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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 summary and recommendations from the virtual meeting of the members of the WHO Programme for International Drug Monitoring (PIDM) and other partners, which was held on 20 October 2022.

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

Amlodipine, nifedipine

Removal of contraindication for use in pregnant women

Japan. The Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA) have announced that the product information for amlodipine and nifedipine should be revised to remove the contraindication in pregnant women and replace it with a precaution for use during pregnancy.

Amlodipine and nifedipine are calcium channel blockers and are indicated for the treatment of hypertension and angina pectoris. Amlodipine was contraindicated in pregnant women based on the result of animal studies in rats which observed the prolongation of the gestational period and duration of delivery. Nifedipine was contraindicated in pregnant women of less than 20 weeks of pregnancy due to the teratogenicity observed in toxicity studies using rats and mice.

The MHLW and PMDA reviewed the available evidence which included: case reports of adverse events, results of observational studies and other publications:

- There were no domestic ICSRs reporting the prolongation of gestational period and duration of delivery with amlodipine or limb anomalies with nifedipine use. There were some reports of congenital anomalies (with both drugs) and foetal death (with nifedipine), but a causal relationship between the drugs and events were not identified. Prolongation of gestational period and duration of delivery concerned with amlodipine can occur in normal delivery and are treatable.
- There are reports of mixed view in the literature and no consensus has been reached on whether these drugs increase the risk of congenital anomalies.
- There is no contraindication for the use of amlodipine during pregnancy in the US, UK, Canada, and Australia. Nifedipine is contraindicated for use during pregnancy in Canada and Australia while not contraindicated in the US and UK.
- In domestic and international clinical guidelines, the benefit of strict blood pressure control throughout pregnancy using calcium channel blockers is recognized while any safety concerns for use in pregnancy has not been identified.

The MHLW and PMDA concluded that the contraindication for use in pregnant women can be removed and replaced with a precaution that amlodipine or nifedipine should be administered to pregnant women only if the potential therapeutic benefits are considered to outweigh the potential risks.

Reference:
Revision of Precautions, MHLW/PMDA, 5 December 2022 *(link1, 2, 3 and 4 to the source within www.pmda.go.jp/english/)*

Amoxicillin

1. Risk of drug-induced enterocolitis syndrome (DIES)

Ireland. The Health Products Regulatory Authority (HPRA) has announced that the product information for amoxicillin will be updated to include the risk of drug-induced enterocolitis syndrome (DIES).

Amoxicillin (as a single substance or in combination with other antimicrobials) is a semi-synthetic broad spectrum penicillin antibiotic, and is indicated for the treatment of bacterial infections caused by amoxicillin-sensitive gam-positive and gram-negative pathogens.

Following a recent review of the available safety data by the EMA PRAC, a causal relationship between amoxicillin and DIES is considered to be reasonable possibility.

DIES is an allergic reaction with the leading symptom of protracted vomiting (1-4 hours after drug administration) in the absence of allergic, skin or respiratory symptoms. Further symptoms could comprise of abdominal pain, diarrhoea, hypotension or leucocytosis with neutrophilia. There have been severe cases of DIES which have progressed to shock. DIES has been reported mainly in children receiving amoxicillin.

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

2. Risk of acute coronary

syndrome accompanying allergic reaction

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

The MHLW and PMDA reviewed cases of acute coronary syndrome accompanying allergic reaction reported domestically and internationally. In internationally reported cases, a causal relationship between the drug and event was reasonably possible. The MHLW and PMDA concluded that acute coronary syndrome accompanying allergic reaction should be added as a clinically significant adverse reaction.

Health-care professionals are advised to interview patients on their medical history of allergic reactions to antimicrobials before treatment with amoxicillin.

Reference:
Revision of Precautions, MHLW/PMDA, 16 November 2022 *(link to the source within www.pmda.go.jp/english/)*

Atezolizumab

Risk of acute kidney injury (AKI)

Republic of Korea. The Ministry of Food and Drug Safety (MFDS) has updated the product information for atezolizumab to include the risk of acute kidney injury (AKI) as an adverse reaction.

Atezolizumab is a monoclonal antibody inhibiting PD-L1 and is indicated for the treatment of locally advanced or metastatic urothelial carcinoma, metastatic non-small cell lung cancer and other types of cancer.

The Korea Institute of Drug safety and Risk Management (KIDS) reviewed reports with serious outcomes. There was one fatal report of AKI in a patient who was administered atezolizumab-containing chemotherapy for extensive-stage small cell lung cancer. A causal association could not be excluded between atezolizumab and AKI in this case. Based on the result of this review and information from the regulatory authorities in the US and Japan, the MFDS updated the product information to include the risk of AKI.

