World Health Organization

WHO Pharmaceuticals NEWSLETTER

2020

No. 6

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:

Safety and Vigilance: Medicines,

EMP-HIS,
World Health Organization,
1211 Geneva 27, Switzerland,
E-mail address: pvsupport@who.int

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 articles on COVID-19 vaccines: Safety Surveillance Manual and the Vaccine Safety Net (VSN) Virtual Meeting.

Contents

WHO Pharmaceuticals Newsletter No. 6, 2020

ISBN 978-92-4-001836-5 (electronic version)
ISBN 978-92-4-001837-2 (print version)

Table of Contents

Regulatory Matters

Safety of medicines

Signal

Feature

Asparaginase

Risk of sepsis

Republic of Korea. The Ministry of Food and Drug Safety (MFDS) has updated the drug label for asparaginase products to include the risk of sepsis.

Asparaginase is a bacterial enzyme used in the treatment of acute lymphoblastic leukemia.

During the evaluation process of serious adverse event (SAE) reports, the Korea institute of Drug Safety and Risk Management (KIDS) reviewed one fatal SAE report of sepsis in a patient who received asparaginase-containing lymphoma treatment regimen. The signal detected from the SAE report was re-assessed through routine signal analysis process.

At the time of review, the KIDS had received three domestic and 76 foreign reports of sepsis with asparaginase through the Korean adverse event reporting system since 1989. Data mining results of the reports within the database identified a statistical association between asparaginase and sepsis. Case evaluation was performed on these reports, in which a causal association could not be excluded.

This recommendation announced by the MFDS was based on the results of SAE review system and signal analysis and evaluation procedure at KIDS.

Health-care professionals should be reminded of the possible hematologic toxicities and myelosuppressive effects of asparaginase-containing chemotherapy regimen and are advised to monitor for any signs of serious infections during use of this drug.

Reference:
Based on the communication from MFDS and KIDS, Republic of Korea, November 2020

Benzodiazepine

Boxed warning updated to improve safe use

USA. The US Food and Drug Administration (FDA) has announced that it is requiring that the Boxed Warnings of benzodiazepine containing products are updated to include information on the risk of abuse, misuse, addiction, physical dependence and withdrawal reactions.

Benzodiazepines are indicated to treat generalized anxiety disorders, insomnia, seizures, social phobia and panic disorders.

Health-care professionals prescribing a benzodiazepine should consider the patient's condition, any concomitant medicines and assess the risk of abuse, misuse and addiction.

Also health-care professionals should limit the dosage and duration of the prescribed benzodiazepine to the minimum needed to achieve the desired clinical effect. Upon discontinuation dosage should be reduced gradually to reduce the risk of acute withdrawal reactions.

Precautions should be taken when benzodiazepines are used in combination with opioid addiction medications.

Reference:
MedWatch, US FDA, 23 September 2020 *(*www.fda.gov*)*

(See also WHO Pharmaceuticals Newsletter No.3, 2020: Risk of potentially fatal respiratory depression in UK, No.5, 2016: Serious risk of slowed or breathing difficulties and deaths in US)

Cytarabine

Risk of cytarabine syndrome

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

Cytarabine is indicated to treat acute leukaemia, gastrointestinal carcinoma, lung cancer, breast cancer, female genital cancer and bladder tumour.

A total of two cases of cytarabine syndrome in patients treated with cytarabine have been reported in Japan during the previous three years, for which a causal relationship between the drug and event was reasonably possible. To date, no patient mortalities have been reported.

Symptoms of cytarabine syndrome include pyrexia, muscle pain, bone pain and malaise. Patients should be carefully monitored, and if any of these symptoms occur, appropriate measures should be taken such as administration of a corticosteroid.

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

Reference:
Revision of Precautions, MHLW/PMDA, 6 October 2020 *(*www.pmda.go.jp/english/*)*

Dolutegravir

Updated advice on increased risk of neural tube defects

United Kingdom. The Medicines and Healthcare products Regulatory Agency (MHRA) has announced that updated safety recommendations have been issued as part of the European review evaluating cases of neural tube defects in babies born to mothers who became pregnant while taking the HIV medicine dolutegravir (Tivicay®, Triumeq® and Juluca®).

Dolutegravir is an integrase

inhibitor indicated in combination with other anti-retroviral medicinal products for the treatment of HIV in adult, adolescents, and children older than six years.

In June 2018, preliminary results from an observational study suggested an increased risk of neural tube defects in infants born to women who took dolutegravir at the time of conception. While a review of this signal was ongoing, the MHRA asked health-care professionals not to prescribe dolutegravir to women who are trying to become pregnant.

