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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 information on the safety and efficacy 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:

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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 feature articles: a summary of discussions at the Fourteenth Meeting of the WHO Advisory Committee on Safety of Medicinal Products (ACSoMP) and the story so far on Integrating Pharmacovigilance in Seasonal Malaria Chemoprevention.

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Bosutinib

Risks of toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome) and erythema multiform

Japan. The Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA) have announced that the package insert for bosutinib (Bosulif®) has been updated to include the risk of toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome) and erythema multiform as clinically significant adverse reactions.

Bosutinib is used for the treatment of chronic myelogenous leukaemia in patients who are resistant or intolerant to prior drug therapies.

Cases of oculomucocutaneous syndrome (four cases), toxic epidermal necrolysis (one case) and erythema multiforme (four cases) have been reported in patients who were treated with bosutinib in Japan. The company core data sheet (CCDS) was also updated to include oculomucocutaneous syndrome as an adverse drug reaction.

Reference:
Revision of Precautions, MHLW/PMDA, 30 May 2017 *(www.pmda.go.jp/english/)*

Codeine, dihydrocodeine and tramadol

Cautions against use in children and teenagers under 18 years of age

Japan. The MHLW and the PMDA have announced that the package inserts for products containing codeine, dihydrocodeine and tramadol have been updated to include a precaution against use in children younger than 12 years and in teenagers between 12 and 18 years of age who are obese, have obstructive sleep apnoea syndrome, or have serious lung disease.

The above update is due to the fact that a serious case of respiratory depression with codeine use was reported in a patient under the age of 12 years who was an ultra-rapid metaboliser (UM) of CYP2D6 in Japan.

A precaution that codeine should not be used in patients younger than 18 years of age for pain relief after tonsillectomy or adenoidectomy was also considered appropriate to add.

Although the frequency of the genetic polymorphism causing UM is thought to be lower amongst the Japanese population compared to the US or European populations, the above precautions were added in view of the adverse drug reactions reported in Japan.

The risk of respiratory depression with codeine also exists with tramadol use. However, it should be noted that in Japan, no tramadol containing products have been approved for paediatric use.

Reference:
Revision of Precautions, MHLW/PMDA, 4 July 2017 *(www.pmda.go.jp/english/)*

(See WHO Pharmaceuticals Newsletters No.3, No.2 and No.1, 2017, No.5 and No.1 in 2016, No.6, No.5, No.4 and No.3 in 2015, No.5 and No.4 in 2013, and No.5 in 2012 for related information)

Daclizumab

Provisional restrictions for use

EU. The European Medicines Agency (EMA) has provisionally restricted the use of the multiple sclerosis medicine daclizumab (Zinbryta®) to patients with highly active relapsing and/or rapidly evolving relapsing disease that has failed to respond to treatment or cannot be treated with other medicines. In addition, it is contraindicated in patients with liver injury.

A review of daclizumab was commenced after a patient died from liver injury (fulminant liver failure) in an ongoing observational study. In addition there were four cases of serious liver injury reported. The risk of liver damage with daclizumab was known at the time it received market authorisation in the EU. Several risk management measures were put in place including the requirement to monitor liver function and educate health-care professionals and patients on the risk of liver damage.

Starting treatment with daclizumab is not recommended for patients with autoimmune diseases other than multiple sclerosis and caution should be used when giving daclizumab together with medicines that can damage the liver. Doctors should continue to monitor the liver function of patients receiving the medicine and closely watch patients for signs and symptoms of liver injury.

Once the review is concluded, the EMA will communicate further and provide updated guidance to patients and health-care professionals.

Reference:
News and press release, EMA, 7 July 2017 *(www.ema.europa.eu)*

Denosumab

Risk of osteonecrosis of the external auditory canal

The United Kingdom. The Medicines and Healthcare Products Regulatory Agency (MHRA) has revised the product information for all denosumab containing

products to include a warning on the risk of osteonecrosis of the external auditory canal.

Denosumab 60 mg solution for injection (Prolia®) is indicated for the treatment of osteoporosis in postmenopausal women and in men with an increased risk of fractures. It is also used to treat bone loss associated with hormone ablation in men with prostate cancer. Denosumab 120 mg solution for injection (Xgeva®) is indicated for the prevention of skeletal-related events in adults with bone metastases from solid tumours, and for the treatment of giant cell tumour of bone that is unresectable or where surgical resection is likely to result in severe morbidity.

The MHRA is closely monitoring the use of bisphosphonates for the potential risk of osteonecrosis of the external auditory canal following published reports in the literature.

Worldwide, five reports of osteonecrosis of the external auditory canal have been received for patients treated with 60mg denosumab for osteoporosis.

The MHRA advised health-care professionals to consider the possibility of osteonecrosis of the external auditory canal in patients receiving denosumab who present with ear symptoms including chronic ear infections or in those with suspected cholesteatoma.

