World Health Organization

WHO Pharmaceuticals NEWSLETTER

2020 No. 2

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 the recommendations from the 42nd Annual Meeting of Representatives of National Pharmacovigilance Centres participating in the WHO Programme for International Drug Monitoring. Given the current interest over the use of chloroquine and hydroxychloroquine in COVID-19, we have also included a summary of case safety reports in Vigibase for these products.

Contents

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Table of Contents

Regulatory Matters

Safety of medicines

Information Note

Signal

Feature

Table of Contents

Acitretin

Changes to pregnancy prevention requirements

New Zealand. Acitretin is used to treat several skin conditions including psoriasis. Acitretin is teratogenic and is contraindicated in women of childbearing potential unless all of the conditions of the Pregnancy Prevention Programme are met.

Medsafe has announced that the period during which effective contraception must be used has increased from two to three years after the end of treatment with acitretin (Novatretin®).

The change was due to the discovery of the formation of etretinate in the presence of alcohol, the half-life of which is 120 days. The package label and foils have been updated to reflect the increased post-treatment contraception requirement from 24 to 36 months.

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

Alemtuzumab

Updated restrictions and strengthened monitoring

United Kingdom. The Medicines and Healthcare Products Regulatory Agency (MHRA) has announced that an EU review recommended a revised indication, additional contraindications and strengthened monitoring for alemtuzumab (Lemtrada®) due to the risk of cardiovascular events, thrombocytopenia and immune-mediated reactions.

Alemtuzumab is a monoclonal antibody and is indicated for the treatment of adults with relapsing-remitting multiple sclerosis.

The review concluded that serious cardiovascular reactions can rarely occur within one to three days of treatment. However unpredictable and potentially fatal immune-mediated reactions can occur within months and up to at least four years post-treatment. This included Epstein-Barr virus reactivation.

Alemtuzumab should only be used as a single disease-modifying therapy in adults with specific conditions. Alemtuzumab is contraindicated in patients with severe active infection until complete resolution, those with a history of stroke and a history of angina.

Patients should only be administered alemtuzumab in a hospital with ready access to intensive care facilities and should be monitored closely for cardiovascular reactions and non-immune thrombocytopenia.

Reference:
Drug Safety Update, MHRA, 12 February 2020 (*www.gov.uk/mhra*)

(See WHO Pharmaceuticals Newsletter No.6, 2019: Risk of cardiovascular disorders and immune-related disorders in EU; No.4, 2019: Risk of serious cardiovascular and immune-mediated adverse reactions in UK; No.3, 2019: Cardiovascular and immune-mediated adverse effects in EU)

Allopurinol

Risk of aseptic meningitis

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

Allopurinol is indicated for management of hyperuricemia in patients with gout or hypertension accompanied by hyperuricemia.

Although no cases involving aseptic meningitis have been reported in patients taking allopurinol in Japan during the previous three years, considering that cases were reported overseas the MHLW and PMDA have determined that the revision was necessary.

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

Aminolevulinic acid

Risk of hypotension

Japan. The MHLW and the PMDA have announced that the package insert for aminolevulinic acid (Alaglio Divided Granules® and Alabel Oral®) should be revised to include hypotension as an adverse drug reaction.

Aminolevulinic acid is indicated for visualization of non-muscle invasive bladder cancer during transurethral resection of the bladder tumour and that of malignant tissue during malignant glioma resection.

A total of 26 cases of corresponding adverse events were reported in patients taking aminolevulinic acid in Japan during the previous three years. For 15 of these 26 cases a causal relationship between aminolevulinic acid and the adverse events could not be ruled out.

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

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

Arsenic trioxide

Risk of Wernicke's encephalopathy

Japan. The MHLW and the PMDA have announced that the package insert for arsenic trioxide (Trisenox®) should be revised to include Wernicke's encephalopathy as an adverse drug reaction.

Arsenic trioxide is indicated for recurrent or refractory acute promyelocytic leukemia.

Although no cases involving Wernicke's encephalopathy have been reported so far in patients taking arsenic trioxide in Japan, the revision was based on cases overseas. It was determined appropriate as currently there is no evidence on ethnic differences in the safety profile of the drug between patients in Japanese and those overseas.

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

Cyproterone

Risk of meningioma

Europe. The European Medicines Agency (EMA) announced that the Pharmacovigilance Risk Assessment Committee (PRAC) has recommended that medicines with daily doses of 10 mg or more of cyproterone should only be used for androgen-dependent conditions such as hirsutism, alopecia, acne and seborrhoea once other treatment options have failed, due to the risk of meningioma.

