World Health Organization

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 includes updates on launch of an ADR Reporting App in Botswana and highlights from the Global Vaccine Safety Summit.

Contents

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Table of Contents

Regulatory Matters

Safety of medicines

Signal

Feature

Alemtuzumab (genetic recombination)

Risk of cervicocephalic arterial dissection

Japan. The Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA) have announced that the package insert for alemtuzumab (MabCampath®) should be revised to include cervicocephalic arterial dissection as an adverse drug reaction.

Alemtuzumab is indicated for treatment of recurrent or refractory chronic lymphocytic leukemia.

One case of cervicocephalic arterial dissection and ischaemic stroke has been reported in a patient taking alemtuzumab in Japan during the previous three years. A causal relationship between alemtuzumab and the event could not be established.

MHLW/PMDA have concluded that revision of the package insert is necessary.

Reference:
Revision of Precautions, MHLW/PMDA, 21 January 2020 *(www.pmda.go.jp/english/)*

Atezolizumab (genetic recombination)

Risk of haemophagocytic syndrome

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

Atezolizumab is indicated for specific types of breast cancers; unresectable, advanced or recurrent non-small cell lung cancer; and extensive-stage small cell lung cancer.

A total of eight cases of haemophagocytic syndrome have been reported in patients taking atezolizumab in Japan during the previous three years. Of the eight cases, a causal relationship between atezolizumab and the event could not be excluded for six. One fatal case has been reported, and the causal relationship could not be excluded.

MHLW/PMDA have concluded that revision of the package insert is necessary.

Reference:
Revision of Precautions, MHLW/PMDA, 3 December 2019 *(www.pmda.go.jp/english/)*

Bilastine

Risk of shock and anaphylaxis

Japan. The MHLW and the PMDA have announced that the package insert for bilastine (Bilanoa®) should be revised to include shock and anaphylaxis as adverse drug reactions.

Bilastine is indicated for allergic rhinitis, urticaria and itching accompanying cutaneous disease.

A total of six cases of shock or anaphylaxis in patients taking bilastine have been reported in Japan during the previous three years. Of the six cases, a causal relationship between the drug and the event could not be excluded for three cases. No patient mortalities have been reported. Additionally, there are a number of cases reported overseas. MHLW/PMDA have concluded that revision of the package insert is necessary.

Reference:
Revision of Precautions, MHLW/PMDA, 3 December 2019 *(www.pmda.go.jp/english/)*

Estradiol (creams)

Four-week limit for use

Europe. The European Medicines Agency (EMA) has announced that the Pharmacovigilance Risk Assessment Committee (PRAC) has recommended that high-strength (0.01%) estradiol creams should only be used as a single treatment for a maximum of four weeks.

Estradiol creams are used as a topical hormone replacement therapy and is indicated to treat symptoms of vaginal atrophy in postmenopausal women.

The PRAC reviewed available data on the safety and effectiveness of high-strength estradiol-containing creams and concluded that absorption of estradiol into the bloodstream is of concern and could result in similar adverse effects to those seen with hormone replacement therapy such as endometrial hyperplasia/carcinoma, breast and ovarian cancer and thromboembolic events.

Reference:
EMA, 17 January 2020 *(www.ema.europa.eu)*

(See WHO Pharmaceuticals Newsletter No.6, 2019: Four-week limit for use of high strength estradiol creams in EU)

Ingenol mebutate

1. Use with caution in patients with a history of skin cancer

Ireland. The Health Products Regulatory Authority (HPRA) has announced that the Summary of Product Characteristics (SmPC) and the Package Leaflets (PL) for ingenol mebutate (Picato®) have been updated to include a warning regarding reports of basal cell carcinoma, Bowen's disease and squamous cell carcinoma. The update advises the use of ingenol mebutate

with caution in patients with a history of skin cancer.

Ingenol mebutate is indicated for the cutaneous treatment of non-hyperkeratotic, non-hypertrophic actinic keratosis in adults.

