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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 newsletter includes a feature article with the recommendations from the 40th Annual Meeting of Representatives of the National Pharmacovigilance Centres participating in the WHO Programme for International Drug Monitoring.

Contents

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Aripiprazole

Risk of impulse-control disorder

Japan. The Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA) have announced that the package insert for aripiprazole (Abilify®) has been updated to include the risk of impulse-control disorder as a precaution.

Aripiprazole is indicated for schizophrenia, improvement of manic symptoms in patients with bipolar disorder, depression, depressed state (within certain limits) and irritability accompanying childhood autism spectrum disorder.

Four cases associated with impulse-control disorder have been reported in Japan. The causal relationship was not evaluated. The company core datasheet (CCDS) has also been updated. In addition, the US Food and Drug Administration (FDA) and the Australian Therapeutic Goods Administration (TGA) have also updated package inserts to include the risk of impulse-control disorder.

Reference:
Revision of Precautions, MHLW/PMDA, 11 January 2018 *(www.pmda.go.jp/english/)*

(See WHO Pharmaceuticals Newsletters No.2, 2017: Risk of impulse control disorders, No.3, 2016: Risk of impulse-control problems in the USA and No.6, 2015: Risk of certain impulse control behaviours in Canada)

Cladribine

Risk of progressive multifocal encephalopathy (PML)

The United Kingdom. The Medicines and Healthcare Products Regulatory Agency (MHRA) has updated the product information for cladribine preparations (Litak®, Leustat ®) to include the risk of progressive multifocal encephalopathy (PML) as a potential adverse drug reaction.

Cladribine is indicated for hairy cell leukaemia and B-cell chronic lymphocytic leukaemia.

As of March 2017, three confirmed reports of PML (including at least one fatal case) have been reported worldwide in patients taking cladribine for various haematological conditions. None of these reports originated from the United Kingdom.

Health-care professionals are advised to consider PML in the differential diagnosis for patients with new or worsening neurological signs or symptoms, even several years after treatment with cladribine. A letter has been sent to haematologists and oncologists about this risk.

Reference:
Drug Safety Update, MHRA, Volume 11, issue 5: 2, December 2017 *(www.gov.uk/mhra)*

Spain. La Agencia Española de Medicamentos y Productos Sanitarios (AEMPS) has recommended that health-care professionals perform a differential diagnosis in patients who present new neurological symptoms or worsening of the pre-existing symptoms while using cladribine, and suspend use in those with suspected PML.

Cladribine is indicated for the treatment of hairy cell leukaemia (PCL) (Leustatin® and Litak®) and chronic lymphocytic leukaemia (Leustatin®).

Several cases of PML associated with the use of cladribine have been reported in Europe. Of these, one had a fatal outcome with a clear diagnosis and no identified confounding factors.

In the cases reported, the diagnosis of PML was made from six months to several years after the end of treatment with cladribine. Additionally, there is a clear biological plausibility since prolonged lymphopenia induced by cladribine is a potential risk factor for PML.

Reference:
Información para profesionales sanitarios, AEMPS, 1 December 2017, Spain (*www.aemps.gob.es*)

Clozapine

Risk of pleurisy

Japan. The MHLW and the PMDA have announced that the package insert for clozapine (Clozaril®) has been updated to include the risk of pleurisy as a clinically significant adverse reaction.

Clozapine is indicated for treatment-resistant schizophrenia.

Six cases associated with pleurisy have been reported in Japan. Of these, a causal relationship could not be excluded in one case. The company core datasheet (CCDS) has also been updated.

Reference:
Revision of Precautions, MHLW/PMDA, 28 November 2017 *(www.pmda.go.jp/english/)*

Dengvaxia®

Risk in individuals with no prior experience of dengue infection

Singapore. The Health Sciences Authority (HSA) has strengthened warnings and recommendations in the prescribing information for Dengvaxia® about the increased risk of developing clinically severe dengue in individuals not previously infected by dengue.

The package insert provides advice on assessing individuals for a history of previous dengue infection before vaccination, and states that vaccination is not recommended for individuals who have not been previously infected with dengue.

Dengvaxia® is used for the prevention of dengue infection caused by dengue virus (serotypes 1, 2, 3 and 4) in individuals aged between 12 and 45 years. Currently in Singapore, dengue vaccination is not part of the national immunisation programme.

Results from clinical and long-term safety studies by the manufacturer confirmed that there is a postulated risk of a higher incidence of severe dengue following vaccination in individuals who have not been previously infected by dengue.

All health-care professionals have been issued advice on these findings and were informed of the recommendation not to vaccinate individuals who have no history of a previous dengue infection. The HSA will monitor the vaccine closely to ensure continued safety and efficacy.

Reference:
HSA Updates, HSA, 1 and 8 December 2017 (*http://www.hsa.gov.sg/*)

Edoxaban

Risk of interstitial lung diseases

Japan. The MHLW and the PMDA have announced that the package insert for edoxaban (Lixiana®) has been updated to include the risk of interstitial lung disease as a clinically significant adverse reaction.