Reference:
Drug Safety Update, MHRA, Volume 10, issue 11:1, 21 June 2017 *(www.gov.uk/mhra)*

Direct-acting antivirals (DAAs)

Risk of hepatitis B virus reactivation

Singapore. The Health Sciences Authority (HSA) has updated package inserts for direct-acting antivirals (DAA)-containing products to include safety information regarding the risk of hepatitis B virus (HBV) reactivation.

DAAs are a class of drugs used for the treatment of hepatitis C virus (HCV) infection.

To date, the HSA has not received any local reports of HBV reactivation in patients receiving treatment with DAAs for HCV infection.

Several cases of HBV reactivation have been reported internationally in patients who were treated with DAAs for HCV infection. In some cases, the HBV reactivation had led to serious outcomes such as hepatic failure and death. Several national regulatory authorities have taken regulatory actions after conducting safety reviews to assess the risk of HBV reactivation associated with the use of DAAs for treatment of HCV infection.

The HSA encourages health-care professionals to be vigilant for HBV reactivation in patients who have a past or current HBV infection, and who have been prescribed DAA-containing products for the treatment of HCV infection.

Reference:
Product Safety Alerts, HSA, 26 May 2017 (*http://www.hsa.gov.sg/*)

(See WHO Pharmaceuticals Newsletters No.1, 2017, No.6 and No.3, 2016 for related information)

Domperidone

Risk minimisation of cardiovascular effects

Singapore. The HSA has re-assessed whether additional measures to further mitigate the cardiovascular (CV) risk associated with the use of domperidone are necessary. The HSA has updated package inserts for products containing domperidone to strengthen cardiovascular warnings and include recommendations on new dosing regimens and treatment durations.

Domperidone is a pro-kinetic and anti-emetic drug used for the treatment of dyspepsia, nausea and vomiting.

Risk factors that increase the risk of cardiotoxicity include: advanced age (>60 years old), underlying CV conditions, high domperidone dose (>30 mg/day) and concomitant use with QT prolongation drugs and CYP3A4 inhibitors. The HSA has received two cases of QT prolongation associated with domperidone (from 2006 to 2016). Considering that domperidone has been used in local clinical settings for a long period of time, and that there is a relatively low incidence of locally reported cardiac-related adverse events, the HSA concluded that the benefit-risk profile of domperidone remains favourable when used appropriately. Additional measures were recommended to mitigate the risk of cardiotoxicity, which included restricting its use in high risk patients.

Reference:
Product Safety Alerts, HSA, 26 May 2017 (*http://www.hsa.gov.sg/*)

(See WHO Pharmaceuticals Newsletters No.2, 2015, No.3 and No.1, 2014 for related information)

Dulaglutide

Risk of anaphylaxis and angioedema

Japan. The MHLW and the PMDA have announced that the package insert for dulaglutide (Trulicity®) has been updated to include the risks of anaphylaxis and angioedema as clinically significant adverse reactions.

Dulaglutide is indicated in type-2 diabetes mellitus to improve glycaemic control.

A total of two cases of anaphylaxis have been reported in patients treated

with dulaglutide in Japan. Cases of anaphylaxis and angioedema have also been reported overseas. In addition, the company core data sheet (CCDS) has been revised to include anaphylaxis as an adverse drug reaction.

Reference:
Revision of Precautions, MHLW/PMDA, 30 May 2017 *(www.pmda.go.jp/english/)*

Finasteride

Potential risk of serious muscle-related adverse effects

Canada. Health Canada has recommended that manufacturers update the product information for finasteride containing products (Propecia®, Proscar® and generics) to include information about the potential risk of serious muscle-related adverse effects.

Finasteride at a dose of 5mg is used to treat and control non-cancerous enlargement of the prostate gland (benign prostatic hyperplasia) and for treatment of androgenic alopecia at a dose of 1mg.

Health Canada reviewed the potential risk of serious muscle-related adverse events such as rhabdomyolysis, myopathy and muscle disorders such as pain, weakness, atrophy or stiffness.

At the time of this review, Health Canada had received 11 Canadian reports of serious muscle-related adverse effects. Four cases were thought to be possibly linked to finasteride use. In three of the four cases individuals recovered after stopping the use of finasteride (the outcome is unknown in the fourth case). There were not enough information to establish a link between finasteride and muscle-related adverse effects in the remaining seven reports.

Three additional cases of serious muscle-related adverse effects with the use of finasteride were reported in the literature. Two cases reported either myalgia with an increase in muscle enzymes, or rhabdomyolysis following the use of finasteride to treat hair loss in men. These patients recovered after they stopped using finasteride.

The WHO global database of Individual Case Safety Reports (ICSRs) contained 508 reports of serious muscle-related adverse effects suspected of being linked to the use of finasteride, mostly atrophy, weakness, myalgia and sudden, strong muscle tightening (spasms). There were not enough information in these reports to suggest a causal effect.

Health Canada's review of the available information concluded that the risk of serious muscle-related adverse effects with the use of finasteride cannot be ruled out.

