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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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Features

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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 switching to alternative treatments.

Health-care professionals are advised to inform patients, before starting treatment, of the possibility of changes to the eye during treatment. These changes are typically mild, can occur as early as one month after initiation of treatment and may cause impaired field of vision. Patients should also be aware 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 combination. Pethidine, dextromethorphan and tramadol are high-risk opioids for serotonin syndrome when used with serotonergic antidepressants. Methadone and fentanyl also have serotonergic properties and are considered medium risk. Morphine, codeine, buprenorphine and oxycodone are not expected to interact with antidepressant medicines 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 substance abuse may be at higher risk for pregabalin misuse, abuse and dependence.

Pregabalin is indicated for the treatment of neuropathic pain in adults, as adjunctive therapy in adults for specific forms of epilepsy, and for generalized anxiety disorder in adults.

The update has been made following a review of available

data by the PRAC of the EMA.

Health-care professionals should carefully evaluate an individual patient's risk of misuse, abuse and dependence before prescribing pregabalin and monitor patients treated with pregabalin for symptoms of misuse, abuse or dependence, such as development of tolerance, dose escalation and drug-seeking behaviour. The occurrence of withdrawal symptoms following discontinuation of pregabalin may indicate drug dependence. It is recommended discontinuation of pregabalin should be done gradually over a minimum of one week independent of the indication.

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

(See also WHO Pharmaceuticals Newsletter No.2, 2021: Gabapentin, pregabalin and Risk of dizziness, somnolence, abuse and dependence in New Zealand)

Ramucirumab

Risks of thrombotic microangiopathy (TMA)

Japan. The MHLW and the PMDA have announced that the product information for ramucirumab (Cyramza®) should be revised to include the risk of thrombotic microangiopathy (TMA).

Ramucirumab is a monoclonal antibody that blocks VEGFR2 and is indicated for solid tumors including gastric and colorectal cancer.

Seventeen cases of TMA reported in Japan were evaluated, of which six cases were assessed to have a reasonably possible causal relationship between the drug and event. It was concluded that TMA is a clinically significant adverse reaction for ramucirumab.

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

Riociguat and Ritonavir, Lopinavir/ritonavir, Atazanavir

Removal of contraindication for co-administration

Japan. The MHLW and the PMDA have announced that the product information for riociguat (Adempas®), ritonavir (Norvir®), lopinavir/ritonavir (Kaletra®) and atazanavir (Reyataz®) should be revised to remove the contraindication for co-administration of riociguat with ritonavir, lopinavir/ritonavir or atazanavir.

Riociguat is a stimulator of soluble guanylate cyclase (sGC) and is indicated for the treatment of chronic thromboembolic pulmonary hypertension (CTEPH) and pulmonary arterial hypertension (PAH). Ritonavir, lopinavir/ritonavir and atazanavir are HIV protease inhibitors. At the time of initial approval of riociguat, its co-administration with riociguat and ritonavir, lopinavir/ritonavir or atazanavir was contraindicated due to drug-drug interaction which may lead to increased exposure of riociguat an resulting in hypotension.

The MHLW and the PMDA reviewed the available evidence including the results of drug interaction studies, case reports of adverse events and publications. In a clinical study, the exposure of riociguat increased by about 1.3 times when HIV protease inhibitors were co-administered compared to the administration of riociguat alone; however, it was considered possible to secure a safety margin by starting riociguat at a lower dose (it is standard use of riociguat to start at a low dose and adjust according to the patient's condition). Also, no other clinical concern regarding the co-administration was identified. It was concluded that the contraindication for co-administration of riociguat and HIV protease inhibitors can be removed by introducing risk minimization measures such as starting riociguat at a lower dose.

Reference:
Revision of Precautions, MHLW/PMDA, 13 September 2022 *(link1 and link2 to the source within www.pmda.go.jp/english/)*

Sorafenib

Risk of thrombotic microangiopathy (TMA)

Canada. Health Canada has announced that the product safety information for sorafenib will be updated to include the risk of thrombotic microangiopathy (TMA). TMA is a group of rare, but serious and life-threatening conditions, such as the formation of clots in small blood vessels.

Sorafenib (Nexavar®) is indicated for the treatment of advanced forms of liver, kidney and thyroid cancers.

Health Canada reviewed information provided by the manufacturer, and information resulting from searches of the Canada Vigilance database and the published literature.

Health Canada reviewed 28 cases (one Canadian, 27 international) of TMA in patients taking sorafenib. Of the 28 cases, 12 (all international) met the criteria for further assessment. All 12 cases, including six published in the scientific literature were found to be possibly linked. Three deaths were reported, two of which were assessed as having a possible link to sorafenib and one unlikely to be linked. Health Canada's review of the available information concluded that there may be a link between the use of sorafenib and the risk of TMA.