Evidence in the latest review shows a smaller increased risk than previously thought, almost comparable to other HIV drugs.

Health-care professionals should counsel women of childbearing potential about the possible risk of neural tube defects with dolutegravir, including consideration of effective contraceptive measures. Also, if a pregnancy is confirmed in the first trimester while a patient is on dolutegravir, the benefits and risks of continuing dolutegravir versus switching to another antiretroviral regimen should be discussed with the patients.

Reference:
Drug Safety Update, MHRA, 22 October 2020 *(www.gov.uk/mhra)*

(See also Full List of WHO Medical Product Alerts, WHO, October 2018 (http://www.who.int/medicines/publications/drugalerts/DTG_followon_may2018.pdf?ua=1) and WHO Pharmaceuticals Newsletter No.6, 2018: Risk of neural tube defects in Europe)

Erythromycin

Risk of cardiovascular event and infantile hypertrophic pyloric stenosis (IHPS)

Ireland. The Health Products Regulatory Authority (HPRA) has announced that the product information (Summary of Product Characteristics (SmPC) and Package Leaflet (PL)) for erythromycin-containing medicines have been updated to reflect current knowledge of the risks of cardiovascular event and, infantile hypertrophic pyloric stenosis (IHPS).

Erythromycin is a macrolide antibiotic known to be associated with a risk of QT-prolongation and cardiac arrhythmia.

The European Medicines Agency's (EMA's) Pharmacovigilance Risk Assessment Committee (PRAC) conducted an assessment of erythromycin-containing medicines and considered data from observational studies that identified a rare, short-term risk of cardiovascular events associated with macrolides including erythromycin. Based on this data, the PRAC recommended that the risk of cardiovascular events should be balanced with known treatment benefits when prescribing erythromycin-containing medicines, particularly in patients at high risk of cardiovascular events.

Also, results of the review supported a potential association between exposure of erythromycin in infants and the risk of IHPS.

Erythromycin should not be administered to patients with a history of QT-prolongation or ventricular cardiac arrhythmia or electrolyte disturbances.

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

Fentanyl (transdermal patch)

Contraindication in opioid-naive patients recommended

United Kingdom. The MHRA has announced that the Commission on Human Medicines (CHM) has recommended that fentanyl transdermal patches are contraindicated in opioid-naive patients, due to the risk of respiratory depression.

Fentanyl is a potent opioid analgesic.

The CHM convened an expert working group to examine the benefits and risks of opioids in the relief of non-cancer pain.

Up to May 2020, the MHRA has received 13 cases of respiratory depression following use of fentanyl in opioid-naive patients.

Because of the risk of respiratory depression, the use of fentanyl patches in non-cancer patients should be limited to only those who have previously tolerated opioids.

The initial dose of fentanyl should be based on a patient's opioid history.

Reference:
Drug Safety Update, MHRA, 23 September 2020 *(www.gov.uk/mhra)*

(See also WHO Pharmaceuticals Newsletter No.6, 2018; Life-threatening and fatal opioid toxicity from accidental exposure in UK; No.4, 2014: Reminder of potential life-threatening harm from accidental exposure, particularly in children)

Flucytosine

Contraindication in patients with dihydropyrimidine dehydrogenase (DPD) deficiency

United Kingdom. The MHRA has announced that flucytosine (Ancotil®) is contraindicated for use in patients with complete and partial dihydropyrimidine dehydrogenase (DPD) deficiency, due to the risk of life-threatening and severe toxicity.

Flucytosine is a prodrug of 5-fluorouracil used to treat systemic yeast and fungal infections.

DPD activity is rate limiting in the catabolism of 5-fluorouracil. Patients with DPD deficiency are therefore at increased risk of toxicity, including stomatitis, diarrhoea, mucosal inflammation, neutropenia and neurotoxicity.

In order to avoid a delay in starting antimycotic therapy, testing for DPD deficiency is not required before treatment with flucytosine. However, determination of DPD activity should be considered when there is a confirmed or suspected drug toxicity. In case of suspected drug toxicity, discontinuation of the treatment with flucytosine should be considered.

Reference:
Drug Safety Update, MHRA, 22 October 2020 *(www.gov.uk/mhra)*

5-Fluorouracil (intravenous), capecitabine, tegafur

Dihydropyrimidine dehydrogenase (DPD) deficiency testing recommended before initiation

United Kingdom. The MHRA has announced that the product information (SmPC and Patient Information Leaflets (PIL)) for 5-fluorouracil, capecitabine and tegafur will be updated to include information on the importance of testing for DPD deficiency before initiation of the treatment.