Reference:
Summary Safety Review, Health Canada, 22 June 2017 (*www.hc-sc.gc.ca*)

Fluconazole and fosfluconazole

Risk of drug-induced hypersensitivity syndrome

Japan. The MHLW and the PMDA have announced that the package inserts for fluconazole (Diflucan®) and fosfluconazole (Prodif®) have been updated to include the risk of drug-induced hypersensitivity syndrome (DIHS) as a clinically significant adverse reaction.

Fluconazole and fosfluconazole (pro-drug of fluconazole) are antifungal medications used for fungal infections with *Candida* or *Cryptococcus.*

A total of two cases associated with DIHS with fluconazole use have been reported in Japan. Of these, a causal relationship could not be excluded in one of the cases. For fosfluconazole, one case associated with DHIS has been reported. The company core datasheet (CCDS) for fluconazole has also been updated.

Reference:
Revision of Precautions, MHLW/PMDA, 4 July 2017 *(www.pmda.go.jp/english/)*

Fulvestrant

Risk of falsely elevated oestradiol levels measured in the blood using immunoassays

Singapore. The HSA has stated that it is working with manufacturers to update the package insert for fulvestrant (Faslodex®) to include information on cross-reactivity with oestradiol (E2) immunoassays.

Fulvestrant is indicated for the treatment of oestrogen receptor (ER)-positive post-menopausal women and locally advanced or metastatic breast cancer, with disease relapse on or after adjuvant anti-oestrogen therapy, or with disease progression on therapy with an anti-oestrogen.

Medical and scientific literature together with international post-marketing reports suggest that fulvestrant can cross-react with E2 immunoassays which can result in falsely elevated E2 levels. This can and potentially lead to misinterpretations and unnecessary surgery or endocrine therapy modification.

To date, the HSA has not received any local ADR reports of falsely elevated E2 levels associated with the use of fulvestrant. However internationally, the EMA, Health Canada, the Therapeutic Good Administration (TGA) and the United States Food and Drug Administration (US FDA) have updated the product labelling with warnings of potential cross-reactivity.

The HSA has advised that health-care professionals should consider alternative methods to E2 immunoassays such as liquid chromatography-mass spectrometry, if their patient is taking fulvestrant.

Reference:
Product Safety Alerts, HSA, 26 May 2017 (*http://www.hsa.gov.sg/*)

Gadolinium agents in body scans

Restrictions on use

EU. The EMA has issued restrictions for the use of intravenous linear gadolinium agents to prevent the risk of brain deposition.

Gadolinium contrast agents are used to improve image quality with magnetic resonance scans.

As a result of the review, the Pharmacovigilance Risk Assessment Committee (PRAC) recommended that gadoxetic acid and gadobenic acid should only be used for liver scans in situations where there is an important diagnostic need. In addition, gadopentetic acid should only be used for joint scans.

All other intravenous linear agents (gadodiamide, gadopentetic acid and gadoversetamide) should be suspended.

The restrictions on linear

Gold (I) sodium thiosulfate containing patch test products

Sensitization to gold (I) sodium thiosulfate

Japan. The MHLW and the PMDA have announced that the package inserts for patch test products containing gold (I) sodium thiosulfate have been updated to include a caution about sensitization to gold (I) sodium thiosulfate.

Patch test products containing gold (I) sodium thiosulfate are indicated for identification of allergens in allergic skin disease.

A total of seven cases associated with sensitization to gold (I) sodium thiosulfate have been reported in Japan. Of these, a causal relationship could not be excluded in four cases. In addition, data related to this safety issue are published in the literature.

Reference:
Revision of Precautions, MHLW/PMDA, 4 July 2017 *(www.pmda.go.jp/english/)*

Hydroxocobalamin

Risk of acute kidney injury

Japan. The MHLW and the PMDA have announced that the package insert for hydroxocobalamin (Cyanokit®) has been updated to include the risk of acute kidney injury

Loperamide (high dose)

Risk of serious cardiac adverse events

Malaysia. The National Pharmaceutical Regulatory Agency (NPRA) has updated the package inserts for all products containing loperamide with warnings and safety information related to the risk of serious cardiac adverse events with high doses.

Loperamide is an antidiarrhoeal medicine.

Between 2000 to December 2016, the NPRA has received 14 reports containing a total of 29 adverse events suspected to be related to loperamide use in Malaysia. More than half the adverse events (15 events, 52%) were related to skin disorders such as rash and pruritus. Other adverse events reported were anaphylaxis, shortness of breath, dizziness, dysaesthesia, face and mouth oedema, nausea, oculogyric crisriskis, stomatitis, and throat tightness. To date, the NPRA has not received any reports of cardiac adverse events related to loperamide use.

A search of the WHO global database of Individual Case Safety Reports (ICSRs), VigiBase, identified 7 431 individual case safety reports involving loperamide since year 1977. A total of 328 reports involved cardiac disorders such as ventricular tachycardia (60