In 2017, following results from a randomised study, the product information for ingenol mebutate was updated to reflect the potential for development of benign skin tumours (keratoacanthoma).

Additionally, an increased incidence of squamous cell carcinoma was observed in the preliminary results of an ongoing randomised study.

A meta-analysis of four randomized, double-blind, vehicle-controlled studies of the related ester, ingenol disoxate, found an increased incidence of skin cancer at 14 months in those treated with ingenol disoxate.

Patients should be advised to be vigilant for any skin lesions and to inform their doctor immediately should any occur.

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

2. Suspension during safety review

Europe. The EMA has recommended that patients should stop using ingenol mebutate during the period in which the PRAC is reviewing data on the risk of skin cancer.

There is concern about a possible link between the use of ingenol mebutate and the development of skin cancer. The PRAC has therefore recommended suspending the medicine's marketing authorization as a precaution and noted that alternative treatments are available.

Health-care professionals should stop prescribing ingenol mebutate, consider different treatment options, and advise patients to be vigilant for any developing skin lesions and to seek medical advice promptly should any occur.

Reference:
EMA, 17 January 2020 *(www.ema.europa.eu)*

(See WHO Pharmaceuticals Newsletter No.6, 2019: Increased incidence of skin tumours in UK; No.5, 2019: Potential risk of skin cancer in EU; No.3, 2017)

Ipragliflozin

Risk of shock and anaphylaxis

Japan. The MHLW and the PMDA have announced that the package insert for ipragliflozin containing products (Suglat® and Sujanu®) should be revised to include shock and anaphylaxis as adverse drug reactions.

Ipragliflozin is indicated to treat type 1 and 2 diabetes mellitus.

A total of two cases involving shock or anaphylaxis in patients treated with ipragliflozin have been reported in Japan during the previous three years. A causal relationship between the drug and the event could not be established in these cases.

MHLW/PMDA have concluded that revision of the package insert is necessary.

Reference:
Revision of Precautions, MHLW/PMDA, 21 January 2020 *(www.pmda.go.jp/english/)*

Lamotrigine

Risk of adverse drug reactions when switching brands

New Zealand. Medsafe has announced that the product information for lamotrigine containing products (Logem® and Lamictal®) have been updated to include information on potential adverse effects that may occur when switching brands.

Lamotrigine is indicated for the treatment of epilepsy and of mood episodes with bipolar disorder.

The CARM has received cases of suicidal ideation, suicide attempt, headache, hot flushes, memory loss, rash and tiredness in patients that have switched brands of lamotrigine. Of these cases five had a fatal outcome. A causal link between switching brands of lamotrigine and these adverse reactions has not been established.

Reference:
Safety Communication, Medsafe, 20 December 2019 *(www.medsafe.govt.nz/)*

Levodopa

Risk of dopamine dysregulation syndrome

Japan. The MHLW and the PMDA have announced that the package inserts for levodopa containing products (Dopaston®, Neodopaston®, Duodopa enteral combination solution®, Stalevo® and Neodopasol Combination®) should be revised to include dopamine dysregulation syndrome as an important precaution.

Dopamine containing products are indicated to treat several conditions including Parkinson's disease, Parkinson's syndrome, akinesia, muscle rigidity, tremor, gait disturbance, language disorder, abnormal posture, pulsion and psychiatric symptom.

A total of three cases of dopamine dysregulation syndrome in patients treated with dopamine containing products have been reported in Japan during the previous three years. No patient mortalities have been reported.

MHLW/PMDA have concluded that revision of the package insert is necessary.

Reference:
Revision of Precautions, MHLW/PMDA, 21 January 2020 *(www.pmda.go.jp/english/)*

Levothyroxine

Potential adverse reactions when switching brands

Ireland. The HPRA has announced that SmPC and PL for levothyroxine preparations (Eltroxin®, Levothyroxine Teva®, Oroxine® and other generic products) will be updated to include advice for patients switching brands or formulation due to the increased risk of adverse drug reactions following a potential imbalance of thyroid hormones. This follows recommendations issued by PRAC.