Reference:
Summary Safety Review, Health Canada, 11 August 2022 *(link to the source within www.hc-sc.gc.ca)*

Triazolam and posaconazole

Contraindication for co-administration due to drug-drug interaction

Japan. The MHLW and the PMDA have announced that the product information for triazolam and posaconazole should be revised to include a contraindication of the co-administration of the two drugs to avoid the increased effect of triazolam due to drug-drug interaction.

Triazolam is indicated for insomnia and anaesthetic premedication. Posaconazole is indicated for the treatment of fungal infections and strongly inhibits CYP3A4.

Based on the prediction using the mechanistic static pharmacokinetics (MSPK) model with parameters obtained from in vivo data, it was estimated that the plasma exposure of triazolam would increase to a level that causes safety concerns when triazolam is co-administered and the risk outweighs the benefit of the treatment.

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

(See also WHO Pharmaceuticals Newsletter No.2, 2022: Blonanserin or suvorexant, and posaconazole and Contraindication for co-administration in Japan; No.1, 2021: Posaconazole, Venetoclax and Co-administration contraindicated due to drug-drug interaction in Japan.)

Triazolam, zolpidem, zopiclone, eszopiclone

Risk of abnormal behaviour as parasomnia

Japan. The MHLW and the PMDA have announced that the product information for triazolam, zolpidem, zopiclone and eszopiclone should be revised to include the risk of abnormal behaviour as parasomnia. In addition, use of triazolam, zolpidem or zopiclone is to be contraindicated in patients who have experienced abnormal behaviour as parasomnia.

Triazolam, zolpidem, zopiclone and eszopiclone are indicated for insomnia and/or anaesthetic premedication.

Based on the published literature on the pharmacological mechanisms of parasomnia and cases of parasomnia reported in Japan, it was concluded the four drugs can increase the risk of abnormal behaviour as parasomnia, which may lead to serious self/other injuries or accidents. Also, contraindication is considered necessary for triazolam, zolpidem and zopiclone in patients with a history of drug-induced parasomnia due to the risk of recurrence. Regarding eszopiclone, careful administration is still required but it is not a contraindication at this time, as there have been no reports of parasomnia in Japan for this drug.

Reference:

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

(See WHO Pharmaceuticals Newsletter No.3, 2019: Insomnia medicines and Risk of serious injuries in US)

Finasteride

Potential risk of suicidal ideation

Singapore. The Health Sciences Authority (HSA) has reminded health-care professionals of the potential risk of suicidal ideation with the use of finasteride following results of a recent pharmacovigilance study that suggests younger patients with alopecia may be more vulnerable to the risk of suicide ideation.

Finasteride is indicated for the treatment of benign prostatic hyperplasia and androgenic alopecia.

In the study, disproportionality analysis was used to assess whether suicidality or psychological adverse events (AEs) were more frequently reported for finasteride than would be expected by chance alone by comparing them against similar reports for all other drugs in VigiBase (WHO global database of ICSRs). The study identified 356 reports of suicidality and 2,926 reports of psychological AEs in users of finasteride, reported from 1993 to 2019. Among the reports with data available, the majority (99%) occurred in males, and 71% occurred in individuals aged between 18 and 44 years. Significant disproportionality signals for suicidality (reporting odds ratio [ROR], 1.63; 95% CI, 1.47-1.81) and psychological AEs (ROR, 4.33; 95% CI, 4.17-4.49) were identified in finasteride users.

Health-care professionals are advised to consider the potential risk of psychological adverse events when assessing the benefit-risk of finasteride for their patients.

Reference:

Safety Alerts, HSA, 30 August 2022 *(link to the source within www.hsa.gov.sg)*

(See also WHO Pharmaceuticals Newsletter No.2, 2019: Finasteride and Potential risk of suicidal ideation in Canada)

Pholcodine

Potential risk of developing anaphylactic reactions to neuromuscular blocking agents (NMBA)

Europe. The EMA has started a review of pholcodine following concerns that it's use may put individuals at risk of developing anaphylactic reactions to neuromuscular blocking agents (NMBAs) medicines.

Pholcodine is an opioid medicine that is used to treat non-productive (dry) cough in adults and children and NMBAs are used in general anaesthesia to prevent spontaneous muscle movements to improve operating conditions.

The review was requested by the French medicines agency (ANSM) following preliminary results of a study carried out in France (ALPHO study). The results of the study suggested that taking pholcodine up to 12 months before general anaesthesia may increase the risk of having an NMBA-related anaphylactic reaction. Based on these results the ANSM is considering, as a precautionary measure, to suspend the use of pholcodine-containing medicines in France.

