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WHO Vision for Safety of Medicinal Products
No country left behind: worldwide pharmacovigilance for safer medicinal products, safer patients

The aim of the Newsletter is to disseminate regulatory information on the safety of medicinal 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:
https://www.who.int/teams/regulation-prequalification

The WHO Pharmaceuticals Newsletter provides you with the latest information on the safety of medicinal products and regulatory actions taken by authorities around the world.

In addition, this edition includes the WHO statement regarding COVID-19 immunization errors in children and the report of WHO-MedDRA-UMC workshop on safety monitoring of medicines and vaccines held on 14 September 2022.

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Bortezomib

Risks of Guillain-Barré syndrome (GBS), demyelinating polyneuropathy

Japan. The Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA) have announced that the product information for bortezomib should be revised to include the risk of Guillain-Barré syndrome (GBS) and demyelinating polyneuropathy.

Bortezomib is indicated for the treatment of multiple myeloma and mantle cell lymphoma.

Cases of GBS or demyelinating polyneuropathy reported in Japan and internationally were evaluated. There was one Japanese case of GBS and eight international cases. Two of the cases were assessed to have a reasonably possible causal relationship between bortezomib and GBS. There were 20 international cases of demyelinating polyneuropathy. Thirteen of these cases were assessed to have a reasonably possible causal relationship between bortezomib and demyelinating polyneuropathy. It was concluded that GBS and demyelinating polyneuropathy are clinically significant adverse reactions for bortezomib.

Reference:
Revision of Precautions, MHLW/PMDA, 20 July 2022 *(link to the source within www.pmda.go.jp/english/)*

Cholinesterase inhibitors

Risk of QT interval prolongation and torsade de pointes

Canada. Health Canada has announced that the product safety information for cholinesterase inhibitors (donepezil-, rivastigmine- and galantamine-containing products) will be updated to strengthen the information on the risk of QT interval prolongation and torsade de pointes.

These cholinesterase inhibitors are indicated for the treatment of dementia associated with Alzheimer's disease and/or Parkinson's disease.

Health Canada reviewed 53 case reports (one Canadian, 52 international) of QT interval prolongation and torsade de pointes in patients taking cholinesterase inhibitors and found that:

- For donepezil (35 reports), two cases were found to be probably linked, 30 cases were possibly linked, two cases were unlikely to be linked and one case could not be assessed. Four deaths were reported (two of which were determined to have a possible link and two unlikely to be linked).
- For galantamine (10 reports including one Canadian), three cases were found to be probably linked, five cases were possibly linked, one case was unlikely to be linked and one case (Canadian) could not be assessed. One death was reported and was unlikely to be linked.
- For rivastigmine (eight reports), seven cases were found to be possibly linked and one case was unlikely to be linked.

Health Canada also reviewed 20 articles published in the scientific literature which contained limited evidence. In conclusion, Health Canada's review supported a link between the use of all three cholinesterase inhibitors and the risk of QT interval prolongation and torsade de pointes.

Health-care professionals are advised that this risk is increased in patients with a history of certain heart conditions; a history or family history of QT interval prolongation; low levels of certain electrolytes, such as magnesium, potassium or calcium in the blood; or taking certain medications that can affect heart rhythm at the same time as the cholinesterase inhibitors.

Reference:
Summary Safety Review, Health Canada, 19 July 2022 *(link to the source within www.hc-sc.gc.ca)*

(See also WHO Pharmaceuticals Newsletter No.2, 2022 Donepezil and Risk of cardiac conduction disorders in Australia)

COVID-19 vaccine Moderna (Elasomeran)

Potential risks of flare-ups of capillary leak syndrome (CLS), acute and delayed urticaria

Australia. The Therapeutic Goods Administration (TGA) has announced that the product information for COVID-19 vaccine Moderna (elasomeran, Spikevax®) has been updated to include warnings about flare-ups of capillary leak syndrome (CLS), and acute and delayed urticaria.

CLS is a rare condition where fluid leaks from the small blood vessels (capillaries) into the

surrounding tissues. People who have had it in the past can experience flare-ups. However, it is not well understood what triggers this.

A few cases of flare-ups of CLS have been reported in the first days after vaccination with COVID-19 vaccine Moderna.