Health-care professionals should be reminded of the possible risk of renal toxicities with the use of atezolizumab - containing chemotherapy regimens and are advised to monitor for any signs of serious renal symptoms while using this drug.

Reference:
Based on the communication from KIDS and Drug Safety Update, MFDS/KIDS, 8 November 2022 *(link to the source within nedrug.mfds.go.kr/index)*

Bupropion

Potential risk of cardiac arrest or sudden death through unmasking of Brugada syndrome

Ireland. The HPRA has announced that the product information for bupropion will be updated to advise that its use may unmask Brugada syndrome, which is a rare hereditary disease that can lead to cardiac arrest or sudden death.

Bupropion is indicated for the treatment of major depressive disorder (MDD), nicotine dependence as an aid to smoking cessation, and for weight management in specific patients.

Patients are advised to talk to their doctor before taking bupropion if they have pre-existing Brugada syndrome or if there is a family history of cardiac arrest or sudden death.

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

Cabergoline

Potential risks of hypertension, myocardial infarction, seizures, stroke or psychiatric disorders

Ireland. The HPRA has announced that the product information for cabergoline will be updated to warn that serious adverse events including hypertension, myocardial infarction, seizures, stroke or psychiatric disorders have been reported in postpartum women treated with cabergoline for inhibition of lactation.

Cabergoline is indicated for the treatment of dysfunctions associated with hyperprolactinaemia in female patients and the management of Parkinson's disease.

Health-care professionals are advised that blood pressure should be carefully monitored after treatment. Cabergoline

should be discontinued, and the patient should be evaluated promptly in case of hypertension, suggestive chest pain, severe, progressive, or unremitting headache (with or without visual disturbances), or evidence of any central nervous system toxicity.

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

Cephalosporins

Risk of fixed drug eruption

India. The Central Drugs Standard Control Organization (CDSCO) has approved the recommendation from the National Coordination Centre – Pharmacovigilance Programme of India (NCC-PvPI), Indian Pharmacopoeia Commission (IPC) to revise the prescribing information leaflet (PIL) for cephalosporins to include fixed drug eruption as an adverse drug reaction.

Cephalosporins are a group of antibiotics that belong to a beta-lactam class, indicated to manage a wide range of infections from gram-positive and gram-negative bacteria.

The NCC-PvPI, IPC reviewed 203 Individual Case Safety Reports (ICSRs) of cephalosporin associated fixed drug eruption and a causal relationship between them was found.

Reference:
Based on the communication from IPC, India, October 2022 *(link to the source within ipc.gov.in)*

Clobetasol

Risk of serious undesirable effects with prolonged use

Ireland. The HPRA has announced that the product information for clobetasol has been updated to include the risk of serious undesirable effects with prolonged use due to its potency. These effects could include osteonecrosis serious infections, and systemic immunosuppression.

Clobetasol is very potent topical corticosteroid in various formulations (e.g., cream, ointment, scalp application and shampoo) and is indicated for the relief of inflammatory and pruritic manifestations of steroid-responsive dermatoses that are resistant to less potent corticosteroids.

Health-care professionals are advised that a less potent corticosteroid preparation should be considered if treatment with a local corticosteroid is clinically justified beyond four weeks. Repeated but short courses of clobetasol may be used to control exacerbations.

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

Codeine with ibuprofen

Risks of serious renal and gastrointestinal harms

Europe. The Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) has recommended a change to the product information for codeine with ibuprofen combination medicines to include a warning of serious harms, including death, particularly when taken for prolonged periods at higher than recommended doses.

Codeine with ibuprofen is a combination of opioid (codeine) and anti-inflammatory (ibuprofen), which is used to treat pain. Repeated use of codeine with ibuprofen may lead to dependence and abuse due to the codeine component.

The PRAC reviewed several cases of renal, gastrointestinal and metabolic toxicities that have been reported in association with cases of abuse of and dependence from codeine with ibuprofen combinations, some of which have been fatal. The PRAC found that, when taken at higher than recommended doses or for a prolonged period of time, codeine with ibuprofen can cause renal tubular acidosis. Kidney malfunction can also cause hypokalaemia, which in turn may cause symptoms such as muscle weakness and light-headedness. Therefore, renal tubular acidosis and hypokalaemia will be added to the product information as new adverse effects.