Edoxaban is used to reduce the risk of ischaemic stroke, systemic embolism, and venous thromboembolism.

Nineteen cases associated with interstitial lung diseases have been reported in Japan. Of these, a causal relationship could not be excluded in eight cases.

Reference:
Revision of Precautions, MHLW/PMDA, 11 January 2018 *(www.pmda.go.jp/english/)*

Eluxadoline

Risk of pancreatitis

The United Kingdom. The MHRA has updated the Summary of Product Characteristics (SPC) and Patient Information Leaflet for eluxadoline (Truberzi®) to include the risk of pancreatitis and also to list new contraindications.

Eluxadoline is no longer indicated for use in individuals who have undergone cholecystectomy or who have biliary disorders. In addition, therapy with eluxadoline should be initiated and supervised by a physician experienced in diagnosis and management of gastrointestinal disorders.

Eluxadoline was approved in 2017 for the treatment of irritable bowel syndrome with diarrhoea in adults.

A routine European review identified 230 suspected cases of pancreatitis in patients taking eluxadoline over an estimated exposure of 26,363 patient-years. All cases of pancreatitis occurred before April 2017 when use in patients without a gallbladder became a contraindication. Of these, 76% of 140 cases with known gallbladder status were in patients who had undergone cholecystectomy and did not have a gallbladder. Four cases were severe and in two of these cases, eluxadoline appears to have contributed to the patient's death. Dehydration and pulmonary complications of acute pancreatitis have been reported in the literature.

Most of the reported cases of pancreatitis occurred within a week of starting treatment and some patients developed symptoms after one or two doses. However, cases of pancreatitis after longer duration of treatment have also been reported.

In most cases, eluxadoline treatment was withdrawn. At the time of review, out of 123 cases with an outcome reported, most (107) patients recovered from the pancreatitis or their condition improved.

Reference:
Drug Safety Update, MHRA, Volume 11, issue 5: 4, December 2017 *(www.gov.uk/mhra)*

(See WHO Pharmaceuticals Newsletter No.2, 2017: Increased risk of serious pancreatitis in patients without a gallbladder in the USA)

Epoetins

Risk of Severe Cutaneous Adverse Reactions (SCARs)

Ireland. The Health Products Regulatory Authority (HPRA) has stated that severe cutaneous adverse reactions (SCARs) are considered to be a class effect of all epoetins.

Human endogenous erythropoietin (EPO) is a growth factor produced primarily by the kidney in response to hypoxia. There are several forms of synthetic erythropoietin (i.e. darbepoetin alfa, epoetin alfa, epoetin beta, epoetin theta, epoetin zeta and methoxy polyethylene glycol-epoetin beta) licensed for anaemias, or in the case of certain epoetins, for use before autologous blood donation, or for high-risk patients prior to specific surgeries.

The Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) recently completed a detailed analysis of SCARs associated with epoetin-containing medicines. This review was initiated following post-market reports

of SCARs including Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) with some epoetins.

The PRAC concluded that SCARs, including SJS and TEN, are considered a class effect for all epoetins and the product information for these medicines will be updated accordingly.

Reference:
Drug Safety Newsletter, HPRA, November 2017 (*https://www.hpra.ie/docs/default-source/publications-forms/newsletters/hpra-drug-safety-newsletter-edition-83.pdf?sfvrsn=5*)

The United Kingdom. The MHRA has updated the product information of all recombinant human erythropoietins (r-HuEPOs; epoetin alfa, darbepoetin alfa, epoetin beta, epoetin zeta and methoxy polyethylene glycol-epoetin beta) to reflect the risk of SCARs and to advise healthcare professionals and patients to permanently discontinue r-HuEPOs should these reactions occur.

A 2017 European review triggered by post-market reports of SCARs concluded that the class of r-HuEPOs is associated with a risk of SCARs, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).

The review assessed all cases worldwide received up to February 2017, and identified a total of 23 reports of SJS and 14 reports of TEN with r-HuEPOs use. The review concluded that eight reports of SJS and one case of TEN were causally associated with r-HuEPOs. More severe cases were observed with long-acting r-HuEPOs (darbepoetin alfa and methoxy polyethylene glycol-epoetin beta. The review concluded that the risk of severe cutaneous adverse reactions was a class effect with all r-HuEPOs.

Reference:
Drug Safety Update, MHRA, Volume 11, issue 6: 2, January 2018 *(www.gov.uk/mhra)*

Fingolimod

1. Potential risk of thrombocytopenia

Canada. Health Canada has updated the product safety information for fingolimod (Gilenya®) to inform health-care professionals about the risk of thrombocytopenia.

Fingolimod is authorized to treat multiple sclerosis and is used in patients who have had a poor response to or, are unable to tolerate one or more other therapies for multiple sclerosis.

Health Canada reviewed the potential link between thrombocytopenia and fingolimod following reports that were received from the manufacturer.

