World Health Organization

WHO Pharmaceuticals NEWSLETTER

2021 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:

Safety and Vigilance: Medicines,

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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 a summary of COVID-19 Subcommittee of the Global Advisory Committee on Vaccine Safety (GACVS).

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Regulatory Matters

Safety of medicines

Signal

Feature

Alemtuzumab (genetic recombination)

Risk of hypothyroidism and hyperthyroidism

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 the risk of hypothyroidism and hyperthyroidism as adverse drug reactions.

Alemtuzumab is indicated for the treatment of recurrent or refractory chronic lymphocytic leukemia and conditioning treatment prior to allogeneic haematopoietic stem cell transplant.

Cases of hypothyroidism or hyperthyroidism have been reported in patients treated with alemtuzumab overseas. Although no cases have been reported in Japan, the MHLW and the PMDA concluded that the revision of the package insert was necessary.

Reference:
Revision of Precautions, MHLW/PMDA, 26 January 2021 *(www.pmda.go.jp/english/)*

Amiodarone and Sildenafil (co-administration)

Concomitant use no longer contraindicated

Japan. The MHLW and the PMDA have announced that the package insert for amiodarone (Ancaron®) and sildenafil (Revatio®) (when used for pulmonary arterial hypertension (PAH)) should be revised to remove the contraindication of co-administration.

Amiodarone is indicated to treat ventricular fibrillation, ventricular tachycardia and cardiac failure. Sildenafil is indicated to treat PAH or erectile dysfunction (ED).

The benefits of using amiodarone and sildenafil for the treatment of arrhythmia accompanied by right heart failure due to PAH outweigh the risks of adverse effects such as QT prolongation. To date, no clinically apparent safety problems have been observed when sildenafil (used for PAH) is co-administered with amiodarone.

It should be appropriate to maintain the current contraindications for sildenafil when used for ED, as this remains a contraindication in patients with conditions such as cardiovascular disorders in which sexual activities are considered inappropriate.

Following the above-mentioned consideration, the package inserts of sildenafil (used for PAH) and amiodarone will be update to reflect the removal of the contraindication, although a precaution will be added.

Reference:
Revision of Precautions, MHLW/PMDA, 26 January 2021 *(www.pmda.go.jp/english/)*

Atezolizumab

Potential risk of autoimmune hemolytic anemia

Canada. Health Canada has announced that they are working with the manufacturer of atezolizumab (Tecentriq®) to update the product safety information to include a warning for the risk of autoimmune hemolytic anemia (AIHA).

Atezolizumab is indicated to treat certain types of lung, liver, breast and bladder cancers.

Health Canada reviewed the potential risk of AIHA with the use of atezolizumab, triggered by safety information from clinical trials and from scientific literature.

Health Canada reviewed the information from the Canadian vigilance database, international databases and published literature. The review focused on 36 case reports (one Canadian, 35 foreign).

The review concluded that there may be a link between the use of atezolizumab and AIHA.

Reference:
Summary Safety Review, Health Canada, 3 February 2021 *(www.hc-sc.gc.ca)*

(See also WHO Pharmaceuticals Newsletter No.1, 2020: Risk of haemophagocytic syndrome in Japan)

COVID-19 vaccine NRVV Ad (ChAdOx1 nCoV-19)

1. Risk of anaphylaxis and hypersensitivity

Europe. The Pharmacovigilance Risk Assessment Committee (PRAC) has recommended that the product information for COVID-19 vaccine NRVV Ad (ChAdOx1 nCoV-19) (Vaxzevria®) should be updated to include anaphylaxis and hypersensitivity as adverse events with an unknown frequency. Additionally, existing warnings should be updated to reflect that cases of anaphylaxis have been reported.

COVID-19 vaccine NRVV Ad (ChAdOx1 nCoV-19) is indicated to prevent COVID-19. Anaphylaxis is a known adverse reaction and is already included in the risk management plan for the product as a potential risk.

The update is based on a review of 41 reports of possible anaphylaxis among

approximately five million vaccinated individuals in the UK. The PRAC considered that a link to the vaccine was likely in at least some of these cases.

