World Health Organization

WHO Pharmaceuticals NEWSLETTER

2022 No.3

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:

Pharmacovigilance,
MHP/RPQ,
World Health Organization,
1211 Geneva 27, Switzerland,
E-mail address:
pvsupport@who.int

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. It also provides signals based on information from the WHO global database of individual case safety reports, VigiBase.

In addition, this edition includes summaries of discussions and recommendations from the first joint meeting of the WHO Global Advisory Committee on Vaccine Safety (GACVS) and the WHO Advisory Committee on Safety of Medicinal Products (ACSoMP), 14-16 June 2022.

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All the previous issues of the WHO Pharmaceuticals Newsletter can be accessed from our website.

Amfepramone

Risk of pulmonary arterial hypertension, dependency, and heart and psychiatric problems

Europe. The Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) has recommended the withdrawal of the marketing authorization for amfepramone containing products in the European Union (EU).

Amfepramone is a sympathomimetic medicine indicated for the treatment of obesity (body mass index of at least 30 kg/m2) in patients who have had no success with other weight-reduction methods. Treatment duration is for 4 to 6 weeks and amfepramone should not be used for more than 3 months.

The recommendation follows a review which found that measures to restrict the use of amfepramone have not been sufficiently effective. It found that the medicines were being used for longer than the recommended maximum period of 3 months, thereby potentially increasing the risk of serious adverse effects, such as pulmonary arterial hypertension and dependency. The medicines were also being used in patients with a history of heart disease or psychiatric disorders, further increasing the risk of heart and psychiatric problems. In addition, there were evidence of use during pregnancy, which could pose risks to the unborn baby.

The review considered all available information relating to these concerns, including data from two studies on the use of amfepramone medicines in Germany and in Denmark. In addition, the PRAC received advice from a group of experts, comprising of endocrinologists, cardiologists and a patient representative.

The PRAC considered introducing further measures to minimize the risk of adverse effects but could not identify any that would be sufficiently effective. The PRAC therefore concluded that the benefits of using amfepramone medicines do not outweigh the risks and recommended that the medicines should be removed from the EU market.

Reference:
Patients and carers, EMA, 10 June 2022 *(link to the source within www.ema.europa.eu)*

Anagrelide

Risk of thrombosis upon abrupt treatment discontinuation

Ireland. The Health Products Regulatory Authority (HPRA) has announced that the product information for anagrelide (Xagrid®) has been updated to reflect the latest data and recommendations on the increased risk of thrombotic complications. This includes cerebral infarction upon abrupt anagrelide discontinuation.

Anagrelide is indicated for the reduction of elevated platelet counts in patients who are at risk of thrombosis and have essential thrombocythemia, are intolerant to other therapies or platelet counts are not sufficiently reduced by alternative therapy.

A cumulative analysis of the company's safety database showed 15 events of thrombotic complications, including cerebral infarction, after a recent discontinuation of anagrelide. It was concluded that cerebral infarction, along with other thrombotic complications, while being part of the pre-existing condition/indication, may also occur upon abrupt anagrelide discontinuation, inadequate dosing, or lack of effect.

It is recommended that patients should avoid abrupt treatment discontinuation, and health-care professionals should monitor platelet counts in the event of dosage interruption or treatment withdrawal. Patients should be advised on how to recognize early signs and symptoms suggestive of thrombotic complications, and if symptoms occur to seek medical assistance.

Reference:
Drug Safety Newsletter, HPRA, 11 April 2022 *(link to the source within www.hpra.ie)*

Cetuximab sarotalocan

Risk of fistula, mucocutaneous ulceration or necrosis

Japan. The Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA) have announced that the product information for cetuximab sarotalocan (Akalux®) should be revised to

include the risk of fistula, mucocutaneous ulceration or necrosis at the site of laser beam irradiation.

Cetuximab sarotalocan is a chemical conjugate of dye (IR700) and cetuximab, a monoclonal antibody against the epidermal growth factor receptor (EGFR). It is injected intravenously to bind EGFR-expressing tumour cells in the body. Subsequently, the dye is activated locally by application of laser beam to selectively kill the EGFR-expressing tumour cells. This treatment is indicated for unresectable, locally advanced or recurrent head and neck cancer.