Reference:
Patients and carers, EMA, 30 September 2022 *(link to the source within www.ema.europa.eu)*

COVID-19 vaccine Astrazeneca (ChAdOx1-S)

Potential risks of acute disseminated encephalomyelitis (ADEM) and cutaneous vasculitis

Australia. The Therapeutic Goods Administration (TGA) has announced that the existing warning on very rare demyelinating disorders in the product information for COVID-19 vaccine Astrazeneca (ChAdOx1-S, Vaxzevria®) has been updated to include the potential risk of acute disseminated encephalomyelitis (ADEM).

The updated warning states that:

- very rare events of demyelinating disorders, including acute disseminated encephalomyelitis, have been reported following vaccination;
- a causal relationship between the vaccine and event has not been established;
- health-care professionals should be alert of signs and symptoms of demyelinating disorders to ensure correct diagnosis, in order to initiate adequate supportive care and treatment, and to rule out other causes.

Cutaneous vasculitis has also been added to the product information as a rare skin disorder that has been reported after vaccination.

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

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

1. Risk of heavy menstrual bleeding

Europe. The PRAC has recommended that heavy menstrual bleeding should be added to the product information as an adverse reaction of unknown frequency for COVID-19 vaccines Moderna (elasomeran, Spikevax®), Pfizer (tozinameran, Comirnaty®) and the bivalent vaccines. Heavy menstrual bleeding may be defined as bleeding characterized by an increased volume and/or duration which interferes with the person's physical, social, emotional and quality of life.

Cases of heavy menstrual bleeding have been reported after the first, second and booster doses of these vaccines. The PRAC reviewed available data, including cases reported during clinical trials, cases spontaneously reported in Eudravigilance and findings from the medical literature. Most cases appeared to be non-serious and temporary in nature. The PRAC concluded that there is at least a reasonable possibility that the occurrence of heavy menstrual bleeding is causally associated with these vaccines.

There is no evidence to suggest the menstrual disorders experienced by some people have any impact on reproduction and fertility. Available data provides reassurance about the use of mRNA COVID-19 vaccines before and during pregnancy.

Reference:
Patients and carers, EMA, 28 October 2022 *(link to the source within www.ema.europa.eu)*

2. Risk of myocarditis and pericarditis

Australia. The TGA has announced that the product information for COVID-19 vaccines Moderna and Pfizer and the bivalent vaccines have been updated to expand on an existing warning on myocarditis and pericarditis to include the following points:

- Rare cases can also occur in females.
- Cases of myocarditis and pericarditis following vaccination have rarely been associated with severe outcomes including death.
- The signs and symptoms of myocarditis and pericarditis following vaccination include atypical presentations and non-specific symptoms of fatigue, nausea and vomiting, abdominal pain, dizziness or syncope, oedema and cough.

Reference:
COVID-19 vaccine safety report, TGA, 20 October 2022 *(link to the source within www.tga.gov.au)*

3. Potential risk of non-sexually acquired genital ulceration and dizziness

Australia. The TGA has announced that the product information for COVID-19 vaccine Pfizer and the bivalent vaccines[1] have been updated to include the potential risk of non-sexually acquired genital ulceration and dizziness.

[1] COVID-19 vaccine Moderna is not included in the scope of this measure.

Cases of non-sexually acquired genital ulceration have been reported after vaccination where other causes have not been established; however, a causal association between the event and vaccine has not been definitively established.

The condition is characterized by painful ulcers that tend to resolve spontaneously within a few weeks without scarring. In rare cases they may cause pain or urinary retention that require hospitalization. These ulcers predominantly affect adolescent females and are generally a diagnosis of exclusion when infectious and non-infectious causes of ulcers have been ruled out.

Dizziness has been added to the product information as a potential adverse event that can occur after vaccination. Dizziness was not observed in clinical trials but has been reported through real-world use of the vaccine after approval. It is not currently known how frequently this reaction occurs.

Reference:
COVID-19 vaccine safety report, TGA, 20 October & 22 December 2022 *(link1 and link2 to the source within www.tga.gov.au)*

Dupilumab

Risk of ocular adverse reactions

United Kingdom. The Medicines and Healthcare Products Regulatory Agency (MHRA) has announced that the product information for dupilumab (Dupixent®) is to be updated to include the risk of dry eyes and also to emphasize the need for prompt and appropriate management of any potential ocular reactions.

Dupilumab is a monoclonal antibody that inhibits interleukin-4 and interleukin-13 signaling and is indicated for the treatment of atopic dermatitis in adults and children.

The MHRA has received 479 UK reports (7 September 2022) which include suspected ocular adverse effects with dupilumab. One hundred and eleven of these reports were considered serious. Nine reports (representing five cases) of ulcerative keratitis were received, of which two cases reported corneal perforation.