Levothyroxine is a thyroid hormone used to treat thyroid hormone deficiency.

Levothyroxine has a narrow therapeutic index. If a switch to a different brand or formulation is necessary, there is a need to closely monitor patients clinically and to perform thyroid function tests during the transition period.

Patients should be made aware of the symptoms that occur due to an imbalance of thyroid hormones and should be encouraged to consult their physician in the event that they experience any of these symptoms.

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

Mecasermin (genetic recombination)

Potential risk of benign or malignant tumours

Japan. The MHLW and the PMDA have announced that the package insert for mecasermin (genetic recombination, Somazon®) should be revised to include the potential risk of benign or malignant tumours as adverse drug reactions.

Mecasermin is indicated for improvement of hyperglycaemia, hyperinsulinemia, acanthosis nigricans, and hypertrichosis in diseases such as type A insulin-receptor abnormality and for improvement of growth disorder in diseases such as growth hormone-resistant isolated growth hormone deficiency type 1A.

No cases involving benign or malignant tumors have been reported in Japan during the previous three years. However, several published articles have suggested an association between human insulin-like growth factor-I, an ingredient of mecasermin, and occurrence of a tumour. Additionally, cases of benign or malignant tumours in patients treated with mecasermin have been reported overseas, although causality is unclear. The MHLW and PMDA have concluded that revision of the package insert is necessary.

Reference:
Revision of Precautions, MHLW/PMDA, 3 December 2019 *(www.pmda.go.jp/english/)*

Methotrexate

New measures to avoid dosing errors

Ireland. The HPRA has announced that SmPCs and PLs for methotrexate containing products (Jylamvo®, Methofill®, Methotrexate®, Metoject® and Nordimet®) will be updated to strengthen warnings regarding dosing errors and to reflect that the medicine is only to be prescribed by doctors with expertise in the use of methotrexate.

Methotrexate is indicated for the treatment of both inflammatory diseases and cancers. When used in the treatment of inflammatory diseases such as rheumatoid arthritis and psoriasis, methotrexate should be taken once a week. However, when used in the treatment of cancers, methotrexate may be taken more frequently. Errors in the prescribing or dispensing of methotrexate leads to serious consequences, including death. The risk of this medication error is well known, and several measures are already being taken, but this medication error continues to occur.

As well as the update of SmPCs and PLs, additional measures include introduction of educational materials for oral methotrexate products for both patients and health-care professionals.

Health-care professionals should provide patients with clear and complete dosing instructions on the once-weekly dosing regimen.

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

Modafinil

Potential risk of congenital malformations

New Zealand. Medsafe has announced that modafinil is contraindicated in patients who are pregnant or may become pregnant due to potential risk of congenital malformations when administered during pregnancy.

Modafinil is used to improve

wakefulness in people with excessive daytime sleepiness associated with narcolepsy, obstructive sleep apnoea/hypopnoea syndrome or, shift work sleep disorder.

Modafinil may reduce the effectiveness of oral contraception due to enzyme induction. Alternative or concomitant methods of contraception are recommended during treatment with modafinil and for two months after stopping treatment.

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

(See WHO Pharmaceuticals Newsletter No.6, 2019: Potential risk of congenital malformations in Ireland)

Olmesartan medoxomil

Risk of interstitial pneumonia

Japan. The MHLW and the PMDA have announced that the package inserts for olmesartan medoxomil containing products (Olmetec® and Rezaltas®) should be revised to include interstitial pneumonia as an adverse drug reaction.

Olmesartan is indicated to treat hypertension.

A total of seven cases of interstitial pneumonia in patients treated with olmesartan medoxomil have been reported in Japan during the previous three years. No patient mortalities have been reported.

MHLW/PMDA have concluded that revision of the package insert is necessary.