Japanese (4) and international (1) cases of fistula, skin ulceration or necrosis following treatment with cetuximab were evaluated. In all of the five cases, a causal relationship between the medicines and event were assessed to be reasonably possible. A caution on the risk of mucosal ulceration and mucosal necrosis was also added to the product information after reviewing these reports.

Health-care professionals are advised to check for tumour invasions into the skin or mucous membrane prior to the administration. In addition, during the treatment, the patient's skin condition should be adequately monitored.

Reference:
Revision of Precautions, MHLW/PMDA, 14 June 2022 *(link to the source within www.pmda.go.jp/english/)*

Clozapine

Risk of gastrointestinal hypomotility

Australia. The Therapeutic Goods Administration (TGA) has announced that the product information for clozapine has been updated to strengthen existing warnings on severe gastrointestinal adverse reactions by including the risk of hypomotility.

Clozapine is a second generation, atypical antipsychotic with potent anticholinergic effects and is indicated for treatment of resistant schizophrenia.

The updates are based on evidence published in the literature and from Australian and International post-market adverse event data. On 1 March 2022, there were 1,523 reports of gastrointestinal disorders with the use of clozapine in the TGA's Database of Adverse Event Notifications (DAEN). This included 260 reports of constipation, 146 of intestinal obstruction, 93 of abdominal pain and 41 of small intestinal obstruction. Of the 1,023 clozapine reports with a fatal outcome, 103 were due to gastrointestinal disorders.

Health-care professionals are advised that any changes in the frequency or character of a patient's bowel movement, as well as signs and symptoms of complications due to hypomotility should be carefully monitored; patients with evidence of constipation or gastrointestinal hypomotility should be managed promptly to prevent severe complications; clozapine should be used with caution and under careful supervision in patients with a current diagnosis or prior history of constipation; and concomitant use of clozapine with anticholinergic medicines should be avoided where possible because of the increased risk of severe gastrointestinal adverse effects or anticholinergic toxicity.

Reference:
Medicines Safety Update, TGA, 22 April 2021 *(link to the source within www.tga.gov.au)*

COVID-19 vaccine Astrazeneca (ChAdOx1-S)

Risk of tinnitus, paraesthesia and hypoaesthesia

Europe. The EMA has announced that the product information for COVID-19 vaccine Astrazeneca (ChAdOx1-S, Vaxzevria®) will be updated to include the risk of tinnitus, paraesthesia (unusual feeling in the skin, such as tingling or a crawling sensation) and hypoaesthesia (decreased feeling or sensitivity, especially in the skin) as adverse effects.

Cases of tinnitus, paraesthesia and hypoaesthesia with use of Astrazeneca vaccine have been reported through routine spontaneous reporting systems. In addition, new data obtained from an ongoing clinical trial were reviewed.

Reference:
COVID-19 vaccines safety update, EMA, 14 July 2022 *(link to the source within www.ema.europa.eu)*

COVID-19 vaccine

Moderna (Elasomeran)

Risk of extensive swelling of the vaccinated limb

Europe. The EMA has announced that the product information for COVID-19 vaccine Moderna (elasomeran, Spikevax®) will be updated to include the risk of extensive swelling of the vaccinated limb as an adverse effect. In general, extensive swelling of the vaccinated limb is a condition that does not require treatment and resolves after a few days.

Up until 2 May 2022 there have been 3,200 cases of extensive swelling of the vaccinated limb with use of Moderna vaccine reported to EudraVigilance. The decision to update the product label was made following the PRAC's assessment.

Reference:
COVID-19 vaccines safety update, EMA, 14 July 2022 *(link to the source within www.ema.europa.eu)*

COVID-19 vaccines Moderna (Elasomeran) and Pfizer (Tozinameran)

Potential risk of Guillain-Barré syndrome (GBS)

Japan. The MHLW and the PMDA have announced that the product information for COVID-19 vaccines Moderna (elasomeran, Spikevax®) and Pfizer (tozinameran, Comirnaty®) should be revised to include a warning on Guillain-Barre syndrome (GBS).

