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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 legal actions taken by regulatory authorities around the world. It also provides signals based on information derived from the WHO global database of individual case safety reports, VigiBase.

In addition, this edition of the Newsletter includes an article on the Global Vaccine Safety Blueprint 2.0 (GVSB 2.0).

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Atezolizumab and other immune-stimulatory anti-cancer drugs

Risk of severe cutaneous adverse reactions (SCARs)

United Kingdom. The Medicines and Healthcare Products Regulatory Agency (MHRA) has announced that the product information for atezolizumab (Tecentriq®) has been updated to include information about the risk of severe cutaneous adverse reactions (SCARs), which includes Stevens-Johnsons syndrome (SJS) and toxic epidermal necrolysis (TEN).

Atezolizumab is an immune-stimulatory drug indicated for cancers including those of the bladder, lung and liver. SCARs were previously known to be potentially associated with the use of atezolizumab.

A review of safety data for atezolizumab and the risk of SCARs was recently completed in Europe. Based on this review SCARs is an identified risk for atezolizumab.

Also, other products used for cancers in the same class as atezolizumab, including cemiplimab, ipilimumab, nivolumab and pembrolizumab list SCARs as possible adverse effects in the Summary of Product Characteristics (SmPC).

Health-care professionals should monitor patients for signs and symptoms for severe skin reactions and exclude other causes.

Reference:
Drug Safety Update, MHRA, 17 June 2021 (*www.gov.uk/mhra*)

(See also WHO Pharmaceuticals Newsletter No.3, 2021: Risk of severe cutaneous adverse reactions (SCAR) in Malaysia)

Bupropion

Risk of serotonin syndrome

Australia. The Therapeutic Goods Administration (TGA) has announced that the product information (PI) for bupropion containing products (Zyban®, Contrave®) have been updated to include the risk of serotonin syndrome when co-administered with other drugs known to be associated with serotonin syndrome, such as selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs).

Bupropion is used as adjunctive therapy for smoking cessation and management of weight in adult.

Post marketing data show a possible pharmacodynamic interaction between bupropion and SSRIs or SNRIs resulting in an increased risk of serotonin syndrome.

The TGA received six cases of serotonin syndrome associated with bupropion (up to 17 June 2021).

Health-care professionals should educate patients about the signs and symptoms of serotonin syndrome, such as mental-status changes, autonomic instability, neuromuscular abnormalities and gastrointestinal symptoms. Patients should be instructed to see health-care professionals if they suspect that they are experiencing these adverse effects.

Reference:
Medicines Safety Update, TGA, 2 July 2021 (*www.tga.gov.au/*)

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

Cefoperazone

Risk of bleeding and hypoprothrombinemia

Saudi Arabia. The Saudi Food & Drug Authority (SFDA) has requested that health-care institutions stop supplying cefoperazone products (Cefobid®) due to the risk of bleeding, and has also advised health-care professionals to prescribe safer alternative antibiotics.

Cefoperazone is indicated for the treatment of a wide range of infections including respiratory tract infections, peritonitis and bacterial septicemia.

Results of several published studies suggest that cephalosporin antibiotics including cefoperazone is associated with the risk of bleeding via inhibiting vitamin K metabolism, which can lead to hypoprothrombinemia.

The SFDA reviewed published literature and post-marketing data to evaluate the potential risk of hypoprothrombinemia and bleeding with cefoperazone use. The SFDA found that the current evidence indicates an increased risk of hypoprothrombinemia and bleeding with the use of cefoperazone compared to other safer therapeutic alternatives that are available in Saudi Arabia for the same indications. Serious and fatal cases of bleeding have been reported with the use of cefoperazone worldwide.

The evaluation of the benefit-risk profile of products containing cefoperazone showed that the potential risks outweigh the benefits.

Reference:
Safety Alerts, SFDA, 14 June 2021 (*www.sfda.gov.sa*)

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

1. Risk of capillary leak syndrome (CLS)

Europe. The Pharmacovigilance Risk Assessment Committee (PRAC) has concluded that people who have previously had capillary leak syndrome (CLS) must not be vaccinated with COVID-19 vaccine NRVV Ad (ChAdOx1 nCoV-19) (Vaxzevria®) and that CLS should be added to the product information as a new adverse drug reaction. CLS is a very rare, serious condition that causes fluid leakage from small blood vessels, resulting in swelling in the arms and legs, low blood pressure and low albumin level.

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

The PRAC carried out an in-depth review of six cases of CLS in people who had received the vaccine.

Health-care professionals should be aware of the signs and symptoms of CLS and of its risk of recurrence in people who have previously been diagnosed with the condition.

People who have been vaccinated with the vaccine should seek immediate medical assistance if they experience rapid swelling of the arms and legs or sudden weight gain in the days following vaccination.

