World Health Organization

WHO Pharmaceuticals NEWSLETTER

2020 No.4

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.

In addition, this edition of the Newsletter includes recommendations from the 42nd Global Advisory Committee on Vaccine Safety (GACVS) meeting.

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WHO Pharmaceuticals Newsletter No. 4, 2020

ISBN 978-92-4-001074-1 (electronic version)
ISBN 978-92-4-001075-8 (print version)

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Apalutamide

Risk of toxic epidermal necrolysis (TEN)

Japan. The Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA) have announced that the package inserts for apalutamide (Erleada®) should be revised to include toxic epidermal necrolysis (TEN) as an adverse drug reaction.

Apalutamide is indicated to treat castration-resistant prostate cancer without remote metastasis.

A total of two cases involving TEN in patients with apalutamide have been reported in Japan during the previous three years, for which a causal relationship between the drug and event was deemed a reasonable possibility. One of the two cases led to patient mortality, for which a causal relationship between the drug and the subsequent death was deemed reasonably possible.

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

Reference:
Revision of Precautions, MHLW/PMDA, 19 May 2020 *(www.pmda.go.jp/english/)*

Bevacizumab

Risk of artery dissection

Japan. The MHLW and the PMDA have announced that the package inserts for bevacizumab (Avastin®) should be revised to include artery dissection as an adverse drug reaction.

Bevacizumab is indicated to treat several conditions such as incurable, unresectable advanced/recurrent colorectal cancer and malignant glioma.

A total of seven cases involving artery dissection in patients with bevacizumab have been reported in Japan during the previous three years, including one case for which a causal relationship between the drug and event was deemed reasonably possible. Two mortalities have been reported among the seven cases. A causal relationship could not be established for either cases.

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

Reference:
Revision of Precautions, MHLW/PMDA, 16 June 2020 *(www.pmda.go.jp/english/)*

Carbimazole

1. Risk of congenital malformations

Ireland. The Health Products Regulatory Authority (HPRA) has announced that the product information (Summary of Product Characteristics (SmPC) and Package Leaflet (PL)) for carbimazole has been updated to reflect the risk of congenital malformations.

Carbimazole is a pro-drug that undergoes rapid metabolism into the active metabolite, thiamazole.

The Pharmacovigilance Risk Assessment Committee (PRAC) completed a review of the known risk of congenital malformations associated with carbimazole exposure during pregnancy. Data from epidemiological studies and case reports strengthens the evidence that carbimazole/thiamazole exposure during pregnancy is associated with an increased risk of congenital malformations, especially when administered in the first trimester of pregnancy and at high doses.

Women of childbearing potential should use effective contraception during treatment with carbimazole. Carbimazole must only be used during pregnancy after a strict individual benefit/risk assessment and only at the lowest effective dose without additional administration of thyroid hormones.

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

(See also WHO Pharmaceuticals Newsletter No.2, 2019: Increased risk of congenital malformations in UK)

2. Risk of acute pancreatitis

Ireland. The HPRA has announced that the product information (SmPC and PL) for carbimazole has been updated to reflect the risk of acute pancreatitis.

Post-marketing reports of acute pancreatitis in association with the use of carbimazole/thiamazole have been received in EU. Although the mechanism is not fully understood, decreased time to onset after re-exposure could suggest an immunological mechanism.

Immediate discontinuation is required in patients who develop pancreatitis following exposure to carbimazole and the patients should be switched to alternative treatment.

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

(See also WHO Pharmaceuticals Newsletter No.2, 2019: Risk of acute pancreatitis in UK)

Cyproterone

Restrictions in use due to risk of meningioma

1. Ireland. The HPRA has announced that the SmPC and PL for cyproterone containing medicines will be updated to include the risk of meningioma associated with treatment.

Cyproterone is an antiandrogen medicine acting in the same way as progesterone. It is

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

A PRAC review concluded that the risk of meningioma increases with increasing cumulative doses of cyproterone. It also noted that most cases occur after prolonged exposure to high doses of cyproterone.