The medicines 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 the use of the medicines in men for prostate cancer.

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.

Overall, the risk of meningioma risk is rare. Although there is no evidence of a risk for low-dose cyproterone in combination with ethinylestradiol or estradiol, as a precaution, these medicines should not be used in people who have or have had a meningioma.

Health-care professionals should monitor patients for clinical signs and symptoms of meningioma. Symptoms include changes in vision, hearing loss, loss of smell, headaches, memory loss, seizures or weakness in extremities.

Reference:
EMA, 14 February 2020 *(www.ema.europa.eu)*

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

Direct-acting antivirals (DAAs)

1. Risk of abnormal blood sugar levels (dysglycemia)

Canada. Health Canada has announced that it is working with the manufacturers to update product safety information of direct-acting antivirals (DAAs) to include the risk of dysglycemia among diabetic patients.

DAAs are indicated for the treatment of chronic hepatitis C virus (HCV) infection. DAAs available in Canada include daclatasvir (Daklinza®), sofosbuvir (Sovaldi®) and the combination of sofosbuvir and ledipasvir (Harvoni®).

Health Canada reviewed the potential risk of abnormal blood sugar levels (dysglycemia) with the use of DAAs, including both high blood sugar levels (hyperglycemia) and low blood sugar levels (hypoglycemia).

Health Canada reviewed 26 Canadian cases and 10 international cases. It found 735 cases in VigiBase® related to dysglycemia with DAAs, but the data could not be used to confirm or exclude a link between the use of DAAs and the event. Also, Health Canada reviewed 26 published studies in the scientific literature, and identified biological mechanisms to explain how DAAs could lead to hypoglycaemia in diabetic patients.

Health Canada's review has concluded that there is a link between the use of DAAs and the risk of dysglycemia.

Reference:
Summary Safety Review, Health Canada, 17 February 2020 *(www.hc-sc.gc.ca)*

(See WHO Pharmaceuticals Newsletter No.2, 2018: Possible effects on blood glucose control when used in patients with type 2 diabetes in New Zealand; No.2, 2017: Possible effects on blood glucose control when used in patients with type 2 diabetes: added to the medicine monitoring scheme in New Zealand)

2. Dose adjustment of concomitant drugs required

Japan. The MHLW and the PMDA have announced that the package inserts for several DAAs, including Asunaprevir (Sunvepra®), Daclatasvir (Daklinza®) and Sofosbuvir (Sovaldi®), should be revised to include the important precautions that dose adjustment for concomitant drugs may be required.

Several studies have reported that dose adjustment may be required for co-administered drugs such as warfarin, tacrolimus and insulin following initiation of DAAs for chronic hepatitis C.

In September 2016, the PRAC of EMA recommended that a

precaution be added to package inserts of DAAs regarding the effects of hepatitis C drugs on the blood coagulability in patients treated with vitamin K antagonists.

A study was conducted in Japan with MID-NET® with data from 2010 to 2017. Although the small sample size limits the interpretation of the results, a tendency was observed that was not inconsistent with the preceding studies. Additionally, based on laboratory test results, a possible link between the changes in the patients' liver function and the changes in warfarin dose-response could not be ruled out.

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

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

(See WHO Pharmaceuticals Newsletter No.5, 2017: Interaction with warfarin in New Zealand; No.6, 2016: Interaction potential with warfarin and other vitamin K antagonists: changes to INR in Ireland)

Fluoroquinolone

Risk of aortic aneurysm and dissection

Australia. The Therapeutic Goods Administration (TGA) has announced that the product information for fluoroquinolone antibiotics has been updated to include the risk of aortic aneurysm and dissection.

Fluoroquinolones are broad-spectrum antibiotics that are active against both Gram-negative and Gram-positive bacteria. Fluoroquinolone antibiotics marketed in Australia include ciprofloxacin, norfloxacin and moxifloxacin.

The TGA investigated a safety signal relating to the rare but serious potential adverse event of aortic aneurysm and dissection associated with fluoroquinolones.

The precaution advises that fluoroquinolones should only be used after careful benefit-risk assessment and after consideration of other therapeutic options.

During the TGA's investigation, it was also identified that the product information for fluoroquinolones should be updated to include the potential adverse events of dysglycemia and psychiatric adverse reactions, including toxic psychosis, psychotic reactions progressing to suicidal ideations, hallucinations or paranoia, as precautions.

