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WHO Pharmaceuticals NEWSLETTER

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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:

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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.

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Risk of palpitations

India. The National Coordination Centre - Pharmacovigilance Programme of India (NCC-PvPI) has made a recommendation to the Central Drugs Standard Control Organisation (CDSCO) to request that the patient information leaflet (PIL) for alfuzosin should be revised to incorporate palpitations as a clinically significant adverse drug reaction.

Alfuzosin is used for the treatment of benign prostatic hyperplasia.

Between July 2011 and November 2019, the NCC-PvPI received a total of three individual case safety reports (ICSRs) of alfuzosin associated palpitations. The cases were evaluated by the Signal Review Panel (SRP), PvPI, and Indian Pharmacopeia Commission (IPC) who found a strong causal relationship between alfuzosin associated palpitations.

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

Baricitinib

Increased risk of diverticulitis

United Kingdom. The Medicines and Healthcare Products Regulatory Agency (MHRA) has announced that the risk of diverticulitis has been added to the product information for baricitinib (Olumiant®).

Baricitinib is a Janus kinase inhibitor and is indicated for the treatment of moderate to severe active rheumatoid arthritis in adults.

A European review has assessed cases of diverticulitis associated with baricitinib reported in clinical trials and in post-marketing use worldwide. There were 21 cases of diverticulitis.

For post-marketing use of baricitinib outside of clinical trials, 35 spontaneous cases of diverticulitis were reported worldwide up until 2019. Of these, 25 cases included a medical history of diverticulitis and/or chronic use of NSAIDs, corticosteroids or opioids, which are known important risk factors for diverticulitis.

Health-care professionals are advised to use baricitinib with caution in patients with diverticular disease and in those concomitantly treated with medications associated with an increased risk of diverticulitis.

Also, health-care professionals should advise patients on baricitinib to seek immediate medical care if they experience severe abdominal pain especially accompanied with fever, nausea and vomiting or other symptoms of diverticulitis.

Reference:
Drug Safety Update, MHRA, 26 August 2020 *(www.gov.uk/mhra)*

Benidipine

Risk of photosensitivity reaction

India. The NCC-PvPI has made a recommendation to the CDSCO to request that the PIL for benidipine is revised to incorporate photosensitivity as a clinically significant adverse drug reaction.

Benidipine is used for the treatment of hypertension and long term prophylactic management of angina pectoris.

Between July 2011 and November 2019, the NCC-PvPI received a total of five ICSRs reporting benidipine associated photosensitivity reaction. The cases were evaluated by the SRP, PvPI, and IPC who found a strong causal relationship between benidipine and associated photosensitivity reaction.

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

Canagliflozin

Risk of amputations removed

USA. The US Food and Drug Administration (FDA) has announced that the boxed warning about the risk of amputation with the use of canagliflozin (Invokana® and Invokamet®) has been removed from the prescribing information.

Canagliflozin is a sodium-glucose cotransporter-2 (SGLT2) inhibitor. It lowers blood sugar by causing the kidneys to remove sugar from the body through the urine. It is used to reduce the risk of major heart-related events such as heart attack, stroke or death in patients with type 2 diabetes, and to reduce the risk of end-stage kidney disease, worsening of kidney function, heart-related death, and being hospitalized for heart failure in certain patients with type 2 diabetes and diabetic kidney disease.

The FDA's review of new clinical trial data demonstrated additional heart and kidney related benefits.

Safety information from recent clinical trials also suggests that the risk of amputation, while still increased with canagliflozin, is lower than previously described. The FDA has concluded that the boxed warning should be removed.

Health-care professionals and patients should continue to recognize the importance of preventative foot care and

monitor for new pain, tenderness, sores, ulcers and infections in the legs and feet.

Reference:
MedWatch, US FDA, 26 August 2020 *(www.fda.gov)*

(See also WHO Pharmaceuticals Newsletter No.3, 2020: Risk of diabetic ketoacidosis in UK; No.1, 2020: Updated advice on monitoring ketone bodies in Ireland)

Hydroxychloroquine

Risk of prolonged QT, ventricular tachycardia

Japan. The Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA) have announced that the package insert for hydroxychloroquine (Plaquenil®) should be revised to include prolonged QT and ventricular tachycardia as adverse drug reactions.

Hydroxychloroquine is indicated for cutaneous lupus erythematosus and systemic lupus erythematosus.