It is not currently possible to predict who may experience the rarer and most serious ocular adverse reactions, such as ulcerative keratitis. It is therefore important, with all ocular reactions, for patients to receive prompt care, with treatment provided as appropriate to prevent or minimize damage to the eye. Health-care professionals should promptly review new onset or worsening ocular symptoms, referring patients for ophthalmological examinations as appropriate.

Reference:
Drug Safety Update, MHRA, 29 November 2022 *(link to the source within www.gov.uk/mhra)*

Durvalumab

Risk of myelitis transverse

Europe. The PRAC has recommended updating the product information for ustekinumab (Imfinzi®) to include the risk of myelitis transverse.

Durvalumab is a monoclonal antibody that blocks PD-L1, and is indicated for the treatment of lung cancer.

Based on the available evidence it is considered that a causal relationship between myelitis transverse and durvalumab is a reasonable possibility.

Reference:
PRAC recommendations on signals, EMA, 21 November 2022 *(link to the source within www.ema.europa.eu)*

Gabapentin

1. Risk of drug dependence and withdrawal symptoms

Ireland. The HPRA has announced that the product information for gabapentin will be updated to indicate that drug dependence at therapeutic doses and withdrawal symptoms following discontinuation can occur.

Gabapentin is indicated for the treatment of neuropathic pain in adults, and as monotherapy or as adjunctive therapy for specific forms of epilepsy.

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 gabapentin. Patients treated with gabapentin should be monitored for these symptoms. If gabapentin use is to be discontinued, it is recommended this should be

done gradually over a minimum of one week independent of the indication.

In addition, neonatal withdrawal syndrome has been reported in newborns exposed in utero to gabapentin. Co-exposure to gabapentin and opioids during pregnancy may increase the risk of neonatal withdrawal syndrome. Newborns should be monitored carefully.

2. Risk of Toxic Epidermal Necrolysis (TEN)

The HPRA has announced that the product information for gabapentin will be updated to include the risk of Toxic Epidermal Necrolysis (TEN) under the heading of severe cutaneous adverse reactions (SCARs), where Steven-Johnson-Syndrome (SJS) and Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) are already listed as known adverse reactions.

SJS, TEN and DRESS, which can be life-threatening or fatal, have been reported with gabapentin treatment.

Health-care professionals should advise patients of the signs and symptoms and closely monitor for skin reactions when starting treatment with gabapentin. If signs and symptoms suggestive of these reactions appear, gabapentin should be withdrawn immediately. If a patient has developed a serious reaction such as SJS, TEN or DRESS, treatment with gabapentin must not be restarted in this patient at any time.

Reference:
Drug Safety Newsletter, HPRA, December 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)

Haloperidol

Risk of cogwheel rigidity

India. The CDSCO has approved the recommendation from the NCC-PvPI, IPC to revise the PIL for haloperidol to include cogwheel rigidity as an adverse drug reaction.

Haloperidol is indicated for the treatment of chronic schizophrenia.

The NCC-PvPI, IPC reviewed 11 ICSRs of haloperidol associated cogwheel rigidity and a causal relationship between them was found.

Reference:
Based on the communication from IPC, India, October 2022 *(link to the source within ipc.gov.in)*

Hydrochlorothiazide

Risk of acute respiratory distress syndrome (ARDS)

Japan. The MHLW and PMDA have announced that the product information for hydrochlorothiazide should be revised to include the risk of acute respiratory distress syndrome (ARDS).

Hydrochlorothiazide is indicated for the treatment of hypertension and oedema.

The MHLW and PMDA reviewed cases of ARDS reported domestically and internationally. In internationally reported cases, a causal relationship between the drug and ARDS was reasonably possible. Considering the severity of ARDS and following the product information revision in the EU, the MHLW and PMDA concluded that ARDS should be added as a clinically significant adverse reaction.

Reference:
Revision of Precautions, MHLW/PMDA, 16 November 2022 *(link to the source within www.pmda.go.jp/english/)*

Imatinib

Risk of thrombotic microangiopathy

Japan. The MHLW and PMDA have announced that the product information for imatinib should be revised to include the risk of thrombotic microangiopathy.

Imatinib is indicated for the treatment of chronic myeloid leukaemia and other cancers.

The MHLW and PMDA reviewed international and national reports of thrombotic microangiopathy, and a causal relationship between the drug and event was reasonably possible. The MHLW and PMDA concluded that thrombotic microangiopathy should be added as a clinically significant adverse reaction.

Health-care professionals are advised to suspend treatment with imatinib when anemia with fragmented red blood cells, thrombocytopenia, or renal dysfunction are observed.