The PRAC recommended that in all indications except prostate carcinoma, treatment with higher doses should be restricted to situations where alternative treatments are unavailable and that low doses should also be contraindicated in patients with a history of meningioma.

Patients should be monitored for meningioma in accordance with clinical practice. If a patient taking cyproterone is diagnosed with meningioma, treatment must be discontinued permanently.

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

2. United Kingdom. The Medicines and Healthcare Products Regulatory Agency (MHRA) has announced that a European review concluded that treatment with high dose cyproterone should be restricted to situations where alternative treatments or interventions are unavailable, for all indications except prostate carcinoma.

Up to 12 May 2020, there have been 10 reports in the UK describing meningioma, which were suspected to be associated with high dose cyproterone. There were no reports of meningioma with low dose cyproterone.

Reference:
Drug Safety Update, MHRA, 29 June 2020 *(www.gov.uk/mhra)*

(See also WHO Pharmaceuticals Newsletter No.3, 2020: Restrictions in use due to risk of meningioma in EU; No.2, 2020: Risk of meningioma in EU; No.4, 2019; Risk of meningioma in EU)

Fluoxetine, levothyroxine

Potential interaction affecting TSH level

New Zealand. Medsafe is highlighting a safety concern and encouraging reporting of cases of potential interaction between fluoxetine (Arrow®, Fluox® etc.) and levothyroxine (Eltroxin®, Synthroid® etc.) leading to reduced serum levels of levothyroxine and increased thyroid-stimulating hormone (TSH) levels.

Fluoxetine is a selective serotonin reuptake inhibitor (SSRI) indicated for depression, bulimia, obsessive-compulsive disorder and premenstrual dysphoric disorder. Levothyroxine is a synthetic form of the natural hormone thyroxine (T4) indicated for the treatment of hypothyroidism.

This investigation was triggered by a report received by the Centre for Adverse Reactions Monitoring (CARM). There are also some published case reports describing reduced thyroid function during treatment with other SSRIs such as escitalopram, paroxetine and sertraline.

The mechanism for this potential interaction and whether this is a class effect of SSRIs are not clear.

The monitoring will continue until November 2020.

Reference:
Safety Communication, Medsafe, 21 May 2020 *(www.medsafe.govt.nz/)*

(See also WHO Pharmaceuticals Newsletter No.6, 2018: Interaction with levothyroxine leading to reduced thyroxine levels in UK; No.1, 2017: Risk of adrenal suppression due to a pharmacokinetic interaction in UK)

Fulvestrant

Risk of injection site necrosis and ulcer

Japan. The MHLW and the PMDA have announced that the package inserts for fulvestrant (Faslodex®) should be revised to include injection site necrosis and ulcer as adverse drug reactions.

Fulvestrant is indicated to treat breast cancer.

A total of six cases involving injection site necrosis and ulcer in patients with fulvestrant have been reported in Japan during the previous three years, including five cases for which a causal relationship between the drug and event was deemed reasonably possible. No patient mortalities have been reported to date.

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

Reference:
Revision of Precautions, MHLW/PMDA, 19 May 2020 *(www.pmda.go.jp/english/)*

Ketamine

Potential risk of liver and bile duct damage

Canada. Health Canada has announced that it will work with manufacturers to update the product safety information of ketamine-containing products (Ketalar® and generic) to inform about the potential risk of liver and bile duct damage.

Ketamine is used to make patients unconscious (anesthesia) during surgery or medical procedures.

Health Canada conducted a review on the risk of liver and bile duct damage with the use of ketamine, following a risk communication published by the French regulatory agency.

The assessment reviewed 19

international epidemiologic studies, which could not confirm or refute a link between the liver and/or bile duct damages and the use of ketamine. An additional 22 individual patient case reports (one was Canadian) were reviewed, among which one was found to be probably linked to the used of ketamine, and 17 possibly linked. Hence, Health Canada concluded that there is a potential link between the use of ketamine and damage to the liver and bile duct.

