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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.

This edition of the Newsletter also includes three short articles, on: the WHO Vaccine Safety Net, a working group meeting on the 'Erice call for change' and the launch of the Med Safety mobile application in Uganda.

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Regulatory Matters

Safety of medicines

Signal

Feature

Aciclovir, valaciclovir

Risk of tubulointerstitial nephritis

Japan. The Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA) have announced that the package inserts for aciclovir (Zovirax®) and valaciclovir (Valtrex®) should be revised to include tubulointerstitial nephritis as an adverse drug reaction.

Aciclovir and valaciclovir are indicated to treat various conditions including herpes simplex and herpes zoster.

A total of six cases involving tubulointerstitial nephritis in patients with valaciclovir have been reported in Japan during the previous three years, including three cases for which a causal relationship between the drug and event could not be excluded. No patient mortalities have been reported. The MHLW and PMDA have concluded that a revision to the package insert for valaciclovir is necessary.

No cases involving tubulointerstitial nephritis have been reported in patients with aciclovir. However, valaciclovir is a prodrug of aciclovir, and therefore, the package insert of aciclovir is also to be revised.

Reference:
Revision of Precautions, MHLW/PMDA, 31 March 2020 (www.pmda.go.jp/english/)

Amenamevir

Risk of erythema multiforme

Japan. The MHLW and the PMDA have announced that the package insert for amenamevir (Amenalief®) should be revised to include erythema multiforme as an adverse drug reaction.

Amenamevir is indicated for herpes zoster.

A total of 10 cases involving erythema multiforme have been reported in Japan during the previous three years, including five cases for which a causal relationship between the drug and event could not be excluded. No patient mortalities have been reported. The MHLW and PMDA have concluded that the revision is necessary.

Inclusion of toxic epidermal necrolysis and oculomucocutaneous syndrome was also considered as adverse drug reactions. Given the paucity of cases, it was concluded that it is not necessary to include them on the package insert.

Reference:
Revision of Precautions, MHLW/PMDA, 31 March 2020 (www.pmda.go.jp/english/)

Baloxavir marboxil

Risk of ischaemic colitis

Japan. The MHLW and the PMDA have announced that the package insert for baloxavir marboxil (Xofluza®) should be revised to include ischaemic colitis as an adverse drug reaction.

Baloxavir marboxil is indicated for Influenza A or B viral infections.

A total of 13 cases involving ischaemic colitis have been reported in Japan during the previous three years, including eight cases for which a causal relationship between the drug and event could not be excluded. No patient mortalities have been reported. The MHLW and PMDA have concluded that the revision is necessary.

Reference:
Revision of Precautions, MHLW/PMDA, 31 March 2020 (www.pmda.go.jp/english/)

Baricitinib

Risk of venous thromboembolism

United Kingdom. The Medicines and Healthcare Products Regulatory Agency (MHRA) has advised to discontinue baricitinib if clinical features of deep vein thrombosis or pulmonary embolism occur.

Baricitinib (Olumiant®) is indicated for the treatment of moderate to severe active rheumatoid arthritis in adults.

Clinical trial findings showed high rates of cases of deep vein thrombosis and pulmonary embolism with baricitinib treatment compared with placebo. Consequently, it was recommended that baricitinib should be used with caution in patients with risk factors for deep vein thrombosis and pulmonary embolism, such as prior medical history of venous thromboembolism, surgery, older age and obesity.

Also, health-care professionals should advise patients undergoing treatment with baricitinib to seek urgent medical attention if they experience a painful swollen leg, chest pain or shortness of breath.

Reference:
Drug Safety Update, MHRA, 18 March 2020 (www.gov.uk/mhra)

(See also WHO Pharmaceuticals Newsletter No.6, 2019: Risk of venous thromboembolism in Japan)

Cyproterone

Restrictions in use due to risk of meningioma

Europe. The European Medicines Agency (EMA) has announced restrictions in the use of cyproterone due to reported occurrence of meningiomas (single and multiple) in association with

the use of cyproterone, primarily at doses of 25 mg/day and above.

Cyproterone is an antiandrogen medicine, indicated to treat various androgen-dependent conditions such as hirsutism, alopecia, acne, prostate cancer, and reduction of sex drive in sexual deviations in men.

EMA's safety committee, the Pharmacovigilance Risk Assessment Committee (PRAC), recommended that cyproterone 10 mg/day or more should only be used for androgen-dependent conditions such as hirsutism, alopecia, acne and seborrhoea once other treatment options have failed. Also, cyproterone should only be used for reduction of sex drive in sexual deviations in men when other treatment options are not suitable. There is no change in use of cyproterone in men for prostate cancer.