A total of four cases of prolonged QT and ventricular tachycardia (including torsades de pointes) were reported in patients that used hydroxychloroquine in Japan during the previous three years. A causal relationship between the drug and event could not be established for any of these cases. One case of patient mortality has been reported and a causal relationship could not be established for that case.

The MHLW and PMDA have concluded that a revision of the package insert is necessary.

Reference:
Revision of Precautions, MHLW/PMDA, 8 September 2020 *(www.pmda.go.jp/english/)*

Opioid

Naloxone helps reverse opioid overdose

USA. The FDA has requested that manufacturers of opioid pain relievers and medicines to treat opioid use disorder (OUD), add new recommendations about naloxone to the prescribing information.

Opioids have serious risks including misuse and abuse, addiction, overdose and death. Naloxone is used to block the effects of opioids (e.g. countering decreased breathing) and can help reverse opioid overdose to prevent death.

The FDA encourages health-care professionals to raise awareness of the availability of naloxone when they prescribe opioid pain relievers or medicines to treat OUD.

Health-care professionals should educate patients on how to recognize respiratory depression and how to administer naloxone.

Reference:
MedWatch, US FDA, 23 July 2020 *(www.fda.gov)*

Pentoxifylline

Risk of palpitations

India. The NCC-PvPI has made a recommendation to the CDSCO to request the revision of the PIL for pentoxyphylline to incorporate palpitations as a clinically significant adverse drug reaction.

Pentoxifylline is a vasodilator indicated for the treatment of atrial and atriovenous circulatory disorder.

Between July 2011 and November 2019, the NCC-PvPI received a total of four ICSRs reporting palpitations associated with pentoxifylline use. The cases were evaluated by the SRP, PvPI, and IPC who found a strong causal relationship between pentoxifylline use and palpitations.

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

Piperacillin, Tazobactam

Risk of acute generalised exanthematous pustulosis (AGEP)

India. The NCC-PvPI has made a recommendation to the CDSCO to request that the PIL for piperacillin/tazobactam is revised to incorporate acute generalised exanthematous pustulosis (AGEP) as a clinically significant adverse drug reaction.

Piperacillin/tazobactam is used for the treatment of moderate to severe lower respiratory tract infections.

Between July 2011 and November 2019, NCC-PvPI received a total of six ICSRs reporting piperacillin/tazobactam associated AGEP. The cases were evaluated by the SRP, PvPI, and IPC who found a strong causal relationship between piperacillin/tazobactam use and AGEP.

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

Relugolix

Risk of severe abnormal uterine bleeding in patients with submucosal fibroid

Japan. The MHLW and the PMDA have announced that the package insert for relugolix (Relumina®) should be revised

to include the risk of severe abnormal uterine bleeding in patients with submucosal fibroid in the careful administration section.

Relugolix is indicated for relief of menorrhagia, lower abdominal pain, lumbar pain and anaemia associated with uterine fibroids.

A total of 13 cases of severe abnormal uterine bleeding were reported in patients using relugolix in Japan during the previous three years. For 10 of the 13 cases, a causal relationship between the drug and event was reasonably possible. No patient mortalities have been reported.

Patients should be carefully monitored and if any abnormalities are observed, appropriate measures should be taken. Patients should be instructed to immediately contact a medical institution if they experience heavy bleeding at one time.

Reference:
Revision of Precautions, MHLW/PMDA, 8 September 2020 *(www.pmda.go.jp/english/)*

Tinidazole

Risk of skin hyperpigmentation

India. The NCC-PvPI has made a recommendation to the CDSCO to request that the PIL for tinidazole is revised to incorporate skin hyperpigmentation as a clinically significant adverse drug reaction.

Tinidazole is used for the treatment of amoebiasis and giardiasis in adult patients only and in the treatment of anaerobic infections.

Between July 2011 and November 2019, the NCC-PvPI received a total of 13 ICSRs of tinidazole associated skin hyperpigmentation. The cases were evaluated by the SRP, PvPI, and IPC who found a strong causal relationship between tinidazole use and skin hyperpigmentation.

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

Ulipristal acetate

Revocation of marketing authorizations recommended

Europe. The European Medicines Agency (EMA) has announced that the Pharmacovigilance Risk Assessment Committee (PRAC) has recommended the revocation of the marketing authorizations for ulipristal acetate preparations (Esmya® and generic medicines) when used to treat symptoms of uterine fibroids, due to the risk of liver injury.

