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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 edition of the Newsletter includes the recommendations from the 16th meeting of the WHO Advisory Committee on Safety of Medicinal Products (ACSoMP).

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Cefepime

Risk of urticaria

India. The National Coordination Centre - Pharmacovigilance Programme of India (NCC-PvPI), Indian Pharmacopeia Commission (IPC) has advised the Central Drugs Standard Control Organisation (CDSCO) to revise the patient information leaflet (PIL) for cefepime to include urticaria as an adverse drug reaction.

Cefepime is indicated for the treatment of pneumonia, bacterial septicaemia, bronchitis, respiratory and urinary tract infections. Between July 2011 and December 2018, NCC-PvPI received seven individual case safety reports (ICSRs) of cefepime associated urticaria. The cases were reviewed by the Signal Review Panel (SRP) at the NCC-PvPI, IPC, and a strong causal relationship between cefepime and urticaria was found. The revision of the package insert was necessary based on the results of the investigation of the currently available evidence.

Reference:
Based on the communication from NCC-PvPI, IPC India (*ipc.gov.in*)

Cefotaxime

Risk of angioedema

India. The NCC-PvPI, IPC has advised the CDSCO to revise the PIL for cefotaxime to incorporate angioedema as a clinically significant adverse drug reaction.

Cefotaxime is an antibacterial indicated for the treatment of infections, septicaemia and prophylaxis of surgical infections. Between July 2011 to July 2018, NCC-PvPI received 16 ICSRs of cefotaxime associated angioedema. The cases were reviewed by SRP, PvPI, IPC and a strong causal relationship between cefotaxime and angioedema was found.

Reference:
Based on the communication from NCC-PvPI, IPC India (*ipc.gov.in*)

Cyclin-dependent kinase 4/6 inhibitors

Rare but severe lung inflammation

USA. The US Food and Drug Administration (FDA) has approved of new warnings of rare but severe inflammation of the lungs in the prescribing information and patient package inserts for palbociclib (Ibrance®), ribociclib (Kisqali®) and abemaciclib (Verzenio®).

Cyclin-dependent kinase 4/6 (CDK 4/6) inhibitors are used to treat adults with hormone receptor-positive, human epidermal growth factor 2-negative, advanced or metastatic breast cancer.

Health-care professionals should monitor patients regularly for pulmonary symptoms indicative of interstitial lung disease and pneumonitis. Patients should not stop taking the medicine without talking to a health-care professional.

Reference:
Safety Alerts for Human Medical Products, US FDA, 13 September 2019 *(www.fda.gov)*

(See WHO Pharmaceuticals Newsletter No.2, 2019: Risk of interstitial lung disease in Japan)

Daratumumab

Risk of reactivation of hepatitis B virus

1. United Kingdom. The Medicines and Healthcare Products Regulatory Agency (MHRA) has announced that the product information for daratumumab will be updated to include the risk of reactivation of hepatitis B virus (HBV).

Daratumumab is indicated for the treatment of adult with newly diagnosed multiple myeloma and relapsed and refractory multiple myeloma.

A recent EU review of worldwide data has identified reports of HBV reactivation in patients treated with daratumumab. There were six cases observed in clinical trials in patients with multiple myeloma.

Previous autologous stem cell transplant and concurrent and/or prior lines of immunosuppressive therapy are risk factors of HBV reactivation.

Health-care professionals should screen all patients for HBV before initiation of daratumumab and monitor patients. Also, they should stop treatment with daratumumab in patients with HBV reactivation and institute appropriate treatment in consultation with experts.

Reference:
Drug Safety Update, MHRA, 19 August 2019 *(www.gov.uk/mhra)*

2. Ireland. The Health Products Regulatory Authority (HPRA) has announced that the product information for daratumumab (Darzalex®) has been updated to include a safety warning about the risk of HBV in patients treated with daratumumab.

Reference:
Drug Safety Newsletter, HPRA, August 2019 *(www.hpra.ie)*

Direct acting oral anticoagulants (DOACs)

Risk of recurrent thrombotic events

1. Australia. The Therapeutic Goods Administration (TGA) has announced that the product information for direct acting oral anticoagulants (DOACs) in Australia is being updated to include information about the increased risk of recurrent thrombotic events in patients diagnosed with antiphospholipid syndrome (APS).

DOACs marketed in Australia are apixaban (Eliquis®), dabigatran etexilate (Pradaxa®) and rivaroxaban (Xarelto®). DOACs are indicated in adults for the prevention of venous thromboembolic events, stroke, systemic embolism, treatment of deep vein thrombosis and pulmonary embolism.

A clinical trial (TRAPS study 1) has shown an increase in the risk of recurrent thrombotic events with rivaroxaban compared to warfarin in patients with APS. While there are currently no completed controlled trials relating to this issue for the other two DOACs in Australia, these medicines may be associated with a similar risk.

