World Health Organization

WHO Pharmaceuticals NEWSLETTER

2018 No.6

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 the 41st Annual Meeting of Representatives of National Pharmacovigilance Centres participating in the WHO Programme for International Drug Monitoring and from an Advanced Workshop for Strengthening Pharmacovigilance (PV) Systems.

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Fingolimod

Risk of worsening of multiple sclerosis after stopping

USA. The US Food and Drug Administration (FDA) has updated the prescribing information for fingolimod (Gilenya®) to include a warning about the risk of worsening of multiple sclerosis (MS) when the medicine is stopped.

Fingolimod is indicated for the treatment of relapsing MS.

Health-care professionals should inform patients before starting treatment about the potential risk of a severe increase in disability after stopping fingolimod.

Also, patients should be carefully observed for evidence of an exacerbation of their MS and treated appropriately when fingolimod is stopped.

Reference:
Safety Alerts for Human Medical Products, US FDA, 20 November 2018
(www.fda.gov)

Fluoroquinolone and quinolone antibiotics

Risk of long-lasting and disabling effects

Europe. The European Medicines Agency (EMA) has announced that the prescribing information for individual fluoroquinolone antibiotics will be updated to include new restrictions on the use due to risk of long-lasting and disabling adverse effects such as inflamed tendon, muscle pain, feeing pins, tiredness, depression, confusion, and sleep disorders.

Fluoroquinolones and quinolones are a class of broad-spectrum antibiotics that are active against bacteria of both Gram-negative and Gram-positive classes.

The restrictions were made following recommendations made by the Pharmacovigilance Risk Assessment Committee (PRAC). PRAC evaluated the adverse effects of fluoroquinolone and quinolone antibiotics. The review incorporated the views of patients, health-care professionals and academics presented at EMA's public hearing.

PRAC recommended that some medicines, including all those that contain a quinolone antibiotic (cinoxacin, flumequine, nalidixic acid and pipemidic acid), should be removed from the market as they are authorised for infections that should no longer be treated with quinolones. PRAC recommendations outlined situations in which the remaining fluoroquinolone antibiotics should not be used (e.g. to treat infections that might get better without treatment); and emphasized that fluoroquinolones should be used with caution in patients at risk (e.g. the elderly, patients with kidney problems and patients who have had an organ transplantation).

EMA's human medicines committee (CHMP) has endorsed the recommendations of PRAC.

Reference:
EMA, 5 October and 16 November 2018
(www.ema.europa.eu)

(See WHO Pharmaceuticals Newsletter No.4, 2018: Strengthened warnings on the risk of hypoglycaemia and mental health adverse effects in USA; No.2, 2017: Potential risk of persistent and disabling side effects in Canada; No.5, 2016: Disabling and potentially permanent adverse effects of the tendons, muscles, joints, nerves, and central nervous system in USA; No.3, 2016: Restricting use in USA; No.5, 2012: Tendon rupture and tendinitis associated with the use of quinolone antibiotics in New Zealand)

HMG-CoA reductase inhibitors and fibrates: co-administration

Risk of rhabdomyolysis: contraindication removed.

Japan. The Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA) have announced that the package inserts for hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins: atorvastatin (Lipitor®), simvastatin (Lipovas®), pitavastatin (Livalo®), pravastatin (Mevalotin®), fluvastatin (Lochol®), rosuvastatin (Crestor®), amlodipine basilate/atorvastatin (Caduet®) and ezetimibe/atorvastatin (Atozet®)) and fibrates (clinofibrate (Lipoclin®), clofibrate (Clofibrate®), fenofibrate (Tricor® and Lipidil®), bezafibrate (Bezatol®) and pemafibrate (Parmodia®)) should be revised to remove the contraindications regarding co-administration of HMG-CoA reductase inhibitors with fibrates.

HMG-CoA reductase inhibitors are indicated for hypercholesterolemia/familial hypercholesterolemia or hyperlipidaemia/familial hyperlipidaemia, whereas fibrates are indicated for hyperlipidaemia.

Available post marketing information concerning the co-administration of HMG-CoA reductase inhibitors and fibrates were investigated. There were limited data in patients with abnormal renal function and cases that reported the co-administration of these medicines were rare. There is a risk of rhabdomyolysis accompanied by rapid deterioration of renal function when HMG-CoA reductase inhibitors are co-administered with fibrates. If prescribing this combination is unavoidable, clinical laboratory

tests examining renal function should be performed periodically.

