World Health Organization

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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 also includes a short report from a recent training activity for strengthening pharmacovigilance in Botswana.

Contents

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Regulatory Matters

Safety of medicines

Signal

Amoxicillin

Risk of drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome

Singapore. The Health Sciences Authority (HSA) has announced that the package inserts for amoxicillin containing products (Amoxil®) and amoxicillin/clavulanate (Augmentin®) will be updated to include the risk of eosinophilia and systemic symptoms (DRESS) syndrome as an adverse drug reaction.

Amoxicillin is indicated for the treatment of commonly occurring bacterial infections such as respiratory tract, genitourinary, skin, and soft tissues infections.

The European Medicines Agency (EMA)'s Pharmacovigilance Risk Assessment Committee (PRAC) conducted a safety review and recommended that the package inserts for amoxicillin-containing products should be updated to include the risk of DRESS syndrome.

HSA has received six serious local reports of DRESS syndrome associated with the use of amoxicillin/clavulanate. Two of the six cases described visceral involvements (hepatitis and myositis).

Reference:
Product Safety Alerts, HSA, 14 September 2018 (*http://www.hsa.gov.sg/*)

Ampicillin and ampicillin prodrugs

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 inserts for ampicillin (Viccillin®), bacampicillin (Viccillin-S®), and sultamicillin (Pengood®) should be revised to include acute generalized exanthematous pustulosis as an adverse drug reaction.

Ampicillin, bacampicillin and sultamicillin are antibiotics used to treat several conditions, such as sepsis, infective endocarditis and superficial skin infections.

A total of two cases involving acute generalized exanthematous pustulosis have been reported in patients treated with preparations containing ampicillin or bacampicillin in Japan during the previous three fiscal years. As bacampicillin and sultamicillin are prodrugs of ampicillin, MHLW/PMDA concluded that the revision of the package inserts was necessary.

Reference:
Revision of Precautions, MHLW/PMDA, 18 September 2018 *(www.pmda.go.jp/english/)*

(See WHO Pharmaceuticals Newsletter No.5, 2017, No.1, 2016 and No.6 and No.3, 2015: Risk of acute generalized exanthematous pustulosis in Japan; No.5, 2016: Risk of acute generalized exanthematous pustulosis in India)

Apremilast

Risk of severe diarrhoea

Japan. MHLW and PMDA have announced that the package insert for apremilast (Otezla®) should be revised to include severe diarrhoea as an adverse drug reaction.

Apremilast is indicated for treatment of psoriasis vulgaris in patients who were not sufficiently responsive to topical therapies for treatment of psoriatic arthritis.

Cases of severe diarrhoea have been reported in overseas patients treated with apremilast, but no cases have been reported in Japan. Taking into account the existing text concerning severe diarrhoea in the US and EU package inserts for apremilast, MHLW/PMDA concluded that revision of the package insert was necessary based on currently available evidence.

Reference:
Revision of Precautions, MHLW/PMDA, 2 August 2018 *(www.pmda.go.jp/english/)*

Azithromycin

Increased risk of cancer relapse in donor stem cell transplant patients

USA. The US Food and Drug Administration (FDA) has advised health-care professionals not to prescribe azithromycin (Zithromax® and Zmax®) for long term use in patients who undergo donor stem cell transplants due to the potential risk of cancer relapse and death.

Azithromycin is an antibiotic used to treat many types of infections affecting the lungs, sinuses, skin and other parts of the body. Although not approved, azithromycin has been used for prophylaxis of bronchiolitis obliterans syndrome in patients who undergo donor stem cell transplants.

Results of a clinical trial show an increased rate of relapse in cancer affecting blood and lymph nodes, and deaths in these patients.

Reference:
Safety Alerts for Human Medical Products, US FDA, 3 August 2018 *(www.fda.gov)*

Beta-lactam antibiotics

Risk of severe cutaneous adverse reactions (SCAR)

Canada. Health Canada has announced that there is evidence of a link between the use of beta-lactam antibiotics and the risk of severe cutaneous adverse reactions (SCAR).

Beta-lactam antibiotics are a widely prescribed group of antimicrobial agents and are indicated to treat many types of bacterial infections. Beta-lactam antibiotics include ampicillin, amoxicillin, piperacillin and penicillin.

Health Canada reviewed the risk of SCAR with beta-lactam antibiotics because information submitted by a manufacturer suggested a potential risk of SCAR with amoxicillin/clavulanic acid. Because the risk of SCAR is included in the product information for some beta-lactam antibiotics, Health Canada decided to review all beta-lactam antibiotics, focusing on products that do not already include SCAR in their product information.

Health Canada has received 45 Canadian reports of SCAR in patients exposed to beta-lactam antibiotics.. At the time of the review there were 8,855 Individual Case Safety Reports (ICSRs) in the WHO global database for ICSRs, VigiBase®. The review established a possible link between the use of beta-lactam antibiotics and the risk of SCAR.