Health-care professionals are advised to identify patients who are receiving treatment with a DOAC and review whether continued treatment is appropriate. Patients should be encouraged to discuss any issues or concerns they have about their treatment with a health-care professional.

Reference:
Medicines Safety Update, TGA, 26 August 2019 (*www.tga.gov.au*)

2. New Zealand. Medsafe has announced that an increased rate of recurrent thrombotic events has been noted in patients with antiphospholipid syndrome (APS) treated with rivaroxaban (Xarelto®) compared to those treated with warfarin.

APS patients included in a recently published study were at high risk of thromboembolic events (triple positive for lupus anticoagulant, anticardiolipin and anti-beta-2 glycoprotein I antibodies). Major bleeding occurred in seven percent of patients in the rivaroxaban group compared to three percent of patients in the warfarin group.

There are no completed similar trials for the other DOACs available in New Zealand (apixaban (Eliquis®) and dabigatran (Pradaxa®)), but since the mechanism of action is similar to rivaroxaban, a precautionary approach is recommended with all DOACs.

Reference:
Prescriber Update, Medsafe, September 2019 (*www.medsafe.govt.nz/*)

(See WHO Pharmaceuticals Newsletter No.4, 2019: Increased risk of recurrent thrombotic events in UK; No.3, 2016: Risk of thrombocytopenia in Japan; No.2, 2016: Benefit-risk balance of rivaroxaban: unchanged in EU; No.6, 2013: Apixaban, dabigatran and rivaroxaban in UK)

Dopamine receptor agonists

Risk of drug withdrawal syndrome

Japan. The Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA) have announced that the package inserts for dopamine receptor agonists should be revised to include drug withdrawal symptoms such as apathy, anxiety, depression, fatigue, sweating and pain as adverse drug reactions.

Dopamine receptor agonists are indicated to treat a variety of conditions, for example Parkinson's disease. They include ropinirole (ReQuip®), pramipexole (Mirapex-LA®), talipexole (Domin®), rotigotine (Neupro patch®) and cabergoline (Cabaser®).

Cases of drug withdrawal syndrome have been reported in Japan and overseas. Taking into consideration the potential mechanisms in which dopamine receptor agonists can induce drug withdrawal syndrome, MHLW and PMDA have concluded that the revision of the package inserts was necessary.

Reference:
Revision of Precautions, MHLW/PMDA, 22 August 2019 (*www.pmda.go.jp/english/*)

Febuxostat

Increased risk of cardiovascular death and all-cause mortality

Ireland. The HPRA has announced that the product information for febuxostat will be updated to include the risk of cardiovascular death and all-cause mortality in patients with gout and a history of major cardiovascular disease, following results of a clinical study (the CARES study).

Febuxostat is a non-purine selective inhibitor of xanthine oxidase indicated for the treatment of chronic hyperuricaemia.

The CARES study is a randomised, double-blind trial that recruited patients from USA, Canada and Mexico. The incidence of cardiovascular death was significantly higher in the group that received febuxostat than in the group that received allopurinol. The rate of all-cause mortality was also higher in patients taking febuxostat than in those taking allopurinol.

Patients with pre-existing major cardiovascular disease should not be treated with febuxostat unless no other treatment options are appropriate.

Reference:
Drug Safety Newsletter, HPRA, August 2019 (*www.hpra.ie*)

(See WHO Pharmaceuticals Newsletter No. 4, 2019: Potential risk of cardiovascular death in Japan; No.2, 2019: Increased risk of death in USA; No.6, 2017: Potential risk of heart-related death in USA; No.3, 2016: Risk of heart failure in Canada)

Fingolimod

Risk of congenital malformations

Europe. The European Medicines Agency (EMA) has recommended that fingolimod (Gilenya®) must not be used in pregnant women of child bearing age who are not using effective contraception, due to the risk of birth defects.

Fingolimod is indicated to treat adults and children over 10 years of age with highly active relapsing-remitting multiple sclerosis.

The recommendations follow a review triggered by reports suggesting that the risk of birth defects in infants exposed to fingolimod during pregnancy is twice as high than the estimated risk in the general population, which is 2-3 % according to the European network of population-based registries for the epidemiological surveillance of congenital anomalies (EUROCAT). Reported major malformations in infants included congenital heart diseases, renal abnormalities and musculoskeletal abnormalities.

Health-care professionals should ensure that female patients of childbearing potential are informed of the risks and that effective contraception is used during treatment and for two months after treatment discontinuation. If a woman becomes pregnant during treatment, fingolimod must be discontinued.

Reference:
EMA, 26 July 2019
(*www.ema.europa.eu*)

Freeze-dried BCG vaccine

Risk of meningitis

Japan. The MHLW and the PMDA have announced that the package insert for freeze-dried BCG vaccine (Freeze-Dried BCG Vaccine®) should be revised to include meningitis as an adverse drug reaction.