The MHLW and the PMDA assessed suspected cases of GBS reported in Japan (30 cases for Moderna vaccine and 181 cases for Pfizer vaccine). A causal association between the vaccine and event could not be excluded in 15 of the Pfizer vaccine cases (zero cases for Moderna vaccine). In the O/E (Observed-to-expected) analysis, no statistically significant difference was observed between the background (expected) rate and reported (observed) rates of GBS for both vaccines.

As a result of the assessment, the MHLW and the PMDA have decided to update the product information for mRNA COVID-19 vaccines to include a warning on GBS as a precaution, and not as an adverse effect.

In other countries and regions such as the US, UK and EU, there are no warnings for GBS following immunization in the package inserts for COVID-19 mRNA vaccines.

Vaccine recipients or their caregivers should be instructed in advance to seek medical attention immediately if a vaccine recipient experiences any symptoms that could suggest GBS (such as flaccid paralysis starting from distal limb, decreased or absent tendon reflex).

Reference:
Revision of Precautions, MHLW/PMDA, 10 June 2022 *(link1 to the source within www.pmda.go.jp/english/ and link 2 within www.mhlw.go.jp/)*

(See also WHO Pharmaceuticals Newsletter No.3, 2021: COVID-19 vaccine NRVV Ad (ChAdOx1 nCoV-19) and Risk of Guillain-Barre syndrome (GBS) in Europe)

COVID-19 vaccine Novavax

1. Risk of anaphylaxis, paraesthesia and hypoaesthesia

(1) Europe. The EMA has announced that the product information for COVID-19 vaccine Novavax (Nuvaxovid®) will be updated to include the risk of anaphylaxis, paraesthesia and hypoaesthesia as adverse effects.

Cases of anaphylaxis, paraesthesia and hypoaesthesia have been reported worldwide.

Advice for managing the risk of anaphylaxis will be updated as follows: appropriate medical treatment and supervision should always be readily available in case of an anaphylactic reaction following the administration of the vaccine; close observation for at least 15 minutes is recommended following vaccination; and a second dose of the vaccine should not be given to those who have experienced anaphylaxis to the first dose of Novavax vaccine.

Reference:
COVID-19 vaccines safety update, EMA, 14 July 2022 *(link to the source within www.ema.europa.eu)*

(2) Australia. The TGA has announced that the product information for COVID-19 vaccine Novavax has been updated to include the risk of anaphylaxis, paraesthesia and hypoaesthesia as potential adverse events.

Reference:
COVID-19 vaccine safety report, TGA, 23 June 2022 *(link to the source within www.tga.gov.au)*

2. Risk of myocarditis and/or pericarditis

(1) Europe. The PRAC has recommended that the product information for COVID-19 vaccine Novavax should be updated to include the risk of myocarditis and pericarditis as adverse effects together with a warning to raise awareness among health-care professionals and people receiving this vaccine.

The PRAC has concluded that myocarditis and pericarditis can occur following vaccination with Novavax vaccine. This conclusion is based on a small number of reported cases.

Reference:
COVID-19 vaccines safety update, EMA, 3 August 2022 *(link to the source within www.ema.europa.eu)*

(2) Untied States. The US Food and Drug Administration (FDA) has announced that the prescribing information for COVID-19 vaccine Novavax will include the risk of myocarditis and pericarditis as adverse reactions.

Data from clinical trials provide evidence for an increased risk of myocarditis and pericarditis following administration of Novavax vaccine. Also, myocarditis and pericarditis were reported following administration of Novavax vaccine during overseas post-authorization use.

Reference:
FDA News Release, US FDA, 13 July 2022 *(link to the source within www.fda.gov)*

(3) Australia. The TGA has announced that the product information for COVID-19 vaccine Novavax has been updated to include the risk of pericarditis as a potential adverse event.

The TGA has received a small number of reports of suspected myocarditis and/or pericarditis in people who have received Novavax vaccine. After assessing these against a set of internationally accepted criteria, three cases were likely to represent myocarditis and 12 were likely to represent pericarditis. As a result of this investigation, the product information has been updated to include pericarditis as a potential adverse event.