Reference:
Revision of Precautions, MHLW/PMDA, 16 November 2022 *(link to the source within www.pmda.go.jp/english/)*

Itraconazole

Risk of hypokalaemia

Japan. The MHLW and PMDA have announced that the product information for itraconazole (oral dosage form and injections) should be revised to include the risk of hypokalaemia.

Itraconazole is indicated for the treatment of fungal infection.

The MHLW and PMDA reviewed three cases of hypokalaemia reported domestically, in which a causal relationship between the drug and event was reasonably possible. The MHLW and PMDA concluded that hypokalaemia should be added as a clinically significant adverse reaction.

Health-care professionals are advised to perform blood electrolyte tests periodically irrespective of particular conditions for use (e.g., dosage and period of administration).

Reference:
Revision of Precautions, MHLW/PMDA, 12 October 2022 *(link to the source within www.pmda.go.jp/english/)*

Janus kinase (JAK) inhibitors

Risks of cardiovascular conditions, blood clots, cancer, serious infections

1. Europe. The PRAC has recommended measures to minimize the risks of serious adverse reactions including cardiovascular conditions, blood clots, cancer and serious infections associated with Janus kinase (JAK) inhibitors (abrocitinib (Cibinqo®) baricitinib (Olumiant®), filgotinib (Jyseleca®) tofacitinib (Xeljanz®) and upadacitinib (Rinvoq®)) used to treat several chronic inflammatory disorders. The product information will be updated with the new recommendations and warnings.

The recommendations follow a review of available data, including the results from a clinical trial of tofacitinib (Xeljanz®) and preliminary findings from an observational study involving baricitinib (Olumiant®). The review confirmed tofacitinib increases the risk of major cardiovascular problems, cancer, venous thromboembolism (VTE), serious infections and death due to any cause when compared with TNF-alpha inhibitors. The PRAC has now concluded that these safety findings apply to all approved uses of JAK inhibitors in chronic inflammatory disorders.

The PRAC recommended that these medicines should be used in the following patients only if no suitable treatment alternatives are available: those aged 65 years or above, those at increased risk of major cardiovascular problems, those who smoke or have done so for a long time in the past, and those at increased risk of cancer. The Committee also recommended using JAK inhibitors with caution in patients with risk factors for VTE and with reduced doses in some patient groups.

Reference:
Patients and carers, EMA, 28 October 2022 *(link to the source within www.ema.europa.eu)*

2. Singapore. The Health Sciences Authority (HSA) has announced that the product information for JAK inhibitors (abrocitinib, baricitinib, tofacitinib and upadacitinib), approved for the treatment of inflammatory conditions are to be updated to include warnings on the increased risks of major adverse cardiovascular events, malignancy, thrombosis and death based on observations made from the ORAL (Oral Rheumatoid Arthritis Trial) Surveillance study.

Based on the currently available evidence, the HSA has concluded that the benefit-risk profile of JAK inhibitors for the treatment of inflammatory conditions remains positive for their approved indications, where the use of JAK inhibitors is already limited to second line or later therapy in Singapore.

Health-care professionals are advised to consider the benefits and risks of JAK inhibitors before prescribing these drugs, and to monitor their patients for the potential risks during treatment, particularly in the elderly, current or past smokers, or in patients with other cardiovascular, thromboembolic or malignancy risk factors.

Reference:
Safety Alerts, HSA, 13 December 2022 *(link to the source within www.hsa.gov.sg)*
(See also WHO Pharmaceuticals Newsletter No.4, 2022: JAK inhibitors and Risk of serious heart-related problems, blood clots, cancer and death in Canada, No.1, 2022: in US, UK and Japan)

Loxoprofen

Risk of acute generalized exanthematous pustulosis (AGEP)

Japan. The MHLW and PMDA have announced that the product information for loxoprofen (oral dosage form) should be revised to include the risk of acute generalized exanthematous pustulosis (AGEP).

The MHLW and PMDA reviewed cases of AGEP reported domestically, in which a causal relationship between the drug and event was reasonably possible. The MHLW and PMDA have concluded that AGEP should be added as a clinically significant adverse reaction.

Reference:
Revision of Precautions, MHLW/PMDA, 12 October 2022 (*link to the source within www.pmda.go.jp/english/*)

Methotrexate

1. Risk of progressive multifocal leukoencephalopathy (PML)

Japan. The MHLW and PMDA have announced that the product information for methotrexate (oral dosage forms, intravenous infusions and parenteral preparations) should be revised to include the risk of progressive multifocal leukoencephalopathy (PML).

Methotrexate is indicated for the treatment of inflammatory diseases and cancers.