Ulipristal acetate is indicated for the treatment of moderate to severe symptoms of uterine fibroids in women who have not reached the menopause. Ulipristal acetate is also used as a single-dose medicine for emergency contraception. The recommendation does not apply for use of ulipristal as a contraception.

The PRAC considered all the available evidence including cases of serious liver injury. Because it was not possible to identify which patients were most at risk or measures that could reduce the risk, the PRAC concluded that the risks of the medicines outweighed the benefits and that they should not be marketed in the EU.

The PRAC recommendation will now be forwarded to EMA's Committee for Medicinal Products for Human Use (CHMP), which will adopt the EMA's opinion.

Reference:
EMA, 4 September 2020 *(www.ema.europa.eu)*

(See also WHO Pharmaceuticals Newsletter No.3, 2020: Licence suspension due to liver injury in UK; No.1, 2020: Risk of hepatic injury in EU; No.5, 2018: New measures to minimize risk of liver injury in EU and Canada)

X-ray contrast media

Risk of contrast-induced encephalopathy

Japan. The MHLW and the PMDA have announced that the package inserts for X-ray contrast media including iopamidol (Iopamiron®), iohexol (Omnipaque®) and meglumine iotroxate (Biliscopin®) should be revised to include contrast-induced encephalopathy as an adverse drug reaction.

X-ray contrast media is indicated for several methods such as arteriography by digital X-ray method, computer-assisted tomography and intravenous urography.

A total of 11 cases of contrast-induced encephalopathy in patients exposed to X-ray contrast media have been reported in Japan during the previous three years, including five cases for which a causal relationship between the drug and event was reasonably possible.

The MHLW and PMDA have concluded that a revision of the package inserts was necessary.

Reference:
Revision of Precautions, MHLW/PMDA, 20 July 2020 *(www.pmda.go.jp/english/)*

Allopurinol

Interaction with azathioprine or mercaptopurine: Bone marrow suppression

New Zealand. The Medsafe has announced that co-administration of allopurinol with azathioprine or mercaptopurine can lead to life-threatening bone marrow suppression.

Allopurinol is a xanthine oxidase inhibitor used to reduce hyperuricaemia in patients with gout. Azathioprine is an immunosuppressive agent, and mercaptopurine is a cytotoxic drug used in the treatment of leukaemia. Azathioprine is metabolized to mercaptopurine, which is metabolized into an inactive compound by xanthine oxidase.

Inhibition of xanthine oxidase by allopurinol increases plasma concentrations of the active metabolites of azathioprine and mercaptopurine, which may lead to life-threatening leukopenia, thrombocytopenia or pancytopenia.

Concomitant use of allopurinol and azathioprine or mercaptopurine is not recommended. If co-administration is necessary, the dose or azathioprine or mercaptopurine should be reduced.

Up to June 2020, the Centre for Adverse Reactions Monitoring (CARM) had received 14 cases describing an interaction between allopurinol and azathioprine. In 13 of the cases the patients experienced bone marrow suppression. Two recent cases reported pancytopenia.

Reference:
Prescriber Update, Medsafe, September 2020
(www.medsafe.govt.nz/)

(See also WHO Pharmaceuticals Newsletter No.1, 2016: Interaction with 6-mercaptopurine and azathioprine in Australia)

Beta-lactam antibiotics, non-steroidal anti-inflammatory drugs, intravenous iron preparations and rocuronium

Risk of Kounis syndrome

New Zealand. The Medsafe has reminded health-care professionals that Kounis syndrome has been associated with a variety of medicines including beta-lactam antibiotics, non-steroidal anti-inflammatory drugs, intravenous iron preparations and rocuronium.

Kounis syndrome is a hypersensitivity reaction affecting the coronary arteries. The underlying mechanism for Kounis syndrome is mast cell activation and release of inflammatory mediators.

The CARM recently received a report of coronary artery spasm associated with the use of amoxicillin/clavulanic acid in a male patient.

Management of Kounis syndrome involves removing the offending allergen, managing the acute coronary vasospasm, and treating the allergic response. Careful selection and use of medicines are needed when managing the acute condition to avoid further histamine release or exacerbation of coronary vasospasm.