The PMDA concluded that the contraindication of combining HMG-CoA reductase inhibitors and fibrates should be removed from the package insert, however a precaution regarding rhabdomyolysis in patients with abnormal renal function values associated with this combination will remain.

Reference:
Revision of Precautions, MHLW/PMDA, 16 October 2018 *(www.pmda.go.jp/english/)*

(See WHO Pharmaceuticals Newsletter No.6, 2016: Risk of immune-mediated necrotizing myopathy in Japan; No.4, 2015: Risk of rhabdomyolysis by drug-drug interaction in Ireland)

Hydrochlorothiazide

Risk of non-melanoma skin cancer

United Kingdom. The Medicines and Healthcare Products Regulatory Agency (MHRA) has announced that the Summary of Product Characteristics and Patient Information Leaflets for hydrochlorothiazide containing products have been updated to include the risk of non-melanoma skin cancer as an adverse effect.

Hydrochlorothiazide is indicated for hypertension and oedema associated with cardiac or hepatic diseases.

Pharmacoepidemiological studies have shown a dose-dependent risk of non-melanoma skin cancer with exposure to increasing cumulative doses of hydrochlorothiazide.

Health-care professionals are advised to inform patients taking hydrochlorothiazide of the risk of non-melanoma skin cancer, particularly when used long-term, and advise them to report and check regularly for new or changed skin lesions or moles.

Patients are also advised to limit exposure to sunlight and UV rays, and use adequate protection to minimise the risk of skin cancer.

Reference:
Drug Safety Update, MHRA, 14 November 2018 *(www.gov.uk/drug-safety-update)*

Insulin-containing products: cartridges and pre-filled pens

Risk of medication errors from extraction of insulin

Ireland. The Health Products Regulatory Authority (HPRA) has updated the product information for insulin cartridges for reusable pens and prefilled (disposable) pens to include a warning on the risk of potential medication errors when extracting insulin, which could lead to serious hyper and/or hypoglycaemic episodes.

Insulin pens and cartridges for reusable pens are for single patient use only. Blood and biological matter can regurgitate into the insulin cartridge during injection. Re-using a cartridge or pen for another patient exposes the second patient to a risk of transmission of any blood borne pathogens.

The HPRA provided advice on actions to take if a device is not working and emphasized that extraction of insulin-containing product from cartridges and pre-filled pens via a syringe is not recommended.

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

Ketoconazole

Risk of severe liver injury and adrenal gland problems

Ghana. The Food and Drugs Authority in Ghana has suspended the registration, importation and manufacturing of oral ketoconazole products due to the risk of severe liver injury, adrenal gland problems and harmful drug interactions.

Ketoconazole is a synthetic antifungal agent available as a preparation for oral administration and as a cream or shampoo for topical application.

Risk minimization measures recommended by the Technical Advisory Committee on Safety of Medicines (TAC-SM) in 2013 were not effective in preventing the risk of liver related adverse drug reactions associated with the use of oral ketoconazole. The use of less harmful alternatives to oral ketoconazole (itraconazole, terbinafine and fluconazole) should be used in place of oral ketoconazole.

Reference:
Food and Drugs Authority, Ghana, 2 November 2018 *(https://fdaghana.gov.gh)*

(See WHO Pharmaceuticals Newsletter No.5, 2013: Potentially fatal liver injury, risk of drug interactions and adrenal gland problems in USA; Suspension of marketing authorisations for oral ketoconazole recommended in Europe; No.4, 2013: Risk of potentially fatal liver toxicity in Canada)

Lamotrigine

Risk of haemophagocytic syndrome

Japan. MHLW and PMDA have announced that the package insert for lamotrigine (Lamictal®) should be revised to include haemophagocytic syndrome as an adverse reaction.

Lamotrigine is indicated for several types of seizures in epileptic patients.

Cases of haemophagocytic syndrome have been reported in patients treated with lamotrigine in Japan and overseas. MHLW/PMDA concluded that revision of the package insert was necessary based on the results of their

investigation using currently available information.

Reference:
Revision of Precautions, MHLW/PMDA, 23 October 2018 *(www.pmda.go.jp/english/)*

(See WHO Pharmaceuticals Newsletter No.3, 2018: Serious immune system reaction in USA)

Lenvatinib

Risk of pneumothorax

Japan. MHLW and PMDA have announced that the package insert for lenvatinib (Lenvima®) should be revised to include pneumothorax as an adverse reaction.

