World Health Organization

WHO Pharmaceuticals NEWSLETTER

2018
No. 2

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 a feature article titled PV strengthening in Armenia and Kyrgyzstan using smart safety surveillance approach; identifying gaps.

Contents

Suggested citation. WHO Pharmaceuticals Newsletter No.2, 2018: World Health Organization; 2018. Licence: CC BY-NC-SA 3.0 IGO.

Cataloguing-in-Publication (CIP) data. CIP data are available at http://apps.who.int/iris.

Printed in Switzerland

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Regulatory Matters

Safety of medicines

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Antihistamines (first generation, oral sedating)

Potential for fatal respiratory depression in children under two years of age

Australia. The Therapeutic Goods Administration (TGA) will work with manufacturers to strengthen warnings in the product information (PI) and consumer medicine information (CMI) for first generation oral antihistamines, to emphasize that they should not be used in children under two years of age due to the potential risk respiratory depression. In addition, TGA will be seeking to include a mandatory warning statement on labels of over-the-counter (OTC) liquid oral formulations of first-generation oral sedating antihistamines about the contra-indication of use in children under two years.

The TGA recently reviewed a fatal case of respiratory depression in a 74-day old infant who was treated with OTC promethazine oral liquid. Although the infant's death was not attributed to use of promethazine, the case raised a safety concern.

Up until 15 November 2017, the TGA database of adverse event notifications contained 45 reports of adverse events in children aged under two years in which a first-generation oral sedating anti-histamine is listed as the sole-suspected medicine. These reports document a range of adverse events including hypersensitivity reactions, agitation, abnormal movements, vomiting and diarrhoea.

Reference:
Medicines Safety Update, TGA, Vol. 9, No. 1, February-March 2018 (*www.tga.gov.au*)

Clarithromycin

Potential risk of heart problems or death in patients with heart disease

USA. The US Food and Drug Administration (FDA) has added a new warning about an increased risk of death in patients with heart disease to the drug labels for clarithromycin (Baxin®). In addition, the FDA has added the results of a clinical trial that indicate this increased risk to clarithromycin drug labels.

Clarithromycin is used to treat a variety of infections and is not approved to treat heart disease.

The FDA's recommendation is based on a review of the results of a 10-year follow-up study of patients with coronary heart disease form a large clinical trial that first observed this safety issue. Results from the trial provide evidence of the increased risk compared to placebo. Other observational studies showed mixed findings. The FDA is unable to determine why the risk of death is greater for patients with heart disease.

Reference:
Safety Alerts for Human Medical Products, US FDA, 2 February 2018 *(www.fda.gov)*

Clopidogrel and selexipag interaction

Co-administration is contraindicated due to increased blood concentrations of selexipag

Japan. The Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA) have announced that the package inserts for clopidogrel containing products (Plavix®, ComPlavin®) and selexipag (Uptravi®)) should be revised to include that co-administration of selexipag and clopidogrel is contraindicated.

Selexipag is indicated for pulmonary arterial hypertension. Clopidogrel is indicated for suppression of recurrent ischemic cerebrovascular disorder.

Clopidogrel is a potent CYP2C8 inhibitor and there is a possibility of an onset of adverse drug reactions and/or symptom exacerbation arising from an increase in blood concentrations of selexipag and its active metabolite. MHLW and PMDA have conducted an investigation and have concluded that the revision of the package inserts of both products should include language regarding the risks associated with co-administration of clopidogrel.

Reference:
Revision of Precautions, MHLW/PMDA, 20 March 2018 *(www.pmda.go.jp/english/)*

(See WHO Pharmaceuticals Newsletters No.5, 2017: Contraindication with potent inhibitors of cytochrome P450 2C8 in Spain)

Daclizumab beta

Immediate suspension: risk of serious inflammatory brain disorders

Europe. The European Medicines Agency (EMA) has recommended the immediate suspension and recall of daclizumab beta (Zinbryta®) following 12 reports of serious inflammatory brain disorders worldwide, including encephalitis and meningoencephalitis in patients with multiple sclerosis. Three of the cases were fatal.

