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WHO Pharmaceuticals NEWSLETTER

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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:

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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.

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Regulatory Matters

Safety of medicines

Signal

Atezolizumab

Risk of severe cutaneous adverse reactions (SCAR)

Malaysia. The National Pharmaceutical Regulatory Agency (NPRA) has announced that the product information for atezolizumab (Tecentriq®) has been updated to include the risk of severe cutaneous adverse reactions (SCAR).

Atezolizumab is indicated to treat non-small cell lung cancer, small cell lung cancer and triple-negative breast cancer. SCARs include acute generalized exanthematous pustulosis (AGEP), Stevens-Johnson syndrome (JSJ), toxic epidermal necrolysis (TEN) and drug rash with eosinophilia and systemic symptoms (DRESS).

Based on analysis from the company's global safety data 99 cases of SCARs have been identified, of which 36 cases were confirmed by histopathology or specialist diagnosis.

Reference:
Safety Alerts, NPRA, 22 April 2021 *(www.npra.gov.my/)*

Cetuximab (genetic recombination)

Risk of hypomagnesaemia

Japan. The Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA) have announced that the package insert for cetuximab (genetic recombination) (Erbitux®) should be revised to include the risk of hypomagnesaemia as an adverse drug reaction.

Cetuximab is indicated to treat RAS wild-type, incurable, unresectable, advance/recurrent colorectal cancer and head and neck cancer.

A total of five cases of hypomagnesaemia have been reported in patients treated with cetuximab in Japan in the past three years, including three cases for which a causal relationship between the drug and event was assessed to be reasonably possible. No patient mortalities have been reported.

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

Reference:
Revision of Precautions, MHLW/PMDA, 30 March 2021 *(www.pmda.go.jp/english/)*

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

Risk of thrombosis with thrombocytopenia syndrome (TTS)

Europe. The Committee for Medicinal Products for Human Use (CHMP) has recommended that COVID-19 vaccine NRVV Ad (ChAdOx1 nCoV-19) (Vaxzevria®) must not be given to anyone who has had thrombosis with thrombocytopenia syndrome (TTS).

COVID-19 vaccine NRVV Ad (ChAdOx1 nCoV-19) is a vaccine for preventing COVID-19 in people aged 18 years and older.

As TTS requires specialist treatment, health-care professionals should consult applicable guidance and/or specialists to diagnose and treat the condition.

Also, health-care professionals should check for signs of thrombosis in any person who has thrombocytopenia within three weeks of vaccination and should advise people to seek urgent medical attention if they have any symptoms suggesting thrombosis or thrombocytopenia.

Reference:
EMA, 21 May 2021 *(www.ema.europa.eu)*

(See also WHO Pharmaceuticals Newsletter No.2, 2021: Possible link to very rare cases of unusual blood clots with low blood platelet counts in Europe)

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))*

COVID-19 vaccine NRVV Ad26 (JNJ 78436735)

Risk of thrombosis with thrombocytopenia syndrome (TTS)

Europe. The Pharmacovigilance Risk Assessment Committee (PRAC) has recommended that the warning of TTS in the product information for COVID-19 vaccine NRVV Ad26 (JNJ 78436735) (Janssen COVID-19 vaccine®) should be refined to include advice on investigating for signs of thrombosis in patients presenting with thrombocytopenia within three weeks of vaccination.

COVID-19 vaccine NRVV Ad26 (JNJ 78436735) is indicated for preventing COVID-19 in people aged 18 years and older.

Also, TTS will be added as an important identified risk in the risk management plan.

The benefits of using the vaccine to prevent COVID-19 outweigh the risks of adverse effects.

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

WHO, Statement of the COVID-19 subcommittee of the WHO Global Advisory Committee on Vaccine Safety (GACVS) on safety signals related to the Johnson & Johnson/Janssen COVID-19 vaccine, 19 May 2021. (*https://www.who.int/news/item/19-05-2021-statement-gacvs-safety-johnson-johnson-janssen-covid-19-vaccine*)

Durvalumab (genetic recombination)

Risk of immune thrombocytopenic purpura

Japan. The MHLW and the PMDA have announced that the package insert for durvalumab (genetic recombination) (Imfinzi®) should be revised to include the risk of immune thrombocytopenic purpura as an adverse drug reaction.

Durvalumab is indicated for the treatment of locally-advanced, unresectable non-small cell lung cancer and extensive stage small cell lung cancer.

A total of 15 cases of immune thrombocytopenic purpura have been reported in patients treated with durvalumab in Japan in the past three years, including four cases for which a causal relationship between the drug and event was assessed to be reasonably possible. No patient mortalities have been reported.

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

Reference:
Revision of Precautions, MHLW/PMDA, 30 March 2021 (*www.pmda.go.jp/english/*)

Iopamidol

Risk of acute generalized exanthematous pustulosis (AGEP)

Japan. The MHLW and the PMDA have announced that the package insert for iopamidol (Iopamiron®) should be revised to include the risk of acute generalized exanthematous pustulosis (AGEP) as an adverse drug reaction.