Health-care professionals should be aware of signs and symptoms of CLS to promptly recognize and treat the condition. In individuals with a medical history of CLS, planning of vaccination should be made in collaboration with appropriate medical experts.

Also, acute and delayed urticaria has also been added as adverse effects in the product information as rare skin reactions that can potentially occur after vaccination.

Reference:
COVID-19 vaccine safety report, TGA, 8 September 2022 *(link to the source within www.tga.gov.au)*

(See also WHO Pharmaceuticals Newsletter No.2, 2022: COVID-19 vaccine Moderna and Potential risk of flare-ups of CLS in Europe)

Durvalumab, avelumab

Risks of encephalitis

Japan. The MHLW and the PMDA have announced that the product information for durvalumab (Imfinzi®) and avelumab (Bavencio®) should be revised to include the risk of encephalitis.

Durvalumab and avelumab are monoclonal antibodies that block PD-L1. Durvalumab is indicated for the treatment of lung cancer, and avelumab is for Merkel cell carcinoma, renal cell carcinoma and urothelial carcinoma.

International and Japanese cases of encephalitis were evaluated. For durvalumab, 10 cases were from Japan and 21 cases were reported internationally. Fifteen of these cases (five Japanese and 10 international) were assessed to have a reasonably possible causal relationship between the drug and risk of encephalitis. For demyelinating polyneuropathy, two cases were Japanese and once case was internationally reported. Of these cases two (one Japanese and one international) were assessed to have a reasonably possible causal relationship between the drug and event. It was concluded that encephalitis is a clinically significant adverse reaction for durvalumab and avelumab.

Reference:
Revision of Precautions, MHLW/PMDA, 20 July 2022 *(link to the source within www.pmda.go.jp/english/)*

Fluorouracil, capecitabine, flucytosine

Risk of dihydropyrimidine dehydrogenase (DPD) deficiency

Australia. The TGA has announced that the product information for fluorouracil and its prodrugs capecitabine and flucytosine are to be updated to include a new warning about the potential for severe and potentially life-threatening toxicity in patients with a partial dihydropyrimidine dehydrogenase (DPD) deficiency.

Fluorouracil is indicated alone or in combination with other medicines for the palliative treatment of malignant tumours, particularly of the breast, colon or rectum. Capecitabine is indicated for the treatment of certain types of colon, colorectal, oesophagogastric and breast cancer. Flucytosine is indicated for the treatment of generalised candidiasis, cryptococcosis and chromoblastomycosis. The product information for fluorouracil, capecitabine and flucytosine already include a contraindication for patients with known complete DPD deficiency.

A review of all adverse event reports submitted to the TGA for fluorouracil, capecitabine and flucytosine up to 20 July 2022 found 11 cases (of which six cases reported a fatal outcome) and the reporter noted adverse events were possibly or likely due to DPD deficiency. In most of these cases DPD deficiency was not tested for or confirmed in the affected patients.

Health-care professionals are advised to consider laboratory testing for total or partial DPD deficiency before therapy is initiated or when evaluating patients experiencing related toxicities and to reduce the starting dose when partial DPD deficiency is detected.

Reference:
Medicines Safety Update, TGA, 14 September 2022 *(link to the source within www.tga.gov.au)*

(See also WHO Pharmaceuticals Newsletter No.6, 2020: Flucytosine, 5-Fluorouracil (intravenous), capecitabine, tegafur and

DPD deficiency in UK; No.2, 2020 Fluorouracil, capecitabine, tegafur and Pre-treatment testing recommended for cancer in Europe)

Hormonal contraceptives

Risk of depressed mood and depression

Ireland. The Health Products Regulatory Authority (HPRA) has announced that the warning of depressed mood and depression in the product information for hormonal contraceptives (both combined and progesterone-only products) have been expanded to highlight that depression can be a risk factor for suicidal behaviour and suicide.

The update has been made following a review of available data by the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA).

Women prescribed with hormonal contraceptives should be advised to contact their physician in case of mood changes and depressive symptoms, even if occurrence is shortly after initiating treatment with a hormonal contraceptive.

Reference:
Drug Safety Newsletter, HPRA, August 2022 *(link to the source within www.hpra.ie)*

Hydroxychloroquine

Risks of hepatic impairment

Japan. The MHLW and the PMDA have announced that the product information for hydroxychloroquine (Plaquenil®) should be revised to include the risk of hepatic impairment.