Daclizumab beta is indicated for treating relapsing forms of multiple sclerosis. Following a 2017 review of the medicine's effects on the liver, the use of the medicine was restricted to patients who have tried at least two other disease-modifying treatments and cannot be treated with other multiple sclerosis treatments.

Also, the available evidence indicate that immune reactions

observed in the reported cases may be linked to the use of daclizumab beta.

To protect patients' health, EMA is recommending the immediate suspension of the medicine's marketing authorisation in the EU and a recall of batches from pharmacies and hospitals.

EMA advises that no new patient should start treatment with daclizumab beta. Health-care professionals should immediately contact patients currently being treated with daclizumab beta, stop treatment, and consider alternatives. Patients stopping treatment must be followed up for at least six months.

EMA's recommendation to suspend daclizumab beta and recall the product is being sent to the European Commission for a legally binding decision.

The company that markets daclizumab beta has already voluntarily requested a withdrawal of the medicine's marketing authorisation and informed EMA of its intention to stop clinical studies.

Reference:
EMA, 2 and 7 March 2018 *(www.ema.europa.eu)*

Dipeptidylpeptidase-4 inhibitors

1. Potential risk of a skin reaction (bullous pemphigoid)

Canada. Health Canada has requested that the product information for dipeptidylpeptidase-4 (DPP-4) inhibitors (alogliptin, saxagliptin, sitagliptin, and linagliptin) is updated to include the risk of bullous pemphigoid.

DPP-4 inhibitors, known as gliptins are prescription medicines indicated for type-2 diabetes in adults.

A total of 24 serious international reports of potential bullous pemphigoid with the use of alogliptin (16) and saxagliptin (8) were identified by manufacturers and from a search in the Canada vigilance database. All 24 reports were considered to show a possible link between the skin reaction and the drug. Of the 24 reports, three deaths were reported, one of which was considered to be possibly linked to bullous pemphigoid from using the DPP-4 inhibitor.

Health Canada's review concluded that there may be a link between any of the DPP-4 inhibitors and the risk of bullous pemphigoid. Health Canada will publish a notice in the Health Product InfoWatch to inform Canadians and health-care professionals of this new safety information.

Health Canada will continue to monitor safety information involving DPP-4 inhibitors to identify and assess potential harms.

Reference:
Summary Safety Review, Health Canada, 25 January 2018 (*www.hc-sc.gc.ca*)

2. Risk of acute pancreatitis (anagliptin, linagliptin, teneligliptin)

Japan. MHLW and PMDA have announced that the package inserts for anagliptin (Suiny®), linagliptin (Trazenta®), and teneligliptin containing products (Tenelia®, Canalia Combination®) should include acute pancreatitis and pemphigoid (anagliptin) as clinically significant adverse reactions.

Dipeptidyl peptidase-4 (DPP-4) inhibitors and are indicated to treat hyperglycemia in adults with two diabetes mellitus.

Cases of acute pancreatitis have been reported in patients treated with anagliptin (four cases), linagliptin (19 cases), and teneligliptin hydrobromide hydrate (9 cases) in Japan. In addition, seven cases of pemphigoid were reported in patients treated with anagliptin. MHLW and PMDA have concluded that revision of the package insert was necessary following the investigation of available evidence and consultations with expert advisors.

Reference:
Revision of Precautions, MHLW/PMDA, 20 March 2018 *(www.pmda.go.jp/english/)*

Efavirenz

Risk of prolonged QT

Japan. MHLW and PMDA have concluded that revision of the package insert for efavirenz (Stocrin Tablets®) should be revised to include the risk of prolonged QT as a precaution.