Reference:
EMA, 12 March 2021
(www.ema.europa.eu)

2. Possible link to very rare cases of unusual blood clots with low blood platelet counts

Europe. The PRAC has concluded that unusual blood clots with low blood platelets should be listed as very rare adverse effects of COVID-19 vaccine NRVV Ad (ChAdOx1 nCoV-19).

Most cases have occurred in women under 60 years of age within two weeks of vaccination. Specific risk factors have not been confirmed.

The PRAC noted that the blood clots occurred in veins in the brain (cerebral venous sinus thrombosis, CVST) and the abdomen (splanchnic vein thrombosis) together with low levels of blood platelets.

The PRAC reviewed 62 cases of CVST and 24 cases of splanchnic vein thrombosis reported in EudraVigilance. The cases came mainly from the European Economic Area and UK, where around 25 million people had received the vaccine.

The combination of blood clots and low blood platelets is very rare, and the overall benefits of the vaccine in preventing COVID-19 outweigh the risks.

One plausible explanation for the combination of blood clots and low blood platelets is an immune response, leading to a condition similar to one sometimes seen in patients treated with heparin.

Health-care professionals should tell people receiving the vaccine that they must seek medical attention if they develop symptoms of blood clots, neurological symptoms or petechiae.

Reference:
EMA, 7 April 2021
(www.ema.europa.eu)

WHO, Global Advisory Committee on Vaccine Safety (GACVS) review of latest evidence of rare adverse blood coagulation events with AstraZeneca COVID-19 Vaccine (Vaxzevria and Covishield), 16 April 2021.
(https://www.who.int/news/item/16-04-2021-global-advisory-committee-on-vaccine-safety-(gacvs)-review-of-latest-evidence-of-rare-adverse-blood-coagulation-events-with-astrazeneca-covid-19-vaccine-(vaxzevria-and-covishield))

Diuretics, including acetazolamide

Risk of eye disorders

Canada. Health Canada has announced that they will work with manufactures of diuretics (such as hydrochlorothiazide, chlorthalidone, indapamide) and acetazolamide, to update the safety information by adding a warning about the risks of choroidal effusion (CE), acute myopia (AM) and acute angle-closure glaucoma (AACG).

Diuretics are indicated to treat oedema and to lower high blood pressure. Acetazolamide has diuretic properties and indicated to treat glaucoma and certain types of seizures.

Triggered by updates made to the product safety information by the EMA, Health Canada reviewed the risks of CE, AM and AACG with the use of diuretics including acetazolamide.

The Canadian product safety information for some of the diuretics already include information on the eye disorders. Assessment of whether additional actions are required were made.

The review considered the Canada vigilance database, international databases and literature. It reviewed 49 cases (one Canadian, 38 foreign) of CE, AM or AACG reported with the use of diuretics or acetazolamide.

Health Canada's review showed a link between the use of the diuretics including acetazolamide and the risks of CE, AM or AACG.

Reference:
Summary Safety Review, Health Canada, 19 March 2021
(www.hc-sc.gc.ca)

Hydrocortisone

Risk of acute adrenal insufficiency in children when switching from tablets to granules

United Kingdom. The Medicines and Healthcare Products Regulatory Agency (MHRA) has announced that the product information for hydrocortisone granules (Alkindi®) will be updated following a report of an infant developing severe adrenal insufficiency when switched from hydrocortisone soluble tablets to hydrocortisone granules.

Hydrocortisone granules are indicated for replacement therapy of adrenal insufficiency in infants, children and adolescents.

Parents or carers should be advised to observe the child carefully in the first week after the switch. Also, the prescriber should instruct parents and carers what to do if the child develops any symptoms of adrenal insufficiency such as tiredness, floppiness, temperature instability, headache or vomiting.

If a child requires additional dosing during the first week after the switch, an increase in the daily dose of hydrocortisone granules should

be considered.