Reference:
Summary Safety Review, Health Canada, 7 August 2018 (*www.hc-sc.gc.ca*)

Ceftriaxone

Risk of convulsions and involuntary movements

Japan. MHLW and PMDA have announced that the package insert for ceftriaxone (Rocephin®) should be revised to include neuropsychiatric symptoms such as convulsions and involuntary movements as adverse reactions.

Ceftriaxone is active against microorganisms of genera: *Streptococcus*, *Pneumococcus*, and *Escherichia coli*. It is indicated for the treatment of bacterial infections such as sepsis, pharyngitis, tonsillitis and acute bronchitis.

A total of 19 cases of neuropsychiatric symptoms have been reported in Japan during the previous three fiscal years, and a causal relationship with ceftriaxone could not be excluded for 11 cases. Also, there are cases of neuropsychiatric symptoms reported in patients treated with ceftriaxone overseas.

MHLW/PMDA concluded that revision of the package insert was necessary based on currently available evidence.

Reference:
Revision of Precautions, MHLW/PMDA, 2 August 2018 *(www.pmda.go.jp/english/)*

Corticosteroids

Risk of central serous chorioretinopathy (CSCR)

New Zealand. Medsafe has informed health-care professionals of reports of central serous chorioretinopathy (CSCR) with the use of both topical and systemic corticosteroids.

Corticosteroids are widely used to treat various symptoms such as, inflammation, immunosuppression and proliferation.

The Centre for Adverse Reactions Monitoring (CARM) received reports for one case of CSCR and two cases of retinal detachment associated with corticosteroid use.

Symptoms of CSCR include blurred or distorted vision, blind spots, micropsia, sensitivity to bright light and reduced contrast sensitivity.

Medsafe is working with sponsors to include safety information about CSCR in the New Zealand data sheets for all corticosteroid-containing products.

Reference:
Prescriber Update, Medsafe, September 2018 *(www.medsafe.govt.nz/)*
(See WHO Pharmaceuticals Newsletter No.5, 2017: Rare risk of central serous chorioretinopathy in UK)

Dolutegravir

Risk of hepatic impairment and jaundice

Japan. MHLW and PMDA have announced that the package inserts for dolutegravir containing products (dolutegravir (Tivicay®) and dolutegravir sodium/abacavir sulfate/lamivudine (Triumeq Combination®)) should be revised to include hepatic impairment and jaundice as adverse reactions.

Four cases of hepatic impairment have been reported in patients exposed to dolutegravir containing products in Japan during the previous three fiscal years.

Reference:
Revision of Precautions, MHLW/PMDA, 18 September 2018 *(www.pmda.go.jp/english/)*

Iodine contrast media (ICM)

Risk of hypothyroidism

Singapore. HSA has announced that the package inserts for products containing iodine contrast media (ICM) will be updated to include warnings of ICM-induced thyroid function changes.

ICM products are used to enhance visualization of vascular structures and organs during radiographic procedures such as angiography and computed tomography. The iodine in ICM products can interfere with thyroid hormone production, which may in turn affect growth and development in infants; and metabolic activity in children and adults.

In April 2017, Health Canada issued a safety alert on the rare potential risk of

hypothyroidism with the use of ICM in certain patients, particularly infants.

HSA has not received any local reports of thyroid dysfunction associated with the use of ICM.

Reference:
Product Safety Alerts, HSA, 14 September 2018 (*http://www.hsa.gov.sg/*)

(See WHO Pharmaceuticals Newsletter No.1, 2018: Possible risk of hypothyroidism in infants in New Zealand)

Isotretinoin

Risk of obsessive compulsive disorder (OCD)

New Zealand. Medsafe has placed oral isotretinoin (Oratane® and Isotane®) on the Medicines Monitoring scheme due to the risk of obsessive compulsive disorder (OCD).

Isotretinoin is indicated to treat severe acne.

CARM has received a report of a 14 year old male who developed OCD and other anxiety symptoms after starting treatment with oral isotretinoin for acne.

There are 106 ICSRs that report OCD with isotretinoin use in the WHO global database for ICSRs, VigiBase. The Medicines Adverse Reactions Committee (MARC) reviewed available information and agreed that at present there is insufficient evidence of a causal association between isotretinoin and OCD. However, the MARC recommended additional monitoring to encourage reporting of OCD cases in patients taking oral isotretinoin.

Reference:
Safety Information, Medsafe, 14 August 2018 *(www.medsafe.govt.nz/)*

(See WHO Pharmaceuticals Newsletter No.5, 2016: Potential risk of psychiatric adverse events in Australia; No.1, 2015: Possible risk of psychiatric disorders in UK)

Methadone

Risk of serious harm in children breastfed by mothers being treated with methadone

Canada. Health Canada has announced a possible link between methadone (Methadose®, Metadol-D®) exposure in children through breast milk and the risk of serious harm (including death).

Methadone is used to treat addiction to opioids, such as heroin, in adults. It works by preventing withdrawal symptoms.