Efavirenz is indicated for HIV-1 infection. Prolonged QT interval was observed in conjunction with increased blood concentrations of efavirenz in an overseas clinical study investigating the effect of this drug on the QT interval. Several cases of prolonged QT have also been reported in patients treated with efavirenz overseas. No cases involving prolonged QT have been reported in the last three fiscal years in Japan.

Reference:
Revision of Precautions, MHLW/PMDA, 13 February 2018 *(www.pmda.go.jp/english/)*

Flupirtine

Withdrawal due to serious liver problems

Europe. The EMA has recommended that the market authorization for flupirtine should be withdrawn due to the risk of serious liver injury. The Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) has endorsed the EMA's decision.

Flupirtine is used to treat acute pain (up to 2 weeks) in

patients who cannot use other painkillers such as opioids or nonsteroidal anti-inflammatory medicines (NSAIDs).

The EMA's recommendation was an outcome following a review of flupirtine carried out by EMA's Pharmacovigilance Risk Assessment Committee (PRAC), who looked at the available data including studies evaluating whether risk minimization measures set in 2013 were followed in clinical practice.

Since 2013, there were reports of serious liver injury with flupirtine use. These included 23 cases of acute liver failure, some of which were fatal or led to transplantation.

PRAC concluded that the restrictions introduced in 2013 have not been sufficiently followed, and cases of serious liver injury, including liver failure, still occurred.

The CMDh therefore agreed that patients taking flupirtine-containing medicines continue to be exposed to serious risks which outweigh the benefits of these medicines. Alternative treatment options to flupirtine are available.

Reference: EMA, 23 March 2018 *(www.ema.europa.eu)*
(See WHO Pharmaceuticals Newsletters No.3, 2013: Review started due to concerns over liver problems in Europe)

Gadolinium-containing contrast agents

Omniscan® and intravenous iv Magnevist® no longer authorised; and restrictions of use for other linear agents

United Kingdom. The Medicines and Healthcare Products Regulatory Agency (MHRA) has announced that two gadolinium-containing contrast agents (Omniscan® and intravenous Magnevist®) are now no longer authorized for use and a product recall of any existing unexpired stock is underway, due to risk of gadolinium deposition in the brain with use of linear gadolinium-containing contrast agents. In addition, the linear agents gadobenic acid and gadoxetic acid (Primovist®) will be limited for use in liver imaging and when imaging in the delayed phase liver is required.

Gadolinium-containing contrast agents (GdCAs) are indicated for the enhancement of magnetic resonance imaging (MRI). GdCAs can be divided into two groups: linear and macrocyclic. The use of linear GdCAs has decreased markedly in the UK, following advice published in 2006 which aimed to reduce risk of nephrogenic systemic fibrosis (NSF).

In view of evidence of retention of gadolinium in brain and other tissues, the risks of gadodiamide and intravenous gadopentetic acid are considered to outweigh their benefits.

There are other GdCAs that will remain on the market, but should only be used when diagnostic information is essential and not available with unenhanced MRI.

Reference:
Drug Safety Update, MHRA, 6 February 2018
(www.gov.uk/mhra)
(See WHO Pharmaceuticals Newsletters No.1, 2018; No.4 and 5, 2017; No.5, 2015; No.6, 2013: for related information)

Hydroxyethyl-starch solution

Risk of kidney injury and death in certain patient populations

Europe. The EMA has recommended the withdrawal of the market authorization license for hydroxyethyl-starch (HES) solutions for infusion due to risk of kidney injury. This has been endorsed by CMDh.

HES solutions for infusion are used for the management of hypovolaemia caused by acute blood loss, where treatment with alternative infusion solutions known as crystalloids alone is not considered to be sufficient.

A review of the safety of HES solutions for infusion has been carried out by EMA's PRAC. HES solutions have continued to be used in critically ill patients and patients with sepsis despite the introduction of restrictions on use in these patients in 2013. The final decision to withdraw the market authorization license, however, will be taken by the European Commission.