Fluoropyrimidines are a group of anti-cancer medicines including 5-fluorouracil and its prodrugs capecitabine and tegafur.

A recent European safety review has recommended that despite uncertainties in the optimal pre-treatment testing methodologies, all patients should undergo testing for DPD deficiency prior to the initiation of these treatments.

Fluorouracil is also available in topical formulations, but due to very low systemic absorption via this route, DPD testing is not required prior to initiation.

Up to 17 June 2020, 30 reports associated with a fatal outcome that describe a known or suspected DPD deficiency with fluorouracil and capecitabine have been received. These include reports of testing and confirmation of DPD deficiency after patients were treated with capecitabine and developed severe and fatal toxicity.

Health-care professionals should test all patients for DPD deficiency before initiation of treatment. Patients with known complete DPD deficiency should not be treated with these medicines. For patients with partial DPD deficiency, a reduced starting dose should be considered.

All patients should be monitored for toxicity particularly during the first cycle of treatment or after a dose increase.

Reference:
Drug Safety Update, MHRA, 22 October 2020 *(www.gov.uk/mhra)*

(See also WHO Pharmaceuticals Newsletter No.2, 2020: Pre-treatment testing recommended for cancer in Europe)

Glatiramer

Risk of hepatic impairment

Japan. The MHLW and the PMDA have announced that the package inserts for glatiramer (Copaxone S.C.®) should be revised to include hepatic impairment as an adverse drug reaction.

Glatiramer is indicated to prevent relapse of multiple sclerosis.

One case of hepatic impairment in a patient treated with glatiramer has been reported in Japan during the previous three years, for which a causal relationship between the drug and event was reasonably possible. No patient mortalities have been reported.

Liver function tests should be performed prior to the initiation and periodically during the administration of glatiramer.

Reference:
Revision of Precautions, MHLW/PMDA, 5 November 2020 *(www.pmda.go.jp/english/)*

Insulin

Risk of cutaneous amyloidosis at injection site

United Kingdom. The MHRA has announced that the SmPC and PIL for all insulin-containing products are being updated to include the risk of cutaneous amyloidosis at injection site.

Insulin is indicated to treat all types of diabetes including type I and II diabetes and gestational diabetes.

In the UK, up until the end of July 2019, two reports of cutaneous amyloidosis in patients receiving insulin therapy have been received.

Patients who inject insulin at the same site regularly, are at an increased risk of developing cutaneous amyloidosis at the injection site and consequently may have poor diabetes control as the amyloid causes absorption to decrease. Health-care professionals should advise patients to rotate injection sites within the same body region to prevent the risk.

There also is a risk of hypoglycaemia in patients that suddenly change injection site from an area with cutaneous amyloidosis to an unaffected area. Health-care professionals should advise patients to carefully monitor blood glucose after a change in injection site and that dose adjustment of

insulin or other antidiabetic medication may be needed.

Reference:
Drug Safety Update, MHRA, 23 September 2020 (www.gov.uk/mhra)

Methotrexate

New measures to reduce risk of fatal overdose

United Kingdom. The MHRA has announced that new measures have been implemented to reduce the risk of fatal overdose of methotrexate.

Methotrexate is indicated to treat autoimmune conditions and should be taken once a week.

Since January 2006 up to July 2020, the MHRA received 11 cases of serious toxicity associated with inadvertent daily dosing of once-weekly methotrexate in the UK, with four of these serious reports received since January 2016.

Overdose of methotrexate can lead to serious adverse drug reactions such as haematopoietic disorders and gastrointestinal reactions.

The product information and outer and inner packaging of methotrexate for once-weekly dosing will carry a warning about the dosing schedule and the consequences of dosing errors.

Also, methotrexate products will come with a patient card, which will prompt patients to take methotrexate once a week and to record the day of the week for intake.

Educational materials for health-care professionals will also be made available for oral products with indications requiring once-weekly dosing.

Reference:
Drug Safety Update, MHRA, 23 September 2020 (www.gov.uk/mhra)

(See also WHO Pharmaceuticals Newsletter No.1, 2020: New measures to avoid dosing errors in Ireland)

Niraparib

Risk of severe hypertension and posterior reversible encephalopathy syndrome (PRES)

United Kingdom. The MHRA has announced that the product information for niraparib (Zejula®) has been updated to strengthen the warning of the risk of severe hypertension and posterior reversible encephalopathy syndrome (PRES).

Niraparib is indicated as monotherapy for the maintenance treatment of adults with platinum-sensitive relapsed high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response to platinum-based chemotherapy.

A recent European review identified worldwide reports of patients who developed severe hypertension including rare cases of hypertensive crisis. Also the review identified rare reports of PRES.