Reference:
EMA, 11 June 2021 (*www.ema.europa.eu*)

2. Risk of Guillain-Barre syndrome (GBS)

Europe. The PRAC has recommended a change to the product information for COVID-19 vaccine NRVV Ad (ChAdOx1 nCoV-19) (Vaxzevria®) to include a warning on Guillain-Barre syndrome (GBS).

The PRAC has assessed all the available evidence including cases reported and data from the scientific literature, but at this stage the data neither confirms nor rules out a possible association with the vaccine.

Health-care professionals should be alert to signs and symptom of GBS to allow early diagnosis and supportive care and treatment.

People taking the vaccine are advised to seek immediate medical attention if they develop weakness and paralysis that can progress to the chest and face.

Reference:
EMA, 9 July 2021 (*www.ema.europa.eu*)

COVID-19 vaccine NRVV Ad26 (JNJ 78436735)

Risk of capillary leak syndrome (CLS)

Europe. The PRAC has recommended that people who have previously had CLS must not be vaccinated with COVID-19 vaccine NRVV Ad26 (JNJ 78436735) (COVID-19 vaccine Janssen®) and that CLS should be added to the product information as a new adverse drug reaction.

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

The PRAC reviewed three cases of CLS in people who have had the vaccine.

Health-care professionals should be aware of the signs and symptoms of CLS and of its risk of recurrence in people who have previously been diagnosed with the condition.

Also, health-care professionals should tell people receiving the vaccine that they must seek medical attention if they experience rapid swelling of the arms and legs or sudden weight gain in the days following vaccination.

Reference:
EMA, 9 July 2021 (*www.ema.europa.eu*)

Cyclin-dependent kinases 4/6 (CDK4/6) inhibitors

Risk of interstitial lung disease and pneumonitis

United Kingdom. The MHRA has announced that the SmPCs and Patient Information Leaflets (PILs) for cyclin-dependent kinase 4 and 6 inhibitors (CDK4/6-inhibitors) such as abemaciclib (Verzenios®), palbociclib (Ibrance®) and ribociclib (Kisqali®) have been updated to include warnings about the risk of interstitial lung disease and pneumonitis.

CDK4/6-inhibitors are indicated for some types of locally advanced or metastatic breast cancer.

Cases of interstitial lung disease and pneumonitis have been reported with the use of CDK4/6-inhibitors. Following European reviews of safety data, the product information has been updated to include this risk.

Health-care professionals should ask patients about pulmonary symptoms indicative of interstitial lung disease and pneumonitis, such as cough or dyspnea and advise them to seek advice if they occur.

Reference:
Drug Safety Update, MHRA, 17 June 2021 (*www.gov.uk/mhra*)

(See also WHO Pharmaceuticals Newsletter No.5, 2019: Rare but severe lung inflammation in USA; No.2, 2019: Risk of interstitial lung disease in Japan)

Diclofenac etalhyaluronate (injection)

Risk of serious shock and

anaphylaxis

Japan. The Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA) have announced that the package insert for diclofenac etalhyaluronate (injection) (Joyclu®) should be revised to include the risk of serious shock and anaphylaxis as adverse drug reactions.

Diclofenac etalhyaluronate is indicated to treat osteoarthritis in the knee and hip joints.

A total of 10 cases of serious shock or anaphylaxis have been reported in patients treated with diclofenac etalhyaluronate in Japan (from March to May in 2021). Seven of the 10 cases were reviewed for causality and a causal relationship between the drug and event was assessed to be reasonably possible. No patient mortalities have been reported.

Sufficient preparation for emergency responses should be ensured prior to administration. Also, patients should be carefully monitored during drug administration.

Reference:
Revision of Precautions, MHLW/PMDA, 1 June 2021 (*www.pmda.go.jp/english/*)

Dienogest

Risk of venous thromboembolism

Australia. The TGA has announced that the product information (PI) for dienogest containing products have been updated to include more detailed information on the risk of venous thromboembolism (VTE).

Dienogest, a progestogen, is used in combined oral contraceptives (COCs) (Valette®, Qlaira®).

A review by the TGA in 2016 found that while the risk of VTE is generally rare, the risk is slightly increased in women using a COC containing ethinylestradiol and progestogen. Since 2016, the sponsor for both products conducted a meta-analysis of four prospective cohort studies investigating the VTE risk associated with the use of contraceptives. As a result of the analysis on VTE, the sponsor has updated the PI for dienogest containing products to include additional detail on this adverse reaction.

Based on the updated information, there is no reason for women to stop taking a dienogest containing contraceptive if they are already using it and have not experienced any problems.

Health-care professionals should consider a women's individual risk factors for thromboembolism, including smoking, obesity, increasing age and a family history of VTE.