The MHLW and PMDA reviewed cases of PML reported domestically and internationally, in which a causal relationship between the drug and event was reasonably possible. A total of 12 patient mortalities were reported internationally during the previous three years, and a causal relationship between the drug and deaths subsequent to the event was not established for any of these cases. The MHLW and PMDA concluded that PML should be added as a clinically significant adverse reaction.

Health-care professionals are advised to monitor patients carefully during and after administration of this drug. If symptoms such as disturbance of consciousness, cognitive dysfunction, paralysis, dysarthria, and aphasia are observed, MRI imaging and cerebrospinal fluid examination should be performed, and administration should be discontinued.

Reference:
Revision of Precautions, MHLW/PMDA, 12 October 2022 (*link to the source within www.pmda.go.jp/english/*)

2. Risk of myelopathy

Republic of Korea. The MFDS has updated the product information for methotrexate injection products to include the risk of myelopathy.

Reports of serious adverse event (SAE) were evaluated, and the KIDS reviewed one fatal SAE in a literature report of myelopathy in a patient who was administered methotrexate intrathecally for Burkitt's tumor. A causal relationship could not be excluded between methotrexate injection and myelopathy. Based on the result of the SAE review, information from the regulatory authority in the US, medical databases, and a literature review, the MFDS concluded that the product information should be updated to include the risk of myelopathy.

Health-care professionals should be reminded that intrathecal administration of methotrexate may affect the spinal cord and bone marrow tissue, which poses the risk of myelopathy.

Reference:
Based on the communication from KIDS and Drug Safety Update, MFDS/KIDS, 25 October 2022 (*link to the source within nedrug.mfds.go.kr/index*)

Nivolumab, ipilimumab and/or pembrolizumab

1. Risk of uveitis

Japan. The MHLW and PMDA have announced that the product information for nivolumab (Opdivo®), ipilimumab (Yervoy®) and pembrolizumab (Keytruda®) should be revised to include the risk of uveitis.

Nivolumab, ipilimumab and pembrolizumab are immune checkpoint inhibitors and are indicated for the treatment of malignant melanoma and other types of cancers.

The MHLW and PMDA reviewed cases of uveitis reported domestically, in which a causal relationship between each of the drugs and event was assessed to be reasonably possible. The MHLW and PMDA concluded that uveitis should be added as a clinically significant adverse reaction.

Health-care professionals are advised to periodically examine presence of ocular abnormality and to instruct patients to immediately seek medical attention if any ocular abnormalities are observed.

Reference:
Revision of Precautions, MHLW/PMDA, 12 October 2022 *(link to the source within www.pmda.go.jp/english/)*

2. Risk of rhabdomyolysis

Republic of Korea. The MFDS has updated the product information for pembrolizumab[2] to include rhabdomyolysis as an adverse reaction.

Reports of serious adverse event (SAE) reports were evaluated, and the KIDS reviewed two cases of rhabdomyolysis in patients treated with pembrolizumab-containing chemotherapy for non-small cell lung cancer, of which one was fatal. A causal relationship could not be excluded in any of these cases. Based on the result of this SAE review and information from the regulatory authority in the US, EU, Japan and UK, the MFDS concluded that the product information should be updated to include the risk of rhabdomyolysis.

Health-care professionals should monitor for any signs of rhabdomyolysis during use of this drug.

Reference:
Based on the communication from KIDS and Drug Safety Update, MFDS/KIDS, 8 November 2022 *(link to the source within nedrug.mfds.go.kr/index)*

Olanzapine

Risk of hyponatraemia

India. The CDSCO has approved the recommendation from the NCC-PvPI, IPC to revise the PIL for olanzapine to include hyponatraemia as an adverse drug reaction.

Olanzapine is indicated for the treatment of schizophrenia in adult patients, rapid control of agitation and disturbed behaviour in patients.

The NCC-PvPI, IPC reviewed 20 ICSRs of olanzapine associated hyponatraemia and a causal relationship between them was found.

Reference:
Based on the communication from IPC, India, October 2022 *(link to the source within ipc.gov.in)*

Pholcodine

Withdrawal of pholcodine medicines from EU market

Europe. The PRAC has recommended the revocation of the marketing authorizations for pholcodine in the European Union.

Pholcodine is used in adults and children to treat non-productive (dry) cough and, in combination with other active substances, for the treatment of symptoms of cold and flu.