Reference:
Summary Safety Review, Health Canada, 10 June 2020 (www.hc-sc.gc.ca)

(See also WHO Pharmaceuticals Newsletter No.5, 2017: Risk of severe liver injury with repeated and/or prolonged high-dose use in France)

Levetiracetam

Risk of abnormal and aggressive behaviours

Ireland. The HPRA communicated a PRAC recommendation that the product information for levetiracetam (Keppra®, Matever® etc.) should be updated to include a warning on the risk of abnormal and aggressive behaviours. The recommendation resulted from a periodic review of safety data in association with levetiracetam.

Levetiracetam is indicated in the treatment of specified forms of epilepsy.

Patients treated with levetiracetam should be monitored for developing psychiatric signs suggesting important mood or personality changes. If such behaviours are noticed, treatment adaptation or gradual discontinuation should be considered.

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

Memantine

Risk of bradyarrhythmia

Japan. The MHLW and the PMDA have announced that the package inserts for memantine (Memary®) should be revised to include bradyarrhythmia such as complete atrioventricular block and severe sinus bradycardia as an adverse drug reaction.

Memantine is indicated to control the progression of moderate to severe dementia of the Alzheimer's type.

A total of four cases involving bradyarrhythmia in patients with memantine have been reported in Japan during the previous three years, for two of which a causal relationship between the drug and event was deemed reasonably possible. No patient mortalities have been reported to date.

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

Reference:
Revision of Precautions, MHLW/PMDA, 16 June 2020 (www.pmda.go.jp/english/)

Nutrition preparations (parenteral)

Contraindication loosened

Japan. The MHLW and the PMDA have announced that the package inserts for parenteral nutrition preparations was revised, regarding the use in patients on dialysis or hemofiltration, from contraindications into careful administration. The implicated products include amino-acid preparations, peripheral parenteral nutrition preparations and total parenteral nutrition preparations (Amizet®, Amiparen®, Pareplus®, Hicaliq®, Rehabix® etc.).

Parenteral nutrition preparations are widely used to supplement nutrition such as water, electrolyte, amino acid under malnutrition of before/after surgery.

The revision is based on a 2020 investigation by MHLW and PMDA, on the safety of the parenteral nutrition preparations in patients with serious renal disorder on dialysis of hemofiltration.

After reviewing published scientific journals, overseas guidelines and package inserts, the PMDA considered acceptable to exclude patients on dialysis or hemofiltration from the contraindication section, but emphasized precautions for administration in those patients. This is due to the abundance of acidic amino acid in amino acid preparations for hepatic failure, which may cause acidosis in patients with renal failure on dialysis.

Reference:
Revision of Precautions, MHLW/PMDA, 25 June 2020 (www.pmda.go.jp/english/)

Ondansetron

Potential risk of oral cleft defects

New Zealand. Medsafe has announced that the data sheets of ondansetron-containing medicines are being updated with information on the increased risk of oral cleft defects associated with first trimester use.

Ondansetron is a selective serotonin receptor antagonist and is used to manage and prevent nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy. Ondansetron is also used off-label during early pregnancy. In New Zealand, first trimester use of ondansetron is increasing.

Two recent epidemiological studies investigated the risk of

orofacial cleft defects and other congenital malformations in infants who were exposed to ondansetron in utero, using data in the United States. The result of one study showed statistically significant increase in oral cleft with the use of ondansetron, whereas the result from the other study was not statistically significant.

The Medicines Adverse Reactions Committee (MARC) noted that although the effect sizes in the studies were small and there is some uncertainty in the data, the current evidence suggests a small increase in the risk of oral cleft defects associated with the use of ondansetron in the first trimester.

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

(See also WHO Pharmaceuticals Newsletter No.2, 2020: Risk of oral clefts in UK; No.6, 2016: Assessing potential harm to the foetus: insufficient information in Canada)

Ruxolitinib, Tofacitinib

Risk of blood clots in the deep veins

Canada. Health Canada has announced that it had worked with the manufacturer for tofacitinib (Xeljanz®) to update the product safety information to include the serious risk of blood clots in the veins and will also work with the manufacturer for ruxolitinib (Jakavi®) to update the product safety information to include the risk of thromboembolic events.