Health-care professionals should monitor patients for clinical signs and symptoms of meningioma, such as changes in vision, hearing loss, headaches, seizures or weakness in arms and legs, in line with clinical practice. If patient is diagnosed with meningioma, treatment with cyproterone must be stopped permanently.

Reference:
EMA, 27 March 2020 (www.ema.europa.eu)

(See also WHO Pharmaceuticals Newsletter No.2, 2020: Risk of meningioma in EU; No.4, 2019; Risk of meningioma in EU)

Durvalumab

Risk of myasthenia gravis

Ireland. The Health Products Regulatory Authority (HPRA) has announced that the Summary of Product Characteristics (SmPC) and the Package Leaflets (PL) for durvalumab (Imfinzi®) have been updated to reflect the risk of myasthenia gravis.

Durvalumab is a monoclonal antibody that acts as an immune checkpoint inhibitor and is indicated to treat locally advanced, unresectable non-small cell lung cancer in adults. Immune checkpoint inhibitors such as durvalumab are known to generate a wide range of immune-mediated adverse reactions.

The EMA's PRAC reviewed the risk of myasthenia gravis associated with durvalumab, considering spontaneous reports and published literature. Evidence for a potential causal relationship between the drug and event was provided including cases with a fatal outcome. Also, several literature articles describe the potential mechanism of action by which durvalumab may induce myasthenia gravis.

The PRAC concluded that there is a risk of myasthenia gravis associated with durvalumab treatment.

Patients should be monitored for signs and symptoms of myasthenia gravis and managed. If there are signs of muscular weakness or respiratory insufficiency, treatment with durvalumab should be permanently discontinued.

Reference:
Drug Safety Newsletter, HPRA, April 2020 (www.hpra.ie)

Fosfomycin

Restrictions for use

Europe. The EMA has recommended, following the advice from the Committee for Medicinal Products for Human Use (CHMP), that fosfomycin intravenous formulation should only be used to treat serious infections when other antibiotic treatments are not suitable. Also, the EMA has recommended that fosfomycin oral formulations for children and intramuscular formulations should no longer be used, as there are insufficient data available to confirm their benefits to patients.

Fosfomycin is an antibiotic to treat a range of infections. Fosfomycin-based antibiotics first became available in the 1960s, and are available in most EU countries under names Afastural®, Fosfocin®, Urofast® etc. Generally, fosfomycin is known to cause several adverse drug reactions such as diarrhea, nausea and headache.

Intravenous formulations should only be used for the treatment of serious infections when other antibiotic treatments are not suitable, which include complicated urinary tract infections, infective endocarditis and bone and joint infections. Oral formulation can continue to be used for acute, uncomplicated cystitis in women. Intramuscular use will also be suspended as the evidence is not sufficient.

The product information for fosfomycin will be updated to take the recommendations into account.

Reference:
EMA, 27 March 2020 (www.ema.europa.eu)

Ingenol mebutate

Risks of skin cancer outweigh benefits

Europe. The EMA has completed its review of ingenol mebutate (Picato®) and concluded that the medicine may increase the risk of skin cancer and that its risks outweigh its benefits.

Ingenol mebutate is a gel applied to skin areas affected by actinic keratosis.

The review looked at results of a study comparing ingenol

mebutate with another medicine for actinic keratosis, imiquimod. A higher incidence of skin tumours, especially squamous cell carcinoma, were observed in patients treated with ingenol mebutate compared with those treated with imiquimod.

Picato® has already been taken off the market and is no longer a treatment option for actinic keratosis. Other treatment options for actinic keratosis include topical diclofenac, fluorouracil and imiquimod.

Health-care professionals should advise patients treated with ingenol mebutate to be vigilant for any skin lesions developing and to seek medical advice promptly should any occur.

Reference:
EMA, 30 April 2020
(www.ema.europa.eu)

(See also WHO Pharmaceuticals Newsletter No.2, 2020: Risk of skin malignancy in UK; No.1, 2020: Use with caution in patients with a history of skin cancer in Ireland; Suspension during safety review in EU)

Leuprorelin

New measures to avoid handling errors

Europe. The EMA has announced that new measures are to be taken to avoid handling errors, that result in insufficient amounts of medicines, in the preparation and administration of leuprorelin depot medicines (Eligard® and Lutrate Depot®).

Depot formulations of leuprorelin are given by injection under the skin or into a muscle and they release the active substance gradually over one to six months. Leuprorelin is indicated to treat prostate cancer, breast cancer, conditions that affect the female reproductive system and early puberty.

The PRAC has recommended that only health-care professionals familiar with the preparation of leuprorelin depot medicines should prepare and administer the medicines to patients. Patients should not inject the medicines themselves.