Reference:
Medicines Safety Update, TGA, 27 February 2020 (www.tga.gov.au/)

(See WHO Pharmaceuticals Newsletter No.6, 2019: Risk of tendon disorders, peripheral neuropathy and psychiatric symptoms in Japan; No.3, 2019: Risk of musculoskeletal and nervous systems damage in UK; No.1, 2019)

Fluorouracil, capecitabine, tegafur

Pre-treatment testing recommended for cancer

Europe. The EMA's PRAC has recommended that patients should be tested for the lack of dihydropyrimidine dehydrogenase (DPD), an enzyme needed to break down fluorouracil, before cancer treatment with fluorouracil and prodrugs (capecitabine and tegafur) via injection or infusion. No pre-treatment testing is needed for topical treatment with fluorouracil.

Fluorouracil is indicated to treat various cancers. Also, it is applied to the skin for actinic keratosis and dermal warts.

Lack of DPD enzyme causes fluorouracil to build up in the blood, which may lead to severe and life-threatening adverse drug reactions such as neutropenia, neurotoxicity, severe diarrhoea and stomatitis.

Patients with a known complete DPD deficiency must not be given fluorouracil, capecitabine or tegafur. For patients with a partial DPD deficiency, a reduced starting dose of these medicines should be considered.

Reference:
EMA, 13 March 2020 (*www.ema.europa.eu*)

Fosravuconazole

Risk of erythema multiforme

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

Fosravuconazole is indicated for dermatophyte and nail tinea.

A total of eight cases have been reported in patients taking fosravuconazole in Japan during the previous three years. For five of the eight cases, a causal relationship between fosravuconazole and the events could not be ruled out. No patient mortalities have been reported to date.

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

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

Ingenol mebutate (gel)

Risk of skin malignancy

United Kingdom. The MHRA has announced that the licence of ingenol mebutate gel (Picato®) has been suspended as a precautionary measure while the EMA continues to investigate an increased incidence of benign and malignant skin tumours in several clinical studies.

Ingenol mebutate gel is indicated for the treatment of actinic keratosis in adults when the outer layer of the skin affected is not thickened or raised.

Several studies have found a higher incidence of skin tumours in the treatment area in patients who had used ingenol mebutate or a related ester. Post-marketing reports of skin tumours in patients treated with ingenol mebutate gel have also been received.

Although the number of uncertainties remain and the data are still being reviewed, given the concerns regarding the possible risk of skin malignancy, the EMA has recommended a precautionary EU-wide suspension of ingenol mebutate gel.

Reference:
Drug Safety Update, MHRA, 12 February 2020 (www.gov.uk/mhra)

(See WHO Pharmaceuticals Newsletter No.1, 2020: Use with caution in patients with a history of skin cancer in Ireland; No.1, 2020: Suspension during safety review in EU; No.6, 2019: Increased incidence of skin tumours in UK; No.5, 2019: Potential risk of skin cancer in EU)

combination with a reduced-calorie diet and increased physical activity to help weight loss in adults who are obese or overweight and have weight-related medical problems. It works by increasing feelings of fullness.

When FDA approved lorcaserin in 2012, the manufacturer was required to conduct a clinical trial to evaluate the risk of cardiovascular problems. The lorcaserin group reported higher frequency of several different types of cancers.

Health-care professionals should stop prescribing lorcaserin; they should contact patients currently taking lorcaserin, inform them of the increased occurrence of cancer, and ask them to stop taking lorcaserin. Additionally, health-care professionals should discuss alternative weight-loss medicines or strategies with the patients.

Reference:
MedWatch, US FDA, 13 February 2020 (www.fda.gov)

(See WHO Pharmaceuticals Newsletter No.1, 2020: Potential risk of cancer in USA)

Montelukast

Boxed warning strengthened for serious behaviour and mood-related changes

USA. The FDA has announced that it is strengthening existing

adverse drug reactions, including suicidal thoughts or actions. However, many health-care professionals and patients are not aware of the risk. FDA decided a stronger warning is needed after conducting an extensive review of available information.

Health-care professionals should ask patients about any history of psychiatric illness prior to initiating treatment, and consider the risks and benefits of montelukast when deciding to prescribe or continue patients on the medicine. Also, they should advice patients of the risk of neuropsychiatric events when prescribing montelukast, and monitor those treated with montelukast for neuropsychiatric symptoms.

Reference:
MedWatch, US FDA, 4 March 2020 (www.fda.gov)

(See WHO Pharmaceuticals Newsletter No.6, 2019: Risk of neuropsychiatric reactions in UK; No.3, 2013: Neuropsychiatric risks in Australia)

Rotigotine

Risk of rhabdomyolysis

Japan. The MHLW and the PMDA have announced that the package insert for rotigotine (Neupro patch®) should be revised to include rhabdomyolysis as an adverse drug reaction.