Reference:
EMA, 26 January 2018
(www.ema.europa.eu)

(See WHO Pharmaceuticals Newsletters No.6, 2017: New review of benefit-risk balance in Europe; No.4, 2017: Acute kidney injury in non-critically ill patients: not enough evidence in Canada; No.1, 2015: Contraindications and warnings in the United Kingdom and Canada)

Iohexol, Iomeprol

Risk of acute generalized exanthematous pustulosis

Japan. MHLW and PMDA have requested the revision of the package inserts for iohexol (Omnipaque®) and iomeprol (Iomeron®) to include the risk of acute generalized exanthematous pustulosis as a clinically significant adverse reaction.

Iohexol and imeprol are indicated for various angiography and x-ray procedures.

Two cases of acute generalized exanthematous pustulosis were reported in patients who used iomeprol and iohexol in the last three fiscal years in Japan. A causal relationship with the products could not be excluded for those patients. No fatal cases have been reported.

Reference:
Revision of Precautions,

MHLW/PMDA, 13 February 2018 *(www.pmda.go.jp/english/)*

Kampo medicines containing Gardenia fruit

Risk of mesenteric phlebosclerosis

Japan. MHLW and PMDA have recommended that the package insert for Japanese traditional medicines containing Gardenia fruit should be revised to include the risk of mesenteric phlebosclerosis as a precaution.

Gardenia fruit preparations have various indications, for example coughing, constipation, obesity and others.

A total of 86 cases of mesenteric phlebosclerosis were reported in the last three fiscal years in Japan. A causal relationship was evaluated in the 20 cases out of 86 cases. A causal relationship could not be excluded in 14 cases. No fatal cases were reported.

Reference:
Revision of Precautions, MHLW/PMDA, 13 February 2018 *(www.pmda.go.jp/english/)*

Miconazole and warfarin interaction

Reminder of reduced

and yeast infections of the skin or vagina.

Miconazole inhibits one of the main cytochrome P450 isoenzymes involved in warfarin metabolism (CYP2C9), which can result in reduced warfarin clearance and an enhanced anticoagulant effect.

This can lead to supra-therapeutic international normalised ratio (INR) values and subsequent bleeding complications. Bleeding events can have fatal outcomes.

The TGA has reminded health professionals that, while the number of Australian reports of warfarin and miconazole interactions are low, the potential of an interaction can be life-threatening.

Reference:
Medicines Safety Update, TGA, Vol. 9, No. 1, February-March 2018 (*www.tga.gov.au*)

(See WHO Pharmaceuticals Newsletters No.6, 2016: Risk of bleeding due to drug-drug interaction in Japan; No.4, 2016: Potential for serious drug-drug interactions with warfarin in the United Kingdom)

Mycophenolate mofetil, mycophenolic acid

Contraception is recommended

Ireland. Mycophenolate (mycophenolate mofetil and mycophenolic acid) is authorized to prevent

Women of child bearing potential should use at least one form of reliable contraception before starting treatment, during treatment and for six weeks after stopping treatment. Two forms of contraception are preferred.

Reference:
Drug Safety Newsletter, HPRA, 16 March 2018 *(www.hpra.ie)*

United Kingdom. MHRA has updated contraception advice for male patients on mycophenolate mofetil.

The available clinical evidence does not indicate an increased risk of malformations or miscarriage in pregnancies where the father was taking mycophenolate medicines, but there is insufficient evidence to exclude any risk.

As a precautionary measure for male patients, it is now recommended that either the patient or their female partner use reliable contraception during treatment with mycophenolate medicines and for at least 90 days after stopping. Female patients of childbearing potential receiving mycophenolate should always use contraception.

Reference:
Drug Safety Update, MHRA, 6 February 2018 *(www.gov.uk/mhra)*

(See WHO Pharmaceuticals Newsletters No.2, 2016: Contraindications relating to pregnancy and breastfeeding in Australia; No.1, 2016: New pregnancy-prevention advice for women and men in the United