Reference:
Prescriber Update, Medsafe, September 2020
(www.medsafe.govt.nz/)

Clozapine, other antipsychotics

Monitoring blood concentrations advised

United Kingdom. The MHRA has announced that monitoring blood concentrations of clozapine preparations (Clozaril®, Denzapine® and Zaponex®) for toxicity is advised in certain clinical situations. Blood level monitoring of other antipsychotics for toxicity may also be helpful in certain circumstances.

Clozapine and other antipsychotic medicines are indicated to treat symptoms related to psychosis, including schizophrenic disorders and some forms of bipolar disorder.

The MHRA received two separate reports raising concerns regarding the need for monitoring of clozapine blood levels in one report and monitoring antipsychotic blood levels during long-term high-dose antipsychotic use in the other.

Expert Advisory Groups of the Commission on Human Medicines considered safety data for clozapine and other antipsychotic drugs and advised that blood concentrations of clozapine should be monitored for toxicity in certain clinical situations (e.g. a patients stopping smoking, with pneumonia, and/or with poor metabolism). The Groups also advised that blood level monitoring of other antipsychotic drugs may be helpful in certain circumstances.

Also, health-care professionals are advised that if blood clozapine level monitoring is carried out, this should be in addition to the required blood tests to manage the risk of agranulocytosis.

Reference:
Drug Safety Update, MHRA, 26 August 2020
(www.gov.uk/mhra)

Cyproterone

Risk of meningioma

New Zealand. The Medsafe has announced that exposure to cyproterone may increase the risk of meningioma.

Cyproterone is an antiandrogen treatment indicated for: inoperable carcinoma of the prostate, reduction of drive in sexual deviations in men, and for severe signs of androgenisation in women.

A recent cohort study in France has demonstrated a dose-dependent association between cyproterone acetate and the risk of meningioma. This risk increases as the cumulative dose rises.

Up until March 2020, the CARM received two reports of meningioma associated with cyproterone. Both patients were women who had been treated with cyproterone for more than 10 years.

Cyproterone is contraindicated in patients with a meningioma or a history of meningioma. If a patient treated with cyproterone is diagnosed with meningioma, treatment must be permanently stopped.

Reference:
Prescriber Update, Medsafe, September 2020
(www.medsafe.govt.nz/)

(See also WHO Pharmaceuticals Newsletter No.4, 2020: Restrictions in use due to risk of meningioma in Ireland and UK; No.3, 2020: Restrictions in use due to risk of

stopping denosumab (Prolia®) for osteoporosis.

Denosumab is indicated for treatment of osteoporosis and bone loss associated with hormone ablation in men with prostate cancer or with long-term systemic glucocorticoid therapy in adult patients.

From 2015 to June 2020, 44 cases of vertebral fracture, including multiple fractures, have been reported in the UK in post-marketing settings in patients after stopping or delaying ongoing treatment with denosumab.

Health-care professionals should evaluate a patient's individual factors for benefits and risks before initiating treatment with denosumab, particularly in patients at increased risk of vertebral fractures (e.g. previous vertebral fracture). Patients should not stop denosumab without specialist review.

Reference:
Drug Safety Update, MHRA, 26 August 2020
(www.gov.uk/mhra)

(See also WHO Pharmaceuticals Newsletter No.3, 2019: Risk of hypercalcaemia and multiple vertebral fractures in Japan; No.4, 2018: Risk of multiple vertebral fractures in Japan)

Emollient

Risk of severe and fatal burns

the presence of a naked flame, fabric with emollient dried on is easily ignited. Although emollients are not flammable in themselves or when on the skin, but when dried on to fabric they act as an accelerant.

In July 2020, the MHRA launched a campaign to raise awareness of this important risk. A toolkit of resources is available for health and social care professionals to support the safe use of emollients.

Health-care professionals are encouraged to inform patients and caregivers of the risks with emollient products.

Reference:
Drug Safety Update, MHRA, 26 August 2020
(www.gov.uk/mhra)

(See also WHO Pharmaceuticals Newsletter No.1, 2019; Risk of severe and fatal burns in UK; No.3, 2013: May cause skin irritation, particularly in children with eczema in UK)

Glecaprevir/ pibrentasvir (combination)

Risk of hepatic toxicity

New Zealand. The Medsafe has announced that severity of liver disease should be assessed before administrating a combination of two direct-acting antivirals (DAAs), glecaprevir and pibrentasvir (Maviret®).