Product information for Eligard® is to be updated with warnings to strictly follow the instructions for preparation and administration, and to monitor patients if a handling error occurs. The MAH must replace the current device, to administer the drug, with one that is easier to handle.

Also, the PRAC recommended that instructions for Lutrate Depot® for handling the medicine be revised to make them easier to follow, and its packaging changed, so that the instructions are easier to find.

Reference:
EMA, 15 May 2020
(www.ema.europa.eu)

Methimazole

Risk of vasculitis

Canada. Health Canada has announced that it is working with the manufacturers to update product safety information of methimazole (Tapazole®) to include information about the risk of inflammation of the blood vessels (vasculitis).

Methimazole is indicated to treat hyperthyroidism and overactive thyroid gland.

Triggered by updates made by the US Food and Drug Administration (FDA) to the product safety information for methimazole related to the risk, Health Canada reviewed the potential risk of vasculitis with the use of methimazole.

Health Canada reviewed 13 international case reports of vasculitis in patients receiving methimazole, where 11 reports showed a possible link to methimazole use. Also, Health Canada assessed 22 articles from the published literature and found that many of them suggested a potential risk of vasculitis with methimazole use although the frequency was very rare.

Health Canada concluded that there is a link between the risk of vasculitis and the use of methimazole.

Reference:
Summary Safety Review, Health Canada, 21 April 2020
(www.hc-sc.gc.ca)

(See also WHO Pharmaceuticals Newsletter No.5, 2019: Risk of inflammation of pancreas in Canada)

Parenteral nutrition products

Risk of oxidative stress when light-exposed

Singapore. The Health Sciences Authority (HSA) has announced that the use of light-exposed parenteral nutrition (PN) products containing amino acids and/or lipids might lead to adverse outcomes in neonates due to their increased susceptibility to oxidative stress arising from PN photodegradation products.

PN products are indicated for use in neonates when oral or enteral nutrition is impossible, insufficient or contraindicated.

In laboratory and clinical studies, light exposure to PN products has been shown to generate peroxides and other photodegradation products in quantifiable amounts, which can lead to oxidative stress including respiratory distress syndrome, bronchopulmonary dysplasia, periventribular leukomalacia and retinopathy of prematurity. Newborns are at a higher risk of oxidative stress compared to children and adults. Studies have shown that the formation of PN photodegradation products can be slowed down or prevented

by implementing various light protection measures.

A review of the safety issue in 2019 among premature neonates led the EMA's PRAC to recommend that light protection of PN products be extended, to neonates and children below two years of age, as a precautionary measure.

HSA has not received local reports on this problem, but is working with companies of affected products to update the local package inserts to reflect the risk.

Health-care professionals should consider the importance of the protection measures when PN products containing amino acids and/or lipids are used, in neonates and children below two years of age, to minimize the risk.

Reference:
Product Safety Alerts, HSA, 5 May 2020 (*www.hsa.gov.sg/*)

Pegfilgrastim

Increased risk of thrombocytopenia

Japan. The MHLW and the PMDA have announced that the package insert for pegfilgrastim (G-Lasta®) should be revised to include an increased risk of thrombocytopenia as a precaution.

Pegfilgrastim is indicated to prevent chemotherapy-induced febrile neutropenia.

Thirty cases involving thrombocytopenia in patients with pegfilgrastim have been reported in Japan during the previous three years, including one case for which a causal relationship between the drug and event could not excluded. No patient mortalities have been reported.

A pharmacoepidemiological study on the association between pegfilgrastim and decreased platelet counts was conducted in Japan. The relative risk of decreased platelet counts was statistically significant in patients with pegfilgrastim.

The MHLW and PMDA have concluded that precaution for thrombocytopenia should be added in the package insert.

Reference:
Revision of Precautions, MHLW/PMDA, 31 March 2020 (*www.pmda.go.jp/english/*)

Propylthiouracil

Potential risk of birth defects

Canada. Health Canada has announced that it is working with the manufacturers, to update product safety information for propylthiouracil (Propyl-Thyracil®), to inform health-care professionals and patients about the potential risk of birth defects.

Propylthiouracil is indicated for hyperthyroidism, several radioiodine therapies, thyroid storm and, to control an overactive thyroid gland.

Triggered by international reports of birth defects linked with propylthiouracil use in pregnant women, Health Canada reviewed the potential risk of birth defects in babies whose mothers were treated with propylthiouracil during pregnancy. The review included 12 reports of birth defects, where seven reports were found to have possible link between the use of propylthiouracil and the birth defects. Also, 22 relevant published studies were found, but the review of the studies did not find sufficient evidence.