Hydroxychloroquine is indicated for the treatment of cutaneous lupus erythematosus and systemic lupus erythematosus.

Japanese (two) and International (21) cases of hepatic impairment were evaluated. Of these cases, four of the international cases were assessed to have a reasonably possible causal relationship between the drug and hepatic impairment. It was concluded that hepatic impairment is a clinically significant adverse reaction for hydroxychloroquine.

Reference:
Revision of Precautions, MHLW/PMDA, 30 August 2022 *(link to the source within www.pmda.go.jp/english/)*

Iopamidol, iohexol, iomeprol

Risk of acute coronary syndrome, accompanying an allergic reaction

Japan. The MHLW and the PMDA have announced that the product information for iopamidol, iohexol and iomeprol should be revised to include the risk of acute coronary syndrome accompanying an allergic reaction.

Iopamidol, iohexol and iomeprol are iodinated contrast media used for X-ray imaging.

Cases of acute coronary syndrome accompanying an allergic reaction were reported in Japan with the use of several iodinated contrast media products. A causal relationship between iodinated contrast media and acute coronary syndrome was evaluated and a reasonably possible causal relationship was found with the use of iopamidol (2/14 cases) iohexol (4/6), and iomeprol (2/2). There are no cases reported for other iodinated contrast media such as amidotrizoate, iotroxate and iodixanol. In addition, there were no evidence to support a class effect for iodinated contrast media. It was concluded that acute coronary syndrome is a clinically significant adverse reaction for iopamidol, iohexol and iomeprol.

Reference:
Revision of Precautions, MHLW/PMDA, 20 July 2022 *(link to the source within www.pmda.go.jp/english/)*

Janus kinase (JAK) inhibitors

Risk of serious heart-related problems, blood clots, cancer and death

Canada. Health Canada has announced that the product safety information for Janus kinase (JAK) inhibitors (including tofacitinib (Xeljanz®), baricitinib (Olumiant®), upadacitinib (Rinvoq®), abrocitinib (Cibinqo®), ruxolitinib (Jakavi®) and fedratinib (Inrebic®)) have been or will be updated to include the risk of serious heart-related problems, blood clots, cancer and death.

These JAK inhibitors are indicated for the treatment of chronic inflammatory diseases.

Health Canada reviewed the final findings from the clinical research study which linked tofacitinib to higher risks of serious heart-related problems, cancer and death, and confirmed the initial findings of an increased risk of blood clots from 2019. Health Canada also reviewed the interim findings from a 2021 observational study with baricitinib, which showed increased rates of serious heart-related problems and blood clots with its use. Given the similar mechanisms of action and indications, Health Canada's review concluded that a drug class effect for the risks of serious heart-related problems, blood clots, cancer and death cannot be excluded with JAK inhibitors used for the treatment of chronic inflammatory diseases, including upadacitinib, abrocitinib, ruxolitinib and fedratinib in addition to tofacitinib and baricitinib.

Reference:
Summary Safety Review, Health Canada, 16 September 2022 *(link to the source within www.hc-sc.gc.ca)*

(See also WHO Pharmaceuticals Newsletter No.1, 2022: Tofacitinib, Baricitinib and Upadacitinib and Risk of serious heart-related events, cancer, blood clots, and death in US, UK and Japan)

Non-steroidal anti-inflammatory drugs (NSAIDs)

Risks of maternal, fetal and neonatal adverse effects in pregnancy

New Zealand. The Medsafe has announced that the product information for non-steroidal anti-inflammatory drugs (NSAIDs) are to be updated and aligned regarding the risks of maternal, fetal and neonatal adverse effects for the use in pregnancy.

The Medicines Adverse Reactions Committee (MARC) reviewed the safety of NSAID use in pregnancy. NSAIDs used in early pregnancy is associated with an increased risk of miscarriage and congenital malformation; NSAIDs used in the second or third trimester may cause fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment; and NSAIDs used in the third trimester may cause premature closure of the fetal ductus arteriosus, fetal renal impairment, inhibition of platelet aggregation, and may delay labour and birth.