Reference:
Medicines Safety Update, TGA, 23 June 2021 (*www.tga.gov.au/*)

Dopamine agonists

Risk of dopamine agonist withdrawal syndrome (DAWS)

Canada. Health Canada has announced that the Canadian Product Monograph (CPM) for pramipexole has been updated to include a warning on the risk of dopamine agonist withdrawal syndrome (DAWS).

Dopamine agonists are indicated to treat Parkinson's disease, restless leg syndrome and acromegaly. Apomorphine, bromocriptine, cabergoline, pergolide, pramipexole, quinagolide, ropinirole, and rotigotine containing products are available as dopamine agonists.

Health Canada has been monitoring the potential risk of DAWS since 2019, following updates made by the PMDA in Japan. In 2020, the manufacturer of pramipexole voluntarily updated the CPM to include a warning of DAWS, which triggered Health Canada's safety review for all dopamine agonists marketed in Canada.

Health Canada reviewed information from Canadian, international databases of reported adverse reactions and the scientific literature. Twenty three (23) case reports (two Canadian and 21 international) of DAWS in patients treated with dopamine agonists were evaluated.

The review has established a link between use of the dopamine agonists pramipexole, quinagolide or ropinirole and the risk of DAWS and therefore Health Canada will work with the manufacturers of quinagolide and ropinirole to update the CPMs to include a warning of the DAWS.

Although there is not enough information to establish a link between other dopamine agonists such as apomorphine, bromocriptine, cabergoline, pergolide and rotigotine and DAWS, Health Canada will work with the manufacturers of these dopamine agonists to include the potential risk of DAWS as a precaution.

Reference:
Summary Safety Review, Health Canada, 8 June 2021 (*www.hc-sc.gc.ca*)

(See also WHO Pharmaceuticals Newsletter No.5, 2019: Risk of drug withdrawal syndrome in Japan)

Ixekizumab (genetic recombination)

Risk of interstitial pneumonia

Japan. The MHLW and the PMDA have announced that the package insert for ixekizumab (Taltz®) should be revised to

include the risk of interstitial pneumonia as an adverse drug reaction.

Ixekizumab is indicated to treat certain diseases such as psoriasis vulgaris, erythrodermic psoriasis and ankylosing spondylitis.

A total of eight cases of interstitial pneumonia have been reported in patients treated with pembrolizumab in Japan in the last 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.

If symptoms such as cough, dyspnea, or pyrexia, are observed, examinations such as chest X-ray, chest CT scan, and serum marker test should be performed immediately. If interstitial pneumonia is suspected, administration of ixekizumab should be discontinued, and appropriate measures such as administration of corticosteroids should be taken.

Reference:
Revision of Precautions, MHLW/PMDA, 15 June 2021 (www.pmda.go.jp/english/)

Nivolumab (genetic recombination)

Risk of febrile neutropenia

the PMDA considered that the revision of the package insert was necessary.

Reference:
Revision of Precautions, MHLW/PMDA, 21 June 2021 (www.pmda.go.jp/english/)

(See also WHO Pharmaceuticals Newsletter No.3, 2021: Potential risk of certain blood disorders and cytokine release and tumor lysis syndromes in Canada; No.4, 2019: Potential risk of hemophagocytic lymphohistiocytosis (HLH) in Canada; No.2, 2019: Risk of serious blood disorder in Japan)

Olanzapine

Potential risk of somnambulism

Saudi Arabia. The SFDA has requested that the product information for olanzapine containing products (Olazine®, Olenza®, Zolan®) is updated to include a potential risk of somnambulism (sleepwalking) as an adverse drug reaction.

Olanzapine is indicated for treatment of schizophrenia and bipolar disorder including mixed or manic episodes.

The SFDA reviewed published literature and post marketing data on the potential risk of sleepwalking associated with olanzapine use. The SFDA identified 64 spontaneous case reports of somnambulism with olanzapine use in the WHO database, reported between 1999 and May 2021. Most

and hepatic failure

Japan. The MHLW and the PMDA have announced that the package insert for pembrolizumab (Keytruda®) should be revised to include the risk of fulminant hepatitis and hepatic failure as adverse drug reactions.

Pembrolizumab is indicated to treat certain types of cancers such as malignant melanoma, unresectable advanced non-small cell lung cancer and relapsed classical Hodgkin lymphoma.

A total of 29 cases of fulminant hepatitis or hepatic failure have been reported in patients treated with pembrolizumab in Japan in the last three years, including five cases for which a causal relationship between the drug and event was reasonably possible. A total of 18 patient mortalities, including three cases of which a causal relationship was assessed to be reasonably possible have been reported.

Patients should be carefully monitored through periodical hepatic function tests.

Reference:
Revision of Precautions, MHLW/PMDA, 15 June 2021 (www.pmda.go.jp/english/)

Remdesivir

Risk of sinus bradycardia