Health Canada's reviews could not confirm or exclude a link between the risk of birth defects in babies and use of propylthiouracil in women during pregnancy.

Reference:
Summary Safety Review, Health Canada, 3 April 2020 (*www.hc-sc.gc.ca*)

Rivaroxaban

Thromboprophylaxis not recommended in patients with TAVR

Ireland. The HPRA has announced that the SmPC for rivaroxaban (Xarelto®) has been updated to reflect that it should not be used for thromboprophylaxis in patients who have recently undergone transcatheter aortic valve replacement (TAVR) due to the risk of all-cause mortality, thromboembolic and bleeding events.

Rivaroxaban is an anticoagulation medicine and is indicated to treat and prevent blood clots.

The EMA's PRAC undertook a review of patients treated with rivaroxaban after TAVR. The committee considered the final results of a phase III clinical study (GALILEO), which identified an increase in all-cause mortality, thromboembolic and bleeding events in patients treated with rivaroxaban after TAVR, other randomized clinical trials and spontaneous reports.

The PRAC concluded that rivaroxaban should not be used for thromboprophylaxis in patients having recently undergone TAVR and recommended an update of SmPCs. It also determined that the benefit-risk balance for rivaroxaban for the approved indications remains positive.

Reference:
Drug Safety Newsletter, HPRA, April 2020 (*www.hpra.ie*)

(See also WHO Pharmaceuticals Newsletter No.6, 2019: Risk of recurrent thrombotic events in Australia and New Zealand; No.4, 2019: Increased risk of recurrent thrombotic events in UK)

SGLT2 inhibitors

Risk of diabetic ketoacidosis

United Kingdom. The MHRA has advised health-care professionals to interrupt sodium-glucose co-transporter 2 (SGLT2) inhibitor treatment in patients who are hospitalised for major surgical procedures or acute serious medical illnesses, and to monitor ketones during the period.

SGLT2 inhibitors are indicated to treat adults with diabetes to improve glycaemic control. In UK, available SGLT2 inhibitors are canagliflozin, dapagliflozin, empagliflozin and ertugliflozin.

A detailed European review in 2016 confirmed diabetic ketoacidosis as a rare risk for the SGLT2 inhibitors.

In 2019, a new European review recommended that warnings should be updated to include routine monitoring of ketones in patients hospitalized for surgery or acute illness. Testing of ketones in blood is recommended rather than measuring ketone bodies in urine because SGLT2 inhibitors may diminish the excretion of ketone bodies in urine. The review of the evidence did not identify a specific type of surgery as being linked to an increased risk of diabetic ketoacidosis.

Health-care professionals should restart treatment with the SGLT2 inhibitor once ketone values are normal and

SSRI, SNRI

Potential risk of sexual dysfunction

Ireland. The HPRA has announced that the SmPC and the PL for medicines containing selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs) will be updated to advise of the possible symptoms of sexual dysfunction which may persist following discontinuation of product.

SSRIs and SNRIs are indicated to treat major depressive disorder and anxiety disorders. SSRI containing medicinal products include citalopram, escitalopram, fluvoxamine, fluoxetine, paroxetine, sertraline; SNRI containing medicinal products include duloxetine, venlafaxine, desvenlafaxine and milnacipram.

After reviewing evidence from EMA database of adverse reactions and literature, the EMA's PRAC considered that the product information for SSRI and SNRI medicinal products should be amended to warn about the possibility of sexual dysfunction, which may persist following discontinuation of the medicinal products.

Reference:
Drug Safety Newsletter, HPRA, April 2020 *(www.hpra.ie)*

such as pneumonia, cellulitis, herpes zoster and urinary tract infections.

Tofacitinib is indicated to treat rheumatoid arthritis, psoriatic arthritis and ulcerative colitis.

In an ongoing trial to assess the use of tofacitinib in ulcerative colitis, cases of pulmonary embolism and deep vein thrombosis were also observed. As a new recommendation, maintenance treatment for ulcerative colitis at the 10mg twice-daily dose is not recommended in patients with known risk factors for venous thromboembolism such as previous venous thromboembolism, myocardial infarction, heart failure, hypertension and diabetes, unless there is no suitable alternative treatment.

Also, tofacitinib increases the risk of serious and fatal infections, with rates of infections greater in older patients. Health-care professionals should only consider use of tofacitinib in patients older than 65 years if there is no suitable alternative treatment available.

Reference:
Drug Safety Update, MHRA, 18 March 2020 *(www.gov.uk/mhra)*

(See WHO Pharmaceuticals Newsletter No.6, 2019: Risk of blood clots in EU; No.5, 2019: Increased risk of blood clots and death with higher dose in US and Japan; No.4, 2019: Risk of pulmonary embolism in EU)