The ALPHO study was carried out as a condition to the marketing authorizations of pholcodine-containing medicines following a previous safety review in 2011. At the time, the EMA's committee found no firm evidence on this risk and recommended that a new study should be carried out to investigate this risk. While the ALPHO study was ongoing, in 2021, a study in Australia linked pholcodine's use to an increased risk of anaphylaxis to NMBA muscle relaxants. This led to a recommendation by the PRAC of the EMA to include relevant warnings in the product information of pholcodine-containing medicines.

The PRAC will review the results of the ALPHO study together with all available data and assess their impact on the benefit-risk balance of pholcodine-containing medicines to issue a recommendation.

Reference:

Patients and carers, EMA, 2 September 2022 *(link to the source within www.ema.europa.eu)*

(See also WHO Pharmaceuticals Newsletter No.6, 2011: Pholcodine and No firm evidence of cross-sensitization between pholcodine and neuromuscular blocking agents used during surgery in Europe.)

Selective Serotonin Reuptake Inhibitors (SSRIs)

Risk of suicidality

Singapore. The HSA has reminded health-care professionals of the risk of suicidality for selective serotonin reuptake inhibitors

(SSRIs), where an increased risk is observed particularly in patients less than 25 years of age although a causal association remains to be conclusively established.

SSRIs are used for the treatment of depression, anxiety and other mood disorders. Although none of the registered SSRIs are approved specifically for the treatment of depression in children and adolescents below 18 years old, they are used off-label in this patient population.

Based on data from the electronic medical records, over the past five years, an increasing trend in the prescriptions of SSRIs was observed (around 4% increase from 2017 to 2020, followed by 9.1% increase from 2020 to 2021). Also, the proportion of patients less than 25 years of age are increasing among the patients prescribed SSRIs: the annual proportion of children or adolescents (<18 years) was stable at around 3.4% from 2017 to 2020 and increased to 4.1% in 2021, while those of young adults (18-24 years) steadily increased over the years from 11.2% in 2017 to 15.5% in 2021.

Health-care professionals are encouraged to refer to the available patient educational materials on SSRIs during medication counselling to their patients and/or caregivers. The materials include warnings on suicidality and mental state worsening and risks in young people aged below 25 years.

Reference:

Safety Alerts, HSA, 30 August 2022 *(link to the source within www.hsa.gov.sg)*

(See also WHO Pharmaceuticals Newsletter No.2, 2022: Antidepressants and Updated analysis on risk of suicide in young people in Australia)

WHO statement regarding COVID-19 immunization errors in children

30 August 2022[1]

WHO is aware of an increasing number of reports regarding COVID-19 immunization errors in children.

The immunization errors have been reported through the passive vaccine safety surveillance systems and included in the media in a number of countries. On 19 May 2022, the US Advisory Committee on Immunization Practices (ACIP) presented data showing that half of all non-serious adverse events following Pfizer BNT162b2 immunization in children aged 5-11 years submitted to the Vaccine Adverse Event Reporting System (VAERS) surveillance system through 24 April 2022 included an event associated with immunization error (1). The Australian Therapeutic Goods Administration (TGA) also reported instances of immunization errors among 5–11-year-olds and made recommendations to reinforce the use of the paediatric version of the Comirnaty (Pfizer) vaccine which comes in a vial with an orange top (2).

According to the WHO global database of individual case safety reports (VigiBase data as of 10 July 2022), about 24% of all case safety reports in children after COVID-19 immunizations are related to immunization errors. The types of immunization errors include the use of adult dose in children, use in inappropriate age groups, underdose, overdose, use of unapproved COVID-19 vaccines, inappropriate scheduling between doses, preparation errors such as omitting a diluent before immunization, administering a COVID-19 vaccine instead of another vaccine, failure to adhere to requisite storage conditions and use of expired doses. Immunization errors have been reported with Pfizer-BioNTech, Moderna, AstraZeneca, Janssen, Sinovac, Novavax and other COVID-19 vaccines.

Although in very rare instances serious adverse events have been documented after immunization against COVID-19 disease, none of these were verified to be related to immunization errors of any kind. Children who received an incorrect dose of a COVID-19 vaccine or who received an inappropriately prepared vaccine have only reported expected adverse events like a sore arm, headache, and fever.