Reference:
Revision of Precautions, MHLW/PMDA, 21 January 2020 *(www.pmda.go.jp/english/)*

Osimertinib mesilate

Risk of congestive cardiac failure and decreased left ventricular ejection fraction

Japan. The MHLW and the PMDA have announced that the package insert for osimertinib mesilate (Tagrisso®) should be revised to include congestive cardiac failure and decreased left ventricular ejection fraction as adverse drug reactions.

Osimertinib mesilate is indicated for epidermal growth factor receptor (EGFR) gene mutation-positive inoperable or recurrent non-small cell lung cancer.

A total of 34 cases involving cardiac failure in patients treated with osimertinib mesilate have been reported in Japan during the previous three years. Of the 34 cases, a causal relationship between the drug and the event could not be excluded for seven cases. MHLW/PMDA have concluded that revision of the package insert is necessary.

Reference:
Revision of Precautions, MHLW/PMDA, 3 December 2019 *(www.pmda.go.jp/english/)*

Secukinumab (genetic recombination)

Risk of erythroderma

Japan. The MHLW and the PMDA have announced that the package insert for secukinumab (genetic recombination, Cosentyx®) should be revised to include erythroderma (dermatitis exfoliative) as an adverse drug reaction.

Secukinumab is indicated to treat psoriasis vulgaris, psoriatic arthritis, pustular psoriasis and ankylosing spondylitis in patients who are not sufficiently responsive to conventional therapies.

A total of three cases of erythroderma in patients treated with secukinumab have been reported in Japan during the previous three years. For one of the cases, a causal relationship between the drug and the event could not be excluded.

MHLW/PMDA have concluded that revision of the package insert is necessary.

Reference:
Revision of Precautions, MHLW/PMDA, 21 January 2020 *(www.pmda.go.jp/english/)*

Sodium-glucose co-transporter 2 (SGLT2) inhibitors

Updated advice on monitoring ketone bodies

Ireland. The HPRA has announced the SmPC for sodium-glucose co-transporter 2 (SGLT2) inhibitors will be updated to include information on how to assess for ketoacidosis in patients who are hospitalized for major surgical procedures or acute serious medical illnesses.

SGLT2 inhibitors are indicated to treat type 2 diabetes, as monotherapy, or in combination with other diabetes medicines.

The decision was based on recommendations from the PRAC following an in-depth review. An initial review in 2016 concluded that a small risk of diabetic ketoacidosis (DKA) associated with exposure to SGLT2 inhibitors could not be excluded. In 2019, newly identified cases of DKA associated with SGLT2 inhibitors prompted further evaluation of the associated risk factors.

Additionally, here is evidence that SGLT2 inhibitors may

diminish the excretion of ketone bodies in the urine, and measurement of blood ketone levels is preferred to measurement of ketone bodies in the urine.

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

(See WHO Pharmaceuticals Newsletter No.1, 2018; Risk of non-traumatic amputations of the lower limbs, diabetic ketoacidosis and renal failure in Chile; No.4, 2016: Risk of serious diabetic ketoacidosis (DKA) in Singapore; No.2, 2016: Risk of diabetic ketoacidosis in EU; No.1, 2016: Risk of acid in blood and serious urinary tract infections in US)

Tocilizumab

Risk of hepatotoxicity

Australia. The Therapeutic Goods Administration (TGA) has announced that the product information for tocilizumab (Actemra®) has been updated to include more information about the risk of hepatotoxicity.

Tocilizumab is indicated for treatment of several conditions including rheumatoid arthritis, giant cell arteritis in adults and polyarticular juvenile idiopathic arthritis.

Eight cases of moderate to severe drug induced liver injury related to tocilizumab use, including acute liver failure, hepatitis and jaundice were identified. These events are of appetite, nausea and vomiting.

Reference:
Medicines Safety Update, TGA, 10 December 2019 (*www.tga.gov.au*)

(See WHO Pharmaceuticals Newsletter No.6, 2019: Risk of hepatic impairment in Japan; No.5, 2019: Rare risk of hepatic injury in Ireland; No.4, 2019: Risk of hepatotoxicity in Australia and in UK)