Freeze-dried BCG vaccine is indicated for prophylaxis of tuberculosis.

One case of tuberculous meningitis has been reported in Japan during the previous three fiscal years. A causal relationship between the vaccine and event could not be excluded. No patient mortalities have been reported. MHLW and PMDA have concluded that revision of the package insert was necessary based on the investigation of the currently available evidence.

Reference:
Revision of Precautions, MHLW/PMDA, 22 August 2019
(*www.pmda.go.jp/english/*)

Glibenclamide

Risk of palpitations

India. The NCC-PvPI, IPC has advised CDSCO to request the revision of the PIL for glibenclamide to include palpitations as an adverse drug reaction.

Glibenclamide is used for the treatment of diabetes mellitus. Between July 2011 and December 2018, NCC-PvPI received 12 ICSRs of glibenclamide associated palpitation. The NCC-PvPI also assessed 103 relevant reports from the WHO global database for reports of adverse events and the literature. A signal was published by the WHO Collaborating Centre for International Drug Monitoring (Uppsala Monitoring Centre, UMC) which identified this reaction as a signal in the Asian population. The cases were reviewed by SRP at the NCC-PvPI, IPC, and a strong causal relationship between glibenclamide and palpitations was suggested. The revision of the PIL was necessary based on the results of the investigation of the currently available evidence.

Reference:
Based on the communication from NCC-PvPI, IPC India (*ipc.gov.in*)

(See WHO Pharmaceuticals Newsletter No. 2, 2019: (Signal) Glibenclamide/glyburide and palpitations in the Asian population)

Liposomal medicines

Name change to avoid medication errors

Europe. The EMA has announced that all marketing authorisation holders of medicines containing liposomal drug delivery systems are requested to change the names of these medicines to avoid medication errors.

This name change aims to make a clearer distinction between liposomal and non-liposomal formulations of the same active substance to avoid medication errors. The two formulations may have different biodistribution and release properties, therefore confusion between formulations can occur and pose serious health risks to patients.

Following consultations with the Pharmacovigilance Risk Assessment Committee

(PRAC), the following actions were agreed:

"Liposomal" or "pegylated liposomal" should be added after the invented name and before the strength in the summary of product characteristics of the medicines containing liposomal drug delivery system. Also, the European Directorate for the Quality of Medicines (EDQM) standard term "dispersion", which includes liposomes in the definition, should be used consistently throughout the product information.

Reference:
EMA, 31 July 2019
(www.ema.europa.eu)

Modafinil

Potential risk of congenital malformations

Ireland. The HPRA has announced that the product information for modafinil products (Nuvigil® and Provigil®) will be amended to include the current understanding of the risk of congenital malformations in the offspring of women treated with modafinil during pregnancy.

Modafinil is used for excessive sleepiness associated with narcolepsy.

The HPRA have received reports of major congenital malformations including treatment options should be discussed.

Reference:
Drug Safety Newsletter, HPRA, August 2019 *(www.hpra.ie)*

Montelukast

Risk of dysphemia

Ireland. The HPRA has announced that existing warnings in the product information for montelukast will be updated to include the risk of neuropsychiatric reactions.

Montelukast is indicated for the prophylaxis and treatment of asthmatic conditions. It is known to be associated with neuropsychiatric reactions including nightmares, insomnia, somnambulism, anxiety, agitation, aggressive behaviour, depression and psychomotor hyperactivity.

The EMA's PRAC completed a periodic review of cases reporting dysphemia with the use of montelukast, and an association between montelukast and dysphemia as well as other closely related speech disorders cannot be excluded.

Health-care professionals and patients should be alert for the occurrence of neuropsychiatric reactions with montelukast.

Reference:
Drug Safety Newsletter, HPRA, August 2019 *(www.hpra.ie)*

Naltrexone/bupropion

Risk of somnolence and loss of consciousness

Ireland. The HPRA has announced that the product information for naltrexone/bupropion will be updated to include the risk of somnolence, and rare loss of consciousness or seizure.

Naltrexone/bupropion is indicated for the management of weight in obese and overweight adults.

An EU review of cumulative data has identified somnolence and loss of consciousness with naltrexone/bupropion, which can affect the ability to drive, operate machinery or perform dangerous tasks.

Health-care professionals should advise patients not to drive, operate machinery or perform dangerous activities while taking naltrexone/bupropion until the patient understands how the medicine affects the patient. If the patient experiences adverse events that may impair driving, the patient must not drive. It is against the law to drive if the patient's ability is impaired by any medicine.

Reference:
Drug Safety Update, MHRA, 19 August 2019
(www.gov.uk/mhra)

Ofloxacin

Risk of Stevens Johnson Syndrome (SJS) / Toxic Epidermal Necrolysis (TEN)

India. The NCC-PvPI, IPC has advised the CDSCO to request that the PIL for ofloxacin is