At the time of the review, Health Canada had received 11 unique Canadian reports of thrombocytopenia suspected to be linked to the use of fingolimod. Eight reports were excluded from further review because there was not enough information. A possible link between fingolimod and thrombocytopenia was found in the remaining three reports.

This safety review also looked at information from 56 international reports and one report from the manufacturer of thrombocytopenia associated with the use of fingolimod. Forty reports were excluded from further review mainly because there was not enough information. Of the remaining 17 reports, 14 suggested a possible link between fingolimod and thrombocytopenia, and in three cases, thrombocytopenia was most likely due to other causes such as infection or another medication.

A search of the literature found some evidence of a potential link between thrombocytopenia and fingolimod use.

Health Canada's safety review concluded that there was a potential link between the use of fingolimod and thrombocytopenia.

Reference:
Summary Safety Review, Health Canada, 6 December 2017 (*www.hc-sc.gc.ca*)

2. Contraindications for patients with pre-existing cardiac disorders.

The United Kingdom. The MHRA has introduced new contraindications for fingolimod (Gilenya®) in patients with pre-existing cardiac disorders.

A routine EU review identified 44 post-market global reports of serious ventricular tachyarrhythmia and six reports of sudden death in patients taking fingolimod up to the end of February 2017. To this date, the cumulative post-market exposure to fingolimod was estimated to be 397,764 patient-years. The review recommended that warnings against the use of fingolimod in patients with underlying cardiac disorders should be strengthened and listed as a contraindication for use.

Reference:
Drug Safety Update, MHRA, Volume 11, issue 5: 5, December 2017
(www.gov.uk/mhra)

(See WHO Pharmaceuticals Newsletter No.6, 2017: Contraindicated in patients with underlying cardiac pathology and risks of skin neoplasms in Spain)

Flucloxacillin and concomitant paracetamol

Interaction: Risk of high anion gap metabolic acidosis

Ireland. The HPRA has stated that the SPC and package leaflet for flucloxacillin-containing medicinal products will be updated to include

information on the risk of high anion gap metabolic acidosis (HAGMA) and concomitant paracetamol therapy.

Flucloxacillin containing medicinal products are licensed for the treatment of specified bacterial infections.

The Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) recently concluded a review of the risk of HAGMA with flucloxacillin and concomitant paracetamol therapy. Evidence in the literature and a limited number of spontaneous reports seem to support the possibility of the appearance of a specific type of HAGMA (pyroglutamic acidosis) in the presence of flucloxacillin and paracetamol.

Reference:
HPRA Drug Safety Newsletter, 83rd edition, 30 November 2017 (http://www.hpra.ie/docs/default-source/publications-forms/newsletters/hpra-drug-safety-newsletter-edition-83.pdf?sfvrsn=5)

Gadolinium-based contrast agents (GBCAs)

Gadolinium retention in body

Japan. The MHLW and the PMDA have announced that the package inserts for gadolinium-based contrast agents (GBCAs) brain tissue after use. However, there has been no clear evidence of clinical symptoms related to gadolinium retention in the brain occurring in patients. It is not known in the long-term if gadolinium retention in the brain can lead to delayed adverse reactions including nerve disorders.

It has been reported that gadolinium retention in the brain is mostly confirmed with linear GBCAs and there is less deposit in the brain tissues in patients who have received macrocyclic GBCAs. Thus, it is considered appropriate to use macrocyclic GBCAs preferentially when MRI scans with GBCAs are required and to use linear GBCAs when macrocyclic GBCAs are not appropriate for the patients for reasons including the incidence of adverse reactions.

Reference:
Revision of Precautions, MHLW/PMDA, 28 November 2017 *(www.pmda.go.jp/english/)*

USA. The US FDA has required several actions to alert health-care professionals and patients about gadolinium retention after a MRI using GBCA, and actions that can help minimize problems. These include requiring a new patient medication guide and providing educational information that every patient will be asked to read before receiving a GBCA. The FDA has also required manufacturers of GBCAs to gadolinium retention could not be established.

Gadolinium retention has not been directly linked to adverse health effects in patients with normal kidney function, and the FDA has concluded that the benefit of all approved GBCAs continues to outweigh any potential risks. However, after additional review and consultation with the Medical Imaging Drugs Advisory Committee, the FDA is requiring several actions as above.

Reference:
Safety Alerts for Human Medical Products, US FDA, 19 December 2017 *(www.fda.gov)*

(See WHO Pharmaceuticals Newsletters No.5, 2017: Retention of gadolinium in the brain in New Zealand, No.4, 2017: Restrictions on use in EU, No harmful effects identified with brain retention in the USA and No.5, 2015: Possible risk of brain deposits with repeated use in the USA)

Idelalisib

Risk of a rare brain infection (progressive multifocal leukoencephalopathy)

Canada. Health Canada has updated the product safety information for idelalisib (Zydelig®) to warn health-care professionals and patients about the risk of progressive multifocal leukoencephalopathy (PML).

Idelalisib is a prescription drug