardiac conditions. Monitoring of these patients is advised and emergency equipment and personnel trained in its use must be readily available.

Hyoscine butylbromide ampoules, administered by intramuscular or slow intravenous injection, are used to treat gastrointestinal tract, biliary and renal spasms, and are used as a diagnostic in radiology.

There are 28 cases describing tachycardia and/or hypotension relating to use of hyoscine butylbromide in the TGA's adverse events database. An additional four cases describe anaphylactic reactions. There is insufficient clinical information provided to determine whether or not these reactions occurred in people with pre-existing cardiac conditions. None of

these cases reported death, cardiac arrest or myocardial infarction.

Reference:
Medicines Safety Update, TGA, Vol. 8, No. 4, August-September 2017 (*www.tga.gov.au*)

(See WHO Pharmaceuticals Newsletter No.2, 2017: Risk of serious adverse effects in patients with underlying cardiac disease in the United Kingdom)

Ibrutinib

Reports of ventricular tachyarrhythmia; risk of hepatitis B reactivation and opportunistic infections

The United Kingdom. The Medicines and Healthcare Products Regulatory Agency (MHRA) has updated the product information of ibrutinib (Imbruvica®) to include ventricular tachyarrhythmia (common) and hepatitis B virus reactivation (uncommon) as adverse reactions. Opportunistic infections are already listed in the product information of ibrutinib.

Ibrutinib is indicated for the treatment of adult patients with:

- mantle cell lymphoma who have received at least one prior therapy
- chronic lymphocytic leukaemia (CLL), including CLL with deletion 17p
- Waldenström's macroglobulinaemia

A routine European review examined the safety profile of ibrutinib. Data from randomised controlled trials and the scientific literature were assessed. Worldwide spontaneous suspected adverse drug reaction (ADR) reports were also reviewed.

In a 2017 study of case reports of relevant events from post-marketing sources and clinical trial data, the authors identified 11 cases of ventricular tachycardia/ventricular fibrillation and six cases of sudden cardiac death in patients exposed to ibrutinib. The review also identified two spontaneous ADRs of ventricular tachyarrhythmia in which the role of ibrutinib could not be excluded.

The review identified eight cases of hepatitis B reactivation in which the role of ibrutinib was considered probable or possible.

Reference:
Drug Safety Update, MHRA, Volume 11, issue 1: 1, August 2017 *(www.gov.uk/mhra)*

Laninamivir

Risk of bronchial spasm, and dyspnoea

Japan. The MHLW and the PMDA have announced that the package insert for laninamivir (Inavir®) has been updated to include the risk of bronchial spasm and dyspnoea as clinically significant adverse reactions.

Laninamivir is indicated for treatment and prophylaxis of influenza A and B virus infection.

Eight cases associated with bronchial spasm and dyspnoea have been reported in Japan. Of these, a causal relationship could not be excluded in three cases.

Reference:
Revision of Precautions, MHLW/PMDA, 8 August 2017 *(www.pmda.go.jp/english/)*

Methylprednisolone injections containing lactose

Contraindication to patients allergic to cow's milk proteins.

EU. The European Medicines Agency (EMA) has made an announcement that the product information for methylprednisolone injections containing lactose will be revised to include a contra-indication in patients allergic to cow's milk proteins. In addition, the vial and packaging of these medicines will be clearly marked with a warning against use in patients with cow's milk allergy.

Methylprednisolone injections are used to treat the symptoms of severe allergic reactions and other inflammatory conditions.

In a review it was found that methylprednisolone injections containing lactose derived from cow's milk may also contain traces of cow's milk proteins which can trigger allergic reactions. This is of particular concern in patients already being treated for an allergic reaction as they are more prone to developing new allergic reactions.

Considering that methylprednisolone is used for the treatment of severe allergic reactions in an emergency setting where details of the patients' allergies may not always be known, the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) confirmed that the most effective way of minimising any risk is to remove cow's milk proteins from the preparation. Companies have been asked to provide data allowing the replacement of formulations containing lactose from cow's milk; this data should be provided by the middle of 2019.

Reference:
News and press releases, EMA, 1 August 2017 *(www.ema.europa.eu)*

Palivizumab

Risk of thrombocytopenia

Japan. The MHLW and the PMDA have announced that the package insert for palivizumab (Synagis®) has been updated to include the risk of thrombocytopenia as a

clinically significant adverse reaction.

Palivizumab is indicated for: prevention of serious lower respiratory tract diseases caused by respiratory syncytial virus infection in high-risk neonates and infants and children.

A total of four cases associated with thrombocytopenia have been reported in Japan. Of these, a causal relationship could not be excluded in one case.

Reference:
Revision of Precautions, MHLW/PMDA, 12 September 2017 *(www.pmda.go.jp/english/)*

Paracetamol (modified- or prolonged-release)

Modified- or prolonged-release preparations should be suspended from marketing

EU. The EMA has recommended that modified- or prolonged-release paracetamol products should be suspended from the market. This is in view of the risks to patients from the complex way these medicines release paracetamol into the body after an overdose.

Paracetamol is a medicine that has been widely used for many years to relieve pain and fever in adults and children.

immediate-release or modified-release products, making it difficult to decide what type of management is needed. The committee could not identify a way to minimise the risk to patients, or a feasible and standardised way to adapt the management of paracetamol overdose across the EU to allow for treatment of cases that involve modified-release preparations. It concluded on balance that the risk following overdose with these medicines outweighs the advantage of having a longer-acting preparation.

Reference:
News and press releases, EMA, 1 September 2017 *(www.ema.europa.eu)*

Riociguat

Increased incidences of serious adverse events and fatal outcomes

Japan. The MHLW and the PMDA have announced that the package insert for riociguat (Adempas®) should be updated to include an important precaution on the risk of serious adverse events and fatal outcomes.

Riociguat is indicated to treat inoperable chronic thromboembolic pulmonary hypertension (CTEPH) or postoperative persistent or recurrent CTEPH, and pulmonary arterial

may outweigh the benefits in some patients.

One case associated with adverse reactions has been reported in patients with symptomatic pulmonary hypertension associated with idiopathic interstitial pneumonias in Japan.

Reference:
Revision of Precautions, MHLW/PMDA, 3 August 2017 *(www.pmda.go.jp/english/)*

(See WHO Pharmaceuticals Newsletters No.1, 2017: Contraindicated for use in patients with pulmonary hypertension associated with idiopathic interstitial pneumonia in Malaysia and No. 5, 2016: Contraindicated in patients with pulmonary hypertension associated with idiopathic interstitial pneumonias in the United Kingdom)

Selexipag

Contraindication with potent inhibitors of cytochrome P450 2C8

Spain. The Agencia Española de Medicamentos y Productos Sanitarios (AEMPS) has informed health-care professionals that the concomitant use of selexipag (Uptravi®) with potent cytochrome P4502C8 (CYP2C8) inhibitors (for example, gemfibrozil) is contraindicated as exposure to the active metabolite of selexipag can be increased causing adverse reactions.

Selexipag is indicated for the