The product information for niraparib had an existing warning for hypertension including hypertensive crisis and recommended that blood pressure should be monitored monthly in the first year. Based on the review safety warnings have been updated to recommend more frequent blood pressure measurements, especially at the start of treatment.

In the UK, up to 30 July 2020, six reports of hypertension associated with niraparib were received. No reports have been received for PRES associated with niraparib.

Health-care professional should control pre-existing hypertension adequately before treatment and monitor blood pressure from initiation. Also, the use of niraparib should be discontinued in case of hypertensive crisis of PRES.

Reference:
Drug Safety Update, MHRA, 22 October 2020 (www.gov.uk/mhra)

Nivolumab (genetic recombination)

Risk of fulminant hepatitis

Japan. The MHLW and the PMDA have announced that the package insert for nivolumab (genetic recombination) (Opdivo®) should be revised to include fulminant hepatitis as an adverse drug reaction.

Nivolumab is indicated to treat a number of cancers including malignant melanoma, unresectable or metastatic renal cell carcinoma, relapsed or refractory classical Hodgkin lymphoma and relapsed or metastatic head and neck cancer.

A total of 18 cases involving fulminant hepatitis in patients treated with nivolumab have been reported in Japan during the previous three years, of which a causal relationship between the drug and event was reasonably possible in three cases. A total of 10 patient mortalities have been reported to date, which a causal relationship between the drug and event was reasonably possible in three cases.

Fulminant hepatitis, hepatic failure, hepatic impairment, hepatitis and sclerosing cholangitis may occur. Patients should be carefully monitored through periodic liver function tests.

Reference:
Revision of Precautions, MHLW/PMDA, 5 November 2020 (www.pmda.go.jp/english/)

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

Risk of kidney problems with foetal exposure

USA. The US FDA has announced that it is requiring changes to the prescribing information for nonsteroidal anti-inflammatory drugs (NSAIDs) and will update the Drug Facts labels to warn about rare but serious kidney problems in unborn babies with the use of NSAIDs around 20 weeks or later in pregnancy.

NSAIDs are some of the most commonly used medicines for pain and fever and used to treat medical conditions such as arthritis, menstrual cramps, headaches, colds and the flu. Examples of NSAIDs include aspirin, ibuprofen, naproxen, diclofenac and celecoxib. Also, common adverse effects of NSAIDs include stomach pain, constipation, diarrhoea, gas, heartburn, nausea, vomiting and dizziness.

Health-care professionals should limit prescribing NSAIDs between 20 to 30 weeks of pregnancy and avoid prescribing them after 30 weeks of pregnancy. Ultrasound monitoring of amniotic fluid should be considered if NSAID treatment extends beyond 38 hours and NSAIDs should be discontinued if oligohydramnios is found.

Complications of prolonged

Opioids

Risk of dependence and addiction

United Kingdom. The MHRA has announced that the CHM has made recommendations on including warnings on packages of opioids about the risk of dependence and addiction.

Opioids are used in the treatment of pain. More than 20 different opioid medicines are authorised in the UK, including alfentanil, dihydrocodeine, meptazinol, oxycodone, fentanyl and morphine.

The CHM convened an expert working group to examine the benefits and risks of opioids in the relief of no-cancer pain. The CHM recommended that the packaging for all opioid medicines in the UK carries the warnings "can cause addiction" and "contains opioid".

Health-care professionals should inform patients of the potential of drug dependence and addiction with the prolonged use of opioids, even at therapeutic doses. Typical signs of addiction include expression of cravings for the drug and experiencing withdrawal adverse effects when opioids are stopped suddenly.

Withdrawal from an opioid is characterised by shivers, diarrhoea, insomnia and myalgia. To minimize the risk

No.3, 2019: Risk of uncontrolled pain and withdrawal symptoms following sudden discontinuation in US)

Ticagrelor

Potential risk of central sleep apnea

Canada. Health Canada has announced that it has requested the manufacturer of ticagrelor (Brilinta®) to update the safety information to add a warning about the potential risk of central sleep apnea (CSA).

Ticagrelor is used with low-dose acetylsalicylic acid (e.g. aspirin) to decrease the risk of having a stroke or dying from heart or blood vessel disease.

Triggered by the publication of two confirmed cases of CSA, Health Canada reviewed the available information from searches of the Canada vigilance database, international databases and published literature. Also, Health Canada has reviewed two Canadian reports of CSA related to ticagrelor use, but these reports did not have enough information to be assessed.

Health Canada's review of the available information concluded that there may be a link between the use of ticagrelor and the risk of CSA.

Reference:

Summary Safety Review