The PRAC evaluated all available evidence including the results of the ALPHO (Allergy to Neuromuscular Blocking Agents and Pholcodine Exposure) study and one post-marketing safety data. The available data showed that the use of pholcodine in the 12 months before general anaesthesia with neuromuscular blocking agents (NMBAs) is a risk factor for developing an anaphylactic reaction to NMBAs. As it was not possible to identify effective measures to minimize this risk, nor to identify a patient population for whom the benefits of pholcodine outweigh its risks, pholcodine is being withdrawn from the EU market.

Health-care professionals should consider appropriate treatment alternatives and advise patients to stop taking pholcodine. Health-care professionals should also check whether patients scheduled to undergo general anaesthesia with NMBAs have used pholcodine in the previous 12 months and remain aware of the risk of anaphylactic reactions in these patients.

Reference:
Patients and carers, EMA, 2 December 2022 *(link to the source within www.ema.europa.eu)*
(See also WHO Pharmaceuticals Newsletter No.4, 2022: Pholcodine and Potential risk of developing anaphylactic reactions to NMBA in Europe)

Remdesivir

Risk of sinus bradycardia

India. The CDSCO has approved the recommendation from the NCC-PvPI, IPC to

[2] Nivolumab and ipilimumab are not included in the scope of this measure.

revise the PIL for remdesivir to include sinus bradycardia as an adverse drug reaction.

Remdesivir is indicated for the treatment of suspected or laboratory confirmed corona virus disease 2019 (COVID-19) in adults and children hospitalised with moderate to severe disease.

The NCC-PvPI, IPC reviewed 11 ICSRs of remdesivir associated sinus bradycardia and a causal relationship between them was found.

Reference:
Based on the communication from IPC, India, October 2022 *(link to the source within ipc.gov.in)*
(See also WHO Pharmaceuticals Newsletter No.1 2022: Remdesivir and Potential risk of sinus bradycardia in Canada, No.4, 2021 in Europe)

Roxadustat

Risk of central hypothyroidism

Japan. The MHLW and PMDA have announced that the product information for roxadustat (Evrenzo®) should be revised to include the risk of hypothyroidism.

Roxadustat is a Hypoxia-inducible factor (HIF) prolyl hydroxylase inhibitor and is indicated for the treatment of nephrogenic anaemia.

The MHLW and PMDA reviewed 29 cases of hypothyroidism reported domestically. In nine cases, a causal relationship between the drug and central hypothyroidism was reasonably possible. The MHLW and PMDA concluded that hypothyroidism should be added as a clinically significant adverse reaction.

Health-care professionals are advised to conduct periodic thyroid function tests (measurement of thyroid-stimulating hormone (TSH), free T3, free T4).

Reference:
Revision of Precautions, MHLW/PMDA, 16 November 2022 *(link to the source within www.pmda.go.jp/english/)*

Systemic corticosteroids

Risks of pheochromocytoma crisis (PC)

New Zealand. The Medsafe has announced that the product information for systemic corticosteroids is to be updated to include the risk of pheochromocytoma crisis. Pheochromocytomas are tumours in the adrenal medulla that typically secrete catecholamines and pheochromocytoma crisis (PC) is a rare, life-threatening emergency in which pheochromocytomas release high levels of catecholamines.

PC has been reported internationally following the administration of systemic corticosteroids to patients with pheochromocytoma. Although several hypotheses exist, the mechanism by which systemic corticosteroids trigger PC is not confirmed.

Health-care professionals are advised that corticosteroids should only be administered to patients with suspected or identified pheochromocytoma after an appropriate risk/benefit evaluation.

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

Terlipressin

Risks of respiratory failure, sepsis

Europe. The PRAC has recommended new measures to reduce the risk of respiratory failure and sepsis when using terlipressin in people with type 1 hepatorenal syndrome (HRS-1), which is a serious kidney problem in people with advanced liver disease.

Terlipressin is a vasopressin analogue indicated for the treatment of HRS-1 and bleeding oesophageal varices.

The recommendations follow the PRAC's review of available data, including results from a clinical trial that included patients with HRS-1. Results of the trial suggested that patients who were treated with terlipressin were more likely to experience and die from respiratory disorders within 90 days after the first dose than those who were given placebo. Although respiratory failure is a known adverse effect of terlipressin, the frequency of respiratory failure seen in the study was higher (11%) than previously reported in the product information. In addition, the study reported sepsis in 7% of patients in the terlipressin arm compared with none in the placebo group.

The new measures include adding a warning to avoid terlipressin in patients with advanced acute-on-chronic liver disease or advanced kidney failure, to the product information. Patients with breathing problems should

receive treatment to manage their condition before starting terlipressin. During and after treatment, patients should be monitored for signs and symptoms of respiratory failure and infection.