Health-care professionals are advised that NSAIDs are contraindicated in the third trimester of pregnancy; NSAIDs should not be used during the first two trimesters of pregnancy unless the expected benefits to the mother outweigh the risks to the fetus. If there is a compelling need for NSAID treatment during the first or second trimester, use should be limited to the lowest effective dose and shortest duration possible. Health-care professionals should enquire about NSAID use in women who are pregnant or planning pregnancy and advise them not to self-medicate with these medicines during pregnancy.

Reference:
Prescriber Update, Medsafe, 1 September 2022 *(link to the source within www.medsafe.govt.nz/)*

Obeticholic acid

Contraindication in patients with decompensated liver cirrhosis or a history of prior hepatic decompensation

Ireland. The HPRA has announced that the product information for obeticholic acid (Ocaliva®) is being updated to include a new contraindication in patients with decompensated liver cirrhosis or a history of prior hepatic decompensation.

Obeticholic acid is indicated for the treatment of primary biliary cholangitis (PBC).

The contraindication was made following the result of clinical trials which did not establish the safety and efficacy of obeticholic acid in patients with PBC with decompensated liver cirrhosis, or with a prior history of hepatic decompensation. In addition, there were post-marketing case reports where a causal association between obeticholic acid treatment and hepatobiliary disorders is possible in PBC patients with cirrhosis.

Health-care professionals are advised that treatment with obeticholic acid should not be started or continued in PBC patients with decompensated cirrhosis or a history of a decompensation, and that patients should be routinely monitored for progression of PBC and laboratory or clinical evidence of hepatic decompensation including progression to Child-Pugh class B or C.

Reference:
Drug Safety Newsletter, HPRA, August 2022 *(link to the source within www.hpra.ie)*

(See also WHO Pharmaceuticals Newsletter No.3, 2021: Obeticholic acid and Risk of serious liver injury in US)

Ocular prostaglandin analogues

Risk of prostaglandin-associated periorbitopathy (PAP)

New Zealand. The Medsafe has announced that the product information for ocular prostaglandin analogues (bimatoprost, travoprost and latanoprost) are to be updated to include the risk of prostaglandin-associated periorbitopathy (PAP).

Ocular prostaglandin analogues are a class of medicines commonly used to treat glaucoma.

The MARC reviewed the risk of PAP and considered that the evidence shows the risk of PAP is a class effect. The risk of PAP is likely to be the highest for bimatoprost (reported in more than 10 percent of patients treated with bimatoprost) and the lowest for latanoprost. Clinical and cosmetic changes can occur as early as one month after starting treatment, and the changes may be partially or fully reversible upon discontinuation or that unilateral treatment may lead to differences in appearance between the eyes.

Reference:
Prescriber Update, Medsafe, 1 September 2022 *(link to the source within www.medsafe.govt.nz/)*

Opioids and serotonergic medicines

Risk of serotonin syndrome due to drug-drug interaction

New Zealand. The Medsafe has announced that the product information for opioids and serotonergic medicines are to be updated regarding the risk of serotonin syndrome due to drug-drug interaction.

Serotonergic medicines include most antidepressants, such as monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs) and tricyclic antidepressants (TCAs).

The MARC reviewed and found the risk of developing serotonin syndrome with concomitant use of opioids and serotonergic medicine(s), which varies depending on the medicine to cause serotonin syndrome and are considered low risk.

Health-care professionals are advised to consider the risk of a drug-drug interaction leading to serotonin syndrome when prescribing opioids with serotonergic medicines.

Reference:
Prescriber Update, Medsafe, 1 September 2022 *(link to the source within www.medsafe.govt.nz/)*

(See also WHO Pharmaceuticals Newsletter No.4, 2021: Bupropion and Risk of serotonin syndrome in Australia; No.1, 2021: Bupropion and Increased risk of serotonin syndrome: drug interaction with other serotonergic drugs in UK; and No.5, 2019: Tapentadol and Risk of dizziness and somnolence in UK)

Pregabalin

Risk of drug dependence and withdrawal symptoms

Ireland. The HPRA has announced that the product information for pregabalin has been updated to expand the warning regarding drug dependence and withdrawal symptoms. The updated warnings state that pregabalin can cause drug dependence at therapeutic doses, and that patients with a history of