Iopamidol is used for diagnostics such as angiocardiography, aortography and extremity angiography.

A total of four cases of AGEP have been reported in patients treated with iopamidol in Japan in the past three years, including three cases for which a causal relationship between the drug and event was assessed to be reasonably possible. No patient mortalities have been reported.

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

Reference:
Revision of Precautions, MHLW/PMDA, 30 March 2021 (*www.pmda.go.jp/english/*)

Levothyroxine (tablet)

Risk of related to aggravating thyroid symptoms when switching between different products

United Kingdom. The Medicines and Healthcare Products Regulatory Agency (MHRA) has announced that the product information for levothyroxine is being updated to include the risk of aggravating thyroid symptoms when switching between different levothyroxine products (tablets).

Levothyroxine is indicated for the control of hypothyroidism. In the UK, prescribing of levothyroxine is usually generic, so patients may switch between different levothyroxine products according to what is available at their local pharmacies.

From 2015 to 2019, the MHRA received 335 reports of the thyroid condition being aggravated or ineffectiveness of the levothyroxine product following substitution with another. Associated symptoms were mostly consistent with hypothyroidism or hyperthyroidism and included fatigue, headache, malaise, anxiety, palpitation, nausea myalgia and dizziness. The underlying causes for the symptoms experienced after switching between products are generally unclear.

Generic prescribing of levothyroxine remains appropriate for the majority of patients and the licensing of these generic products is supported by bioequivalence testing.

If a patient reports persistent symptoms of their condition being aggravated when switching between different levothyroxine products, health-care professionals should consider consistently prescribing a specific product known to be well tolerated by the patient. Also, if symptoms or poor control of thyroid function persist, prescribing an oral solution formulation of levothyroxine should be considered.

Reference:
Drug Safety Update, MHRA, 19 May 2021 (*www.gov.uk/mhra*)

(See also WHO Pharmaceuticals Newsletter No.1, 2020: Potential adverse reactions when switching brands in Ireland)

Nivolumab

Potential risk of certain blood disorders and cytokine release and tumor lysis syndromes

Canada. Health Canada has announced that the product

safety information (Canadian Product Monograph, CPM) for nivolumab (Opdivo®) has been updated to include a warning of the risk of autoimmune hemolytic anemia and it is working with the manufacturers to include the risks of aplastic anemia, cytokine release syndrome and tumor lysis syndrome in CPM.

Nivolumab is used alone or in combination to treat certain type of cancers of the skin, head and neck, blood cells, lungs and kidneys.

Health Canada reviewed information received from the manufacturer by searching the Canada vigilance database, international databases and published literature. It concluded that there may be a link between nivolumab and the risks of autoimmune hemolytic anemia, aplastic anemia, cytokine release syndrome and tumor lysis syndrome.

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

(See also WHO Pharmaceuticals Newsletter No.4, 2019: Potential risk of hemophagocytic lymphohistiocytosis (HLH) in Canada; No.2, 2019: Risk of serious blood disorder in Japan)

Obeticholic acid

Risk of serious liver injury

USA. The US Food and Drug Administration (FDA) has announced that it has revised the boxed warning for obeticholic acid (Ocaliva®) to include the risk of serious liver injury in patients with primary biliary cholangitis (PBC) and advanced cirrhosis of the liver.

Obeticholic acid is indicated to treat PBC.

The FDA identified 25 cases of serious liver injury that led to liver decompensation or liver failure associated with the use of obeticholic acid in PBC patients with cirrhosis. The FDA believes the benefits of obeticholic acid outweigh the risks for PBC patients who do not have advanced cirrhosis.

Health-care professionals should determine whether a patient with PBC has advanced cirrhosis before starting obeticholic acid.

Also, health-care professionals should routinely monitor patients during the treatment for progression of PBC with laboratory and clinical assessments to determine whether to discontinue obeticholic acid.

Reference:
MedWatch, US FDA, 26 May 2021 *(www.fda.gov)*

(See also WHO Pharmaceuticals Newsletter No.4, 2018: Risk of serious liver injury in Ireland; No.3, 2018: Risk of serious liver injury in UK; No.5, 2017: Risk of serious liver injury in USA)

Polyethylene glycol (PEG) laxatives and starch-based thickeners

Potential interaction: risk of aspiration

United Kingdom. The MHRA has announced that it has requested that the manufacturers of Polyethylene glycol (PEG) laxatives to update the summary of product characteristics (SmPC) and the patient information leaflet (PIL) to include information about a potential interaction with starch based thickeners that can increase the risk of aspiration in patients with dysphagia.

PEG laxative products are used to treat constipation through an osmotic effect. Thickeners are used to thicken liquids taken by patients with dysphagia, including elderly and those who have trouble swallowing. There are two main types of thickening agents: starch- and gum-based.

Adding a PEG-based laxative to a liquid that has been thickened with a starch-based thickener may counteract the thickening action.

Constipation and dysphagia coexist more commonly in the elderly and in those with swallowing difficulties.