Reference:
Drug Safety Update, MHRA, 18 February 2021 *(www.gov.uk/mhra)*

(See also WHO Pharmaceuticals Newsletter No.1, 2021: Risk of acute adrenal insufficiency when switching oral formulations in Europe; No.1, 2019: Risk of insufficient cortisol absorption and life-threatening adrenal crisis in UK)

Ifosfamide (solution)

Potential risk of encephalopathy

Europe. The EMA has announced that the PRAC has recommended that the product information for ifosfamide is revised to update the existing warning on ifosfamide-induced encephalopathy.

Ifosfamide is indicated to treat several cancers, including various solid tumours and lymphomas.

Two recent studies suggested that the risk of encephalopathy with the use of ifosfamide solution is higher than with the use of the powder form. The PRAC considered all available data and concluded that an increased risk of encephalopathy with ifosfamide solution could neither be confirmed nor excluded due to limitations in the data.

The PRAC also concluded that the benefits of ifosfamide solution continue to outweigh the risks in the treatment of different types of cancers.

Patients should be closely monitored for symptoms of encephalopathy such as confusion, somnolence, coma, hallucination and blurred vision, particularly for those with an increased risk of encephalopathy. Also, co-administered medicines acting on the central nerves system such as antiemetics and sedatives must be used with particular caution or be discontinued if necessary.

Reference:
EMA, 12 March 2021 *(www.ema.europa.eu)*

(See also WHO Pharmaceuticals Newsletter No.2, 2020: Risk of encephalopathy in Europe)

Non-steroidal anti-inflammatory Drugs (NSAIDs) that inhibit cyclooxygenase

Exposure during pregnancy: Risk of renal impairment, decreased urine output and oligohydramnios in fetus

Japan. The MHLW and the PMDA have announced that the package insert for non-steroidal anti-inflammatory drugs (NSAIDs) that inhibit cyclooxygenase should be revised to include a precaution for pregnant women due to the risk of renal impairment, decreased urine output in foetuses and oligohydramnios in pregnant women.

NSAIDs are widely used anti-inflammatory drugs, and they include aspirin, ampiroxicam, isopropylantipyrine, ibuprofen, indometacin, etodolac, esflurbiprofen, clopidogrel, ketoprofen and salicylic acid.

The MHLW and PMDA considered the FDA's measure to alert health-care professionals that prescribing NSAIDs in women between 20 to 30 weeks of pregnancy should be limited. Also, the MHLW and PMDA considered literature including clinical studies and observational studies and ascribed the risks to the effects of cyclooxygenase 2 inhibitors.

A total of five cases of fetal renal impairment and/or oligohydramnios have been reported in Japan in the last three years. A causal relationship between the drug and event could not be established in any of the cases. No patient mortalities have been reported.

The MHLW/PMDA concluded that the revision of the package inserts is necessary for all the NSAIDs that inhibit cyclooxygenase.

Reference:
Revision of Precautions, MHLW/PMDA, 25 February 2021 *(www.pmda.go.jp/english/)*

(See also WHO Pharmaceuticals Newsletter No.6, 2020: Risk of kidney problems with foetal exposure in US; No.1, 2015: Risks during pregnancy in US)

Pomalidomide

Risk of progressive multifocal leukoencephalopathy (PML)

Japan. The MHLW and the PMDA have announced that the package insert for pomalidomide (Pomalyst®) should be revised to include the risk of progressive multifocal leukoencephalopathy (PML) as an adverse drug reaction.

Pomalidomide is indicated for the treatment of relapsed or refractory multiple myeloma.

A total of three cases of PML have been reported in Japan in the last three years. A causal relationship between the drug and event was assessed to be reasonably possible for these cases. No patient mortalities have been reported.

Patients should be carefully monitored if treated with pomalidomide, for symptoms such as disturbed consciousness, cognitive disorder and paralytic symptoms imaging through MRI. If these symptoms occur, a cerebrospinal fluid test should be performed and administration should be discontinued.

Reference:
Revision of Precautions, MHLW/PMDA, 26 January 2021 *(www.pmda.go.jp/english/)*

Pregabalin

Risk of severe respiratory depression

United Kingdom. The MHRA has announced that the product information for pregabalin (Lyrica®) will be amended to include new warnings for respiratory depression.