Tofacitinib is used for the treatment of inflammatory diseases such as rheumatoid arthritis, psoriatic arthritis and ulcerative colitis. Ruxolitinib is used for the treatment of certain rare blood cancers, such as primary myelofibrosis and polycythemia vera.

Health Canada conducted a safety review and found that an ongoing safety study for tofacitinib showed an increased risk of blood clots in the lungs and death. A review of an additional 51 cases (eight Canadian and 43 international) of thromboembolic events in people taking tofacitinib showed that 38 were possibly linked to tofacitinib.

A further assessment of eight Canadian cases of thromboembolic events in patients taking ruxolitinib found that three cases showed a possible link to ruxolitinib.

Health Canada concluded that there is a link between the risk of thromboembolic events and the use of tofacitinib or ruxolitinib.

Reference:
Summary Safety Review, Health Canada, 18 June 2020 (www.hc-sc.gc.ca)

(See also WHO Pharmaceuticals Newsletter No.3, 2020: Risk of venous thromboembolism and serious and fatal infections in UK; 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)

Testosterone

Caution in patients with thrombophilia or risk factors for venous thromboembolism

Ireland. The HPRA warned that testosterone-containing medicinal products should be used with caution in patients with thrombophilia or risk factors for venous thromboembolism, following a PRAC recommendation to update the product information (SmPC and PL) for these products.

Testosterone-containing medicinal products are used as testosterone replacement therapy for male hypogonadism in Ireland.

Cases of venous thromboembolism have been reported in patients with thrombophilia, some of whom were on anticoagulant treatment. Continuing testosterone treatment in such patients requires careful evaluation after a first thrombotic event.

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

(See also WHO Pharmaceuticals Newsletter No.3, 2017: Risk of arterial thromboembolism/venous thromboembolism in Australia; No.4, 2014: Risk of venous blood clots in the USA)

Ticagrelor

Potential risk of bradyarrhythmia

Canada. Health Canada has announced that it will work with manufacturers to update the product safety information of ticagrelor (Brilinta®) to inform about the potential risk of worsening of a slow and irregular heartbeat (bradyarrhythmia) and partial or complete block in the transmission of heart impulses (second-and third-degree atrioventricular block).

Ticagrelor is used to decrease the risk of having a stroke, another heart attack or dying from heart or blood vessel disease.

Triggered by published international reports of partial or complete block in the transmission of heart impulses in patients with ticagrelor, Health Canada reviewed two potential risks, bradyarrhythmia and second- and third-degree atrioventricular block.

Of the 18 international cases of patients with bradyarrhythmia taking ticagrelor assessed, 15 were found to be possibly linked to the use of ticagrelor.

Among the 44 cases (42 international and two

Canadian) assessed regarding the risk of second or third-degree atrioventricular block related to the use of ticagrelor, two reports were found to be probably linked to the use of ticagrelor, 40 including two Canadian cases were possibly linked. Of the 9 mortalities among the 44 reports, three were found to be possibly linked with the use of ticagrelor.

Health Canada concluded that there may be a link between the use of ticagrelor and the risk of bradyarrhythmia including second- and third-degree atrioventricular block.

Reference:
Summary Safety Review, Health Canada, 6 July 2020 (www.hc-sc.gc.ca)

Tramadol

Contraindication in children

New Zealand. Medsafe has informed health-care professionals of updated advice on the use of tramadol in children.

Tramadol is centrally-acting synthetic analgesic, used to relieve moderate to severe pain when paracetamol or non-steroidal anti-inflammatory drug (NSAID) is not adequate. Tramadol is metabolized by CYP2D6 to yield principal active metabolite. Patients with a deficiency of CYP2D6 may have frequent ADRs were rash, vomiting, and nausea. Serotonin syndrome and convulsions were also reported in five cases each.

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

(See also WHO Pharmaceuticals Newsletter No.6, 2015; Risk of slowed or difficult breathing in children in USA; No.5, 2015: Tramadol oral drops not for children under the age of 12 years in Australia)