Lenvatinib is indicated for unresectable thyroid cancer and unresectable hepatocellular carcinoma.

There was a total of 11 cases reporting pneumothorax in Japan during the last three fiscal years. In ten of the 11 cases, a causal relationship with lenvatinib could not be excluded. One of the 11 cases reported a fatality. MHLW/PMDA concluded that revision of the package insert was necessary based on the results of their investigation using currently available information.

Reference:
Revision of Precautions, MHLW/PMDA, 23 October 2018 *(www.pmda.go.jp/english/)*

Ponatinib

Risk of posterior reversible encephalopathy syndrome (PRES)

United Kingdom. The MHRA has updated the Summary of Product Characteristics and Patient Information Leaflet for ponatinib to include the risk of posterior reversible encephalopathy syndrome (PRES) as an adverse reaction.

PRES is a neurological disorder that can present with signs and symptoms such as seizure, headache, decreased alertness, vision loss and neurological disturbances.

Ponatinib is indicated for adult patients with chronic myeloid leukaemia or Philadelphia chromosome positive acute lymphoblastic leukaemia.

Five cases of posterior reversible encephalopathy syndrome (PRES) have been identified in patients receiving ponatinib (Iclusig®) in a routine EU review.

Health-care professionals are advised to interrupt treatment if PRES is confirmed and resume treatment only once the event is resolved and if the benefit of continuing treatment outweighs the risk of PRES.

Reference:
Drug Safety Update, MHRA, 11 October 2018 *(www.gov.uk/drug-safety-update)*

Ritonavir

Interaction with levothyroxine leading to reduced thyroxine levels

United Kingdom. The MHRA has updated Summaries of Product Characteristics and Patient Information Leaflets for ritonavir-containing medicines and levothyroxine to include a potential drug interaction which could lead to reduction in thyroxine levels.

An EU review identified reduced thyroxine levels in patients taking ritonavir-containing products and levothyroxine concomitantly.

Ritonavir is indicated in combination with other antiretroviral agents for the treatment of HIV infected patients, and for the treatment of chronic hepatitis C.

Health-care professionals are advised to monitor thyroid-stimulating hormone (TSH) in patients treated with levothyroxine for at least the first month after the start and end of ritonavir treatment.

Reference:
Drug Safety Update, MHRA, 11 October 2018 *(www.gov.uk/drug-safety-update)*

(See WHO Pharmaceuticals Newsletter No.1, 2017: Risk of adrenal suppression due to a pharmacokinetic interaction in UK; No.3, 2012: Drug Interactions with ritonavir-boosted Human Immunodeficiency Virus (HIV) protease inhibitor drugs in USA)

Secukinumab

Risk of inflammatory bowel disease

Japan. MHLW and PMDA have announced that the package insert for secukinumab (Cosentyx®) should be revised to include risk of inflammatory bowel disease as an adverse reaction.

Secukinumab is indicated for psoriasis vulgaris, psoriatic arthritis and pustular psoriasis in patients who were not sufficiently responsive to conventional therapies.

Cases of inflammatory bowel disease have been reported in patients treated with secukinumb in Japan. MHLW/PMDA concluded that revision of the package insert was necessary based on the results of their investigation of currently available information.

Reference:
Revision of Precautions, MHLW/PMDA, 23 October 2018 *(www.pmda.go.jp/english/)*

Zoster and Influenza vaccines

Possible risk of lichen planus or lichenoid drug eruption

New Zealand. Medsafe has placed zoster and influenza vaccines on the medicines monitoring scheme to obtain further information on the risk of lichen planus or lichenoid drug eruption.

Zoster vaccine (Zostavax®) is a live attenuated virus vaccine used to prevent herpes zoster (shingles). Annual influenza vaccination (Afluria Quad®, Fluarix Tetra®, FluQuadri® and Influvac Tetra®) is an important measure for preventing influenza infection and mortality. Patients can receive both vaccines at the same time using separate syringes and injection sites.

The potential safety signal was triggered by a report received by the Centre for Adverse Reaction Monitoring (CARM). The report describes a 67-year-old female patient who experienced a lichen planus rash after receiving both zoster and influenza vaccines.

The overall benefit-harm balance of zoster and influenza vaccines remains positive.

Reference:

Early Warning System – Monitoring Communication Medsafe, 26 October 2018 *(www.medsafe.govt.nz/)*