Health Canada reviewed a published article that reported two Canadian cases of death in children who had increased levels of methadone in their blood because they were being breastfed by mothers being treated for opioid addiction. Health Canada also reviewed 13 international cases of methadone toxicity in children exposed through breast milk, 10 of which reported death. A possible link between methadone and the risk of serious harm in children was found in 12 of these cases.

Health Canada's review of the available information found that there may be a link between methadone and the risk of serious harm in children breast fed by mothers taking methadone. Health Canada will be working with the manufacturers of methadone containing products to strengthen the product information, to warn of the risk of serious harm.

Reference:
Summary Safety Review, Health Canada, 3 August 2018 (*www.hc-sc.gc.ca*)

Methotrexate

Risk of teratogenicity

Ireland. The Health Products Regulatory Authority (HPRA) has announced that the product information and Package Leaflet for oral methotrexate will be updated to reflect current knowledge in relation to teratogenicity, use of methotrexate in women of child bearing potential, and in male patients.

Oral methotrexate is indicated for the treatment of active rheumatoid arthritis, adult psoriasis and in a number of oncology related indications. Methotrexate is a known teratogen and is contraindicated for use during pregnancy and lactation.

Women are advised not to become pregnant while taking methotrexate and effective contraception should be used throughout treatment and for at least six months after treatment cessation. It is also advised that male patients taking methotrexate are recommended to use reliable contraception.

HPRA recommends that methotrexate should be administered as a once weekly dose only for rheumatology and dermatology indications.

Reference:
Drug Safety Newsletter, HPRA, August 2018 (*https://www.hpra.ie*)

Neuromuscular blocking agents

Prevention of unintended paralysis through medication errors

Australia. The Therapeutic Goods Administration (TGA) has announced that package labels for medicines containing neuromuscular blocking agents (NMBAs) will include a warning indicating that the product is a paralysing agent.

NMBAs, such as suxamethonium, pancuronium, and vecuronium, are used to cause paralysis during anaesthesia. Errors in the administration of NMBAs present significant risk to patient safety due to potential

for unintended paralysis, respiratory arrest, severe permanent harm and/or death.

Administration errors involving these medicines in Australia can be caused by look-alike selection errors.

Reference:
Medicines Safety Update, TGA, Vol. 9, No. 3, August-September 2018 (*www.tga.gov.au*)

Oseltamivir and other anti-influenza medicines

Potential risk of abnormal behaviour

Japan. MHLW and PMDA have announced that the package insert for oseltamivir (Tamiflu®) should be revised to remove the contraindication for use in patients aged 10 to 19 years. Instead, additional text informing patients and health-care professionals of reports of severe abnormal behaviour (e.g. falls) in male school-age children will be included in the package inserts for oseltamivir and other anti-influenza medicines such as amantadine (Atenegine® and Symmetrel®), baloxavir marboxil (Xofluza®), favipiravir (Avigan®), laninamivir (Inavir®), peramivir (Rapiacta®) and zanamivir (Relenza®).

The contraindication for use of

Pembrolizumab

Risk of immune-mediated adverse reactions

New Zealand. Medsafe has announced that the data sheet for pembrolizumab (Keytruda®) has been updated to include advice on dose modifications in the occurrence of immune-mediated and/or infusion-related adverse reactions.

Pembrolizumab is a monoclonal antibody used to treat some metastatic cancers including melanoma, non-small cell lung carcinoma, classical Hodgkin lymphoma and urothelial carcinoma.

As of 30 June 2018, CARM received 21 reports suspected to be related to the use of pembrolizumab. Reported adverse reactions include: changes in renal function, diabetes related reactions, symptoms of hypophysitis and, a fatal case of pneumonitis.

Reference:
Prescriber Update, Medsafe, September 2018
(www.medsafe.govt.nz/)

(See WHO Pharmaceuticals Newsletter No.5, 2017: Risk of using pembrolizumab for multiple myeloma in combination with immunomodulatory agents in USA; No.4, 2017: Reports of organ transplant rejection in UK)

Prednisone, prednisolone

product safety information for oral and injectable prednisone and prednisolone products by the EMA in July 2017. Health Canada reviewed the potential risk of SRC with the use of oral prednisone and prednisolone products in patients with systemic sclerosis. Two Canadian reports and six published international reports were reviewed and a link between the use of oral prednisone and prednisolone, especially at higher doses, and the risk of SRC in patients with systemic sclerosis was found.

Health Canada will be working with the manufacturers to update the Canadian product safety information for oral prednisone and prednisolone products to inform health-care professionals and patients about this risk.

Reference:
Summary Safety Review, Health Canada, 7 August 2018 (*www.hc-sc.gc.ca*)

Radium-223 dichloride

New restrictions for use

1. Ireland. The HPRA has announced that further restrictions on the use of radium-223 (Xofigo®) will be applied due to the increased risk of fractures.

Radium-223 is used to treat prostate cancer in adult men.

A previous restriction consisted