Pregabalin is indicated for the treatment of peripheral and central neuropathic pain with partial seizures and for generalized anxiety disorder in adults.

Use of pregabalin with opioid medicines or other central nervous system (CNS) depressant medicines has been previously associated with reports of respiratory failure, coma and deaths.

A recent European review considered reports of severe respiratory depression thought to be related to the action of pregabalin alone on the CNS.

Similar warnings are already in place for gabapentin (Neurotonin®) and other gabapentinoids medicines.

Health-care professionals should consider whether adjustments are necessary for patients at higher risk of respiratory depression including those with compromised respiratory function and aged older than 65 years.

Reference:
Drug Safety Update, MHRA, 18 February 2021 *(www.gov.uk/mhra)*

(See also WHO Pharmaceuticals Newsletter No.1, 2020: Risk of serious breathing problems in US; No.6, 2017: Risk of severe respiratory depression in UK; No.5, 2016: Risk of serious breathing problems (respiratory depression) in Canada)

Salbutamol

Risk of shock and anaphylaxis

Japan. The MHLW and the PMDA have announced that the package insert for salbutamol (Venetlin®, Sultanol®) should be revised to include the risk of shock and anaphylaxis as adverse drug reactions.

Salbutamol is indicated for relief of symptoms associated with airflow obstruction and bronchospasm.

A total of three cases of shock or anaphylaxis have been reported in Japan in the last three years, one of which was assessed to have a possible causal relationship between the drug and event. No patient mortalities have been reported.

Patients should be carefully monitored and if any abnormalities are observed, administration of salbutamol should be discontinued and appropriate measures should be taken.

Reference:
Revision of Precautions, MHLW/PMDA, 25 February 2021 *(www.pmda.go.jp/english/)*

Sofosbuvir

Potential risk of severe cutaneous adverse reactions (SCAR)

Canada. Health Canada has announced that they will be working with the manufacturer to update the safety information for sofosbuvir to include the risk of Stevens–Johnson syndrome (SJS).

Sofosbuvir is indicated to treat chronic hepatitis C virus infection.

Health Canada reviewed the potential risk of severe cutaneous adverse reactions (SCAR) with the use of sofosbuvir. This was triggered by an update to the product safety information made by the EMA.

The safety review focused on specific types of SCAR: SJS and toxic epidermal necrolysis (TEN), acute generalized exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS), erythema multiforme (EM) and bullous dermatitis (BD).

Health Canada reviewed 13 foreign reports from available information in the Canada vigilance database, international databases and published literature.

The conclusion of the review was that there may be a link between the use of sofosbuvir and the risk of SJS.

Reference:
Summary Safety Review, Health Canada, 27 January 2021 *(www.hc-sc.gc.ca)*

Ulipristal acetate

Further restrictions for use due to risk of serious liver injury

United Kingdom. The MHRA has announced that further restrictions for use of ulipristal acetate 5mg (Esmya®) have been issued, due to the risk of serious liver injury and liver failure.

Following restrictions, ulipristal acetate can only be used for intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women who have not reached menopause and when surgical procedures are not suitable or have failed.

In 2018, a safety review in Europe was conducted following four reports of severe liver injury which resulted in liver transplantation. As a result several risk minimization measures were introduced in 2018.

In 2020, a fifth case of severe liver injury resulting in liver transplantation was reported and a recent European review

recommended that the risk of severe liver injury does not justify its use for the pre-operative treatment of uterine fibroids.

Also, liver function tests must be performed before starting treatment with ulipristal acetate 5mg. If a patient shows signs or symptoms compatible with liver injury, such as fatigue, asthenia, nausea and vomiting, treatment should be stopped.

Reference:

Drug Safety Update, MHRA, 18 February 2021 (www.gov.uk/mhra)

(See also WHO Pharmaceuticals Newsletter No.6, 2020: Risk of liver injury: restricting use recommended in Europe; No.5, 2020: Revocation of marketing authorizations recommended in Europe; No.3, 2020: Licence suspension due to liver injury in UK)

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