However, given the increasing number of reports of immunization errors in children, WHO would like to remind health-care providers to be alert when storing, preparing, and administering COVID-19 vaccines. National immunization programs and relevant stakeholders should implement risk minimization activities to reduce the occurrence of immunization errors, including procedures to check the date of birth and current age of the child. Vaccine providers should have access to clear instructions for vaccine administration, including visual aids, and vaccine vials should be clearly labelled (3). Training for healthcare providers involved in COVID-19 immunization of children should be reinforced.

If an immunization error does occur, healthcare providers should immediately inform individuals and/or their guardians as well as report the incident to the relevant local vaccine safety surveillance system or immunization programme. Children who have received an incorrect dose or an incorrectly prepared vaccine should be monitored for any adverse events. Some countries have also prepared guidance on what to do with subsequent doses if an error in administration occurs (4).

WHO will continue to consult the Global Advisory Committee on Vaccine Safety (GACVS) and other relevant experts as well as WHO advisory committees on the problem of immunization errors and will work closely with countries to manage potential risks, using science and data to drive response and recommendations.

(1) Shimabukuro T. COVID-19 vaccine safety updates: Primary series in children ages 5-11 years. Advisory Committee on Immunization Practices (ACIP). 19 May 2022 (https://www.cdc.gov/vaccines/acip/meetings/slides-2022-05-19.html)

(2) Australian Therapeutic Goods Administration (TGA) COVID-19 vaccine weekly safety report - 10-02-2022. 10 February 2022 (https://www.tga.gov.au/periodic/covid-19-vaccine-weekly-safety-report-10-02-2022)

(3) Examples of practical guides on use of COVID-19 vaccines in children:

[1] This statement is published on our website: https://www.who.int/news/item/30-08-2022-statement-covid-19-immunization-errors-children

1) COVID Vaccine Dosing Quick Reference by American Academy of Pediatrics (https://downloads.aap.org/AAP/PDF/COVID%20Vaccine%20Dosing_Quick%20Reference.pdf?_ga=2.233317982.1540468903.1657898439-1537646742.1653333380)
2) COVID-19 Vaccine Interim COVID-19 Immunization Schedule for 6 Months of Age and Older by US CDC (https://www.cdc.gov/vaccines/covid-19/downloads/COVID-19-immunization-schedule-ages-6months-older.pdf)

(4) Examples of guidance on what to do with subsequent doses if an error in administration occurs:
1) US CDC: https://www.cdc.gov/vaccines/covid-19/clinical-considerations/interim-considerations-us-appendix.html
2) Department of Health and Aged Care, Australia: https://www.health.gov.au/resources/publications/atagi-clinical-guidance-on-covid-19-vaccine-administration-errors

Report of WHO-MedDRA-UMC workshop on safety monitoring of medicines and vaccines

14 September 2022

MedDRA (Medical Dictionary for Regulatory Activities) is a rich and highly specific standardised medical terminology, currently available in 16 languages, to facilitate sharing of regulatory information internationally for medical products and is under the governance of the MedDRA Management Committee of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)[2]. MedDRA is incorporated in the WHO global database for Individual Case Safety Report (ICSR), VigiBase, which contains ICSRs submitted by participating Member States enrolled under the WHO Programme for International Drug Monitoring (WHO PIDM). Since 2017, WHO has organized several workshops on the use of MedDRA for the WHO PIDM member organizations as the coding of drug adverse reactions (ADRs) and adverse events following immunizations (AEFIs). The use of MedDRA is vital to integrate ICSRs reported in various countries and in various languages to VigiBase[3].

On 14 September 2022, WHO hosted an online workshop on safety monitoring of medicines and vaccines in collaboration with the MedDRA Maintenance and Support Services Organization (MSSO) and the WHO Collaborating Center for International Drug Monitoring, Uppsala Monitoring Centre (UMC). This two-hour, introductory course was intended to provide an overview of the technical tools used in post-market adverse event reporting and analysis of medicines and vaccines including MedDRA, and to encourage collaboration with the WHO PIDM, for regulators and vaccine safety officers in low- and middle- income countries (LMICs).

The workshop started with an introduction of WHO PIDM by WHO, then an overview of MedDRA coding and analysis was provided by the MedDRA MSSO, followed by a signal management overview and methods (introduction part and statistical methods part) by the UMC. Around 280 people from 59 countries from various part of the world participated in the workshop.

The recording and materials of this workshop are accessible for staff members of National Regulatory Authorities (NRAs) and National Immunization Policies (NIPs). Those who are interested in the workshop and are part these organizations can contact WHO Pharmacovigilance Team <pvsupport@who.int> for further information.

[2] See MedDRA's website for further information: https://www.meddra.org/how-to-use/support-documentation/english/welcome
[3] See WHO Pharmaceuticals Newsletter No.6, 2017 on the first WHO-MedDRA workshop in 2017.

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