Although the MHRA is not aware of any cases of this potential interaction in the UK, an institute in Canada has issued a safety bulletin discussing a potential harmful interaction between PEG laxative and starch-based thickeners.

Reference:
Drug Safety Update, MHRA, 27 April 2021 *(www.gov.uk/mhra)*

Pomalidomide, thalidomide

Potential risk of progressive multifocal leukoencephalopathy (PML)

Canada. Health Canada has announced that the product safety information for pomalidomide (Pomalyst®) has been updated to include a warning of the risk of progressive multifocal leukoencephalopathy (PML). Health Canada will also include this warning in the safety information for thalidomide (Thalomid®).

Pomalidomide and thalidomide are indicated to treat multiple myeloma.

Health Canada reviewed the available information by performing a search in the Canada vigilance database, international database, published literature and using information provided by the manufacturer.

Health Canada's review concluded that there is a possible link between pomalidomide or thalidomide and the risks of PML.

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

(See also WHO Pharmaceuticals Newsletter No.2, 2021: Risk of progressive multifocal leukoencephalopathy (PML) in Japan)

Ritodrine and Magnesium sulfate (co-administration)

Increased risk of hyperkalaemia

Japan. The MHLW and the PMDA have announced that the package inserts for ritodrine (Utemerin®) and magnesium sulfate (Magsent® and Magnesol®) should be revised to include the risk of hyperkalaemia in preterm infants born to mothers who were co-administered ritodrine and magnesium sulfate.

Ritodrine is indicated for threatened abortion/premature labor. Magnesium sulfate is indicated for inhibition of uterine contractions and for prophylaxis and treatment of eclampsia.

A total of eight cases of neonatal hyperkalaemia have been reported in the newborns of patients treated with ritodrine and magnesium sulfate in Japan in the past three years, including four cases for which a causal relationship between the drug and event was assessed to be reasonably possible. There has been one death reported, but a causal relationship could not be established.

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

Reference:
Revision of Precautions, MHLW/PMDA, 30 March 2021 *(www.pmda.go.jp/english/)*

Shosaikotokakikyosekko

Risk of interstitial pneumonia

Japan. The MHLW and the PMDA have announced that the package insert for shosaikotokakikyosekko (Tsumura Shosaikotokakikyosekko Extract Granules®) should be revised to include the risk of interstitial pneumonia as an adverse drug reaction.

Shosaikotokakikyosekko is indicated for relief of tonsillitis and peritonsillitis accompanied by painful swollen throat.

A total of two cases of interstitial pneumonia have been reported in patients treated with shosaikotokakikyosekko in Japan in the past three years, including one case for which a causal relationship between the drug and event was reasonably possible. No patient mortalities have been reported.

If symptoms such as cough, dyspnoea, pyrexia and abnormal chest sounds are observed, administration of the shosaikotokakikyosekko should be discontinued.

Reference:
Revision of Precautions, MHLW/PMDA, 13 May 2021 *(www.pmda.go.jp/english/)*

Tozinameran

Risk of facial swelling

Europe. The PRAC has recommended that the SmPC and the PIL for tozinameran (Comirnaty®) should be revised to include facial swelling in people with a history of injections with dermal fillers as an adverse reaction.

Tozinameran is indicated for active immunization to prevent COVID-19 caused by SARS-CoV-2 virus, in individuals 12 years of age and older.

The PRAC reviewed the available evidence including cases of facial swelling reported to the European database for suspected adverse effects (EudraVigilance) and scientific literature. A causal association between the vaccine and the reported cases of facial swelling in people with a history of injections with dermal fillers was considered to be reasonably possible.

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

Vascular endothelial growth factor (VEGF) inhibitors (systemic use)

Risk of artery dissections and aneurysms

Malaysia. The NPRA has issued a directive for all registration holders of vascular endothelial growth factor (VEGF) inhibitors for systemic use, requesting that the local package inserts should be updated to include the risk of artery dissections and aneurysms.

VEGF inhibitors are indicated to treat various types of cancers including renal cell carcinoma, thyroid and soft tissue cancers. There are 21 registered products containing VEGF inhibitors for systemic use in Malaysia.

The NPRA has received two reports of aneurysms associated with bevacizumab use in Malaysia.

The mechanism of VEGF inhibitors causing artery dissections and aneurysms is unclear but thought to be due to the weakening of vascular wall integrity. Risk factors include hypertension or aggravation of pre-existing hypertension, a previous history of aneurysm, smoking,

diabetes mellitus, coronary, cerebrovascular or peripheral arterial disease.

Health-care professionals should carefully consider the risk of artery dissections and aneurysms in patients with risk factors before prescribing VEGF inhibitors for systemic use.

Reference:

Safety Alerts, NPRA, 20 April 2021 *(www.npra.gov.my/)*

(See also WHO Pharmaceuticals Newsletter No.5, 2020: Risk of aneurysms and artery dissections in New Zealand; No.6, 2020: Risk of aneurysm and artery dissection in Ireland; No.1, 2019: Risk of artery dissections and artery aneurysms in Canada)