Reference:
COVID-19 vaccine safety report, TGA, 30 June 2022 *(link to the source within www.tga.gov.au)*

Crizotinib

Risk of ocular disorders in children

Europe. The EMA has announced that the product information for crizotinib (Xalkori®) has been updated to include the risk of ocular toxicity, including severe vision loss in children.

Crizotinib is a cancer medicine used to treat adults with advanced non-small cell lung cancer (NSCLC). Crizotinib use in children has been studied in those aged 6 to 18 years of age as a monotherapy for the treatment of relapsed or refractory systemic anaplastic large cell lymphoma (ALCL) that is ALK positive or patients with unresectable, recurrent, or refractory ALK positive inflammatory myofibroblastic tumour (IMT).

Ocular disorders have been reported in 61% of paediatric patients treated with crizotinib in clinical trials for these indications. Paediatric patients should be monitored for ocular toxicity, including the risk of severe vision loss. They should receive a baseline ophthalmologic examination prior to starting crizotinib with follow-up examinations.

Health-care professionals are advised to inform patients and caregivers of symptoms related to vision and remind them to contact their doctor if any of these symptoms develop. Any ocular symptoms should be referred to an eye specialist. Health-care professionals are also advised to consider a dose reduction of crizotinib for patients who develop Grade 2 ocular disorders. If Grade 3 and 4 ocular disorders occur, treatment with the medicine should be discontinued permanently, unless another cause is identified.

Reference:
Patients and carers, EMA, 10 June 2022 *(link to the source within www.ema.europa.eu)*

Denosumab

Risk of hypercalcaemia in children and adolescents

United Kingdom. The Medicines and Healthcare Products Regulatory Agency (MHRA) has announced that

the product information for denosumab 60mg (Prolia®*) has been updated to advise against use in children and adolescents younger than 18 years, due to the risk of serious hypercalcaemia.

Denosumab 60mg is indicated in adults for the treatment of osteoporosis in postmenopausal women and men at increased risk of fractures. Use of denosumab 60mg in children for the treatment of osteoporosis is off-label use.

Cases of serious and life-threatening hypercalcaemia requiring hospitalization and complications due to acute renal injury have been reported in children and adolescents younger than 18 years receiving denosumab 60mg in clinical trials, investigating the treatment of osteogenesis imperfecta. Worldwide, 20 cases of hypercalcaemia were reported, during off-label treatment with denosumab 60mg in children and adolescents younger than 18 years. There were also a small number of reports of hypercalcaemia in patients younger than 18 years after stopping treatment (rebound hypercalcaemia). A recent European review assessed the cases of severe hypercalcaemia

within www.gov.uk/mhra)

(Another denosumab product, denosumab 120mg (Xgeva®) remains authorised for adults and skeletally mature teenagers with giant cell tumour of bone.)*

Dexamethasone, betamethasone

Risk of phaeochromocytoma crisis

Japan. The MHLW and the PMDA have announced that the product information for dexamethasone and betamethasone containing products should be revised to include the risk of phaeochromocytoma crisis.

Dexamethasone and betamethasone are steroids, that are available in various formulations. Products for oral use, injections and suppositories are subject to this revision.

Cases of phaeochromocytoma crisis reported with the use of dexamethasone (oral dosage form and injections) and betamethasone (injections) in Japan and overseas were evaluated. Several cases were assessed to have a possible causal relationship between the drug and event. There were no case reports of

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

Interferon beta

Removal of contraindication in pregnant women

Japan. The MHLW and the PMDA have announced that the product information for interferon beta-1a (Avonex®) and interferon beta-1b (Betaferon®) (hereafter referred as "IFNβ") should be revised to remove the contraindication in pregnant women and replaced with a precaution on the use in pregnancy.

IFNβ is used to prevent relapse of multiple sclerosis. In Japan, administration of IFNβ to pregnant women has been contraindicated from the time of initial approval in 2000.

The MHLW and the PMDA reassessed the risk of foetal death or spontaneous abortions that were observed in reproductive toxicity studies in monkeys, and concluded that there is no need for a blanket contraindication of IFNβ in pregnant women based on these studies.