Reference:
Patients and carers, EMA, 11 November 2022 *(link to the source within www.ema.europa.eu)*

Tigecycline

Risk of coagulopathy

India. The CDSCO has approved the recommendation from the NCC-PvPI, IPC to revise the PIL for tigecycline to include coagulopathy as an adverse drug reaction.

Tigecycline is indicated for the treatment of skin and abdominal infections.

The NCC-PvPI, IPC reviewed three ICSRs of tigecycline associated coagulopathy and a causal relationship between them was found.

Reference:
Based on the communication from IPC, India, October 2022 *(link to the source within ipc.gov.in)*

Ustekinumab

Risk of infection from live vaccines in infants exposed in utero

Europe. The PRAC has recommended adding a warning to the product information for ustekinumab (Stelara®) on the use of live vaccines in infants whose mothers received ustekinumab during their pregnancy.

Ustekinumab is indicated for the treatment of severe plaque psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis. The product information already advises that it is preferable to avoid use of ustekinumab during pregnancy.

The PRAC has reviewed the available evidence including observational studies from the EU, United States and Canada, as well as a review by the marketing authorisation holder. Ustekinumab can cross the placenta and it has been detected in the serum of infants who were exposed to ustekinumab in utero. The risk of infection may be increased after birth in infants who were exposed to ustekinumab in utero. Therefore, the PRAC recommends that, in infants who were exposed to ustekinumab in utero, the administration of live vaccines is not recommended for six months following birth or until the infant's serum levels of ustekinumab are undetectable.

Reference:
Patients and carers, EMA, 28 October 2022 *(link to the source within www.ema.europa.eu)*

Vitamin B6 (pyridoxine)

Risk of peripheral neuropathy

Australia. The TGA has strengthened labelling requirements for products containing daily doses of 10mg of vitamin B6 (pyridoxine) to include a warning about peripheral neuropathy.

Previously, products containing daily doses over 50mg were required to carry the warning. The maximum permitted daily dose of vitamin B6 in products has also been reduced from 200 mg to 100 mg for adults, with lower daily dose limits in place for children depending on their age.

Vitamin B6 is present in many multivitamin and mineral supplements. Peripheral neuropathy is a known adverse reaction of vitamin B6, where delayed diagnosis and continued exposure can lead to its progression.

Up to 5 August 2022, the TGA had received 32 adverse event reports with sufficient information to establish a possible causal association between peripheral neuropathy and products containing vitamin B6. The TGA found that peripheral neuropathy can occur at doses less than 50 mg, and when people are taking multiple products containing vitamin B6. The risk appears to vary between individuals, with no minimum dose, duration of use or specific patient risk factors identified.

Health-care professionals should consider vitamin B6 toxicity in patients presenting with symptoms of peripheral neuropathy. A review of the patient's vitamin B6 intake is recommended paying close attention to potential sources such as multivitamins, magnesium and zinc products, particularly when taken in combination.

Reference:
Medicines Safety Update, TGA, 1 November 2022 *(link to the source within www.tga.gov.au)*

Denosumab

Potential risk of severe hypocalcemia in patients on dialysis

United States. The US Food and Drug Administration (FDA) is investigating the potential risk of severe hypocalcemia with serious outcomes, including hospitalization and death, in patients with advanced kidney disease on dialysis treated with denosumab (Prolia®). The US FDA is alerting health-care professionals and patients of these potentially serious risks as the investigation is going on.

Denosumab is indicated for the treatment of osteoporosis in postmenopausal women and men at high risk for bone fracture. There is a warning in the product information of the increased risk of hypocalcemia in patients with severe renal impairment or receiving dialysis.

The US FDA's review of interim results from an ongoing safety study of denosumab suggests an increased risk of hypocalcemia in patients with advanced kidney disease. Preliminary results from a separate internal study by the US FDA further investigating hypocalcemia in dialysis patients treated with denosumab show a substantial risk with serious outcomes, including hospitalization and death.

Health-care professionals should consider the risks of hypocalcemia with the use of denosumab in patients on dialysis. When denosumab is used in these patients, adequate calcium and vitamin D supplementation and more frequent blood calcium monitoring, may help decrease the likelihood or severity of these risks. Patients on dialysis should be advised to seek help immediately, if they experience symptoms of hypocalcemia.

Reference:
FDA News Release, US FDA, 22 November 2022 *(link to the source within www.fda.gov)*

Gadoteric acid

Risk of cardiac arrest

Egypt. The Egyptian Pharmacovigilance Center (EPVC), Egyptian Drug Authority (EDA) has reminded health-care professionals of the risk of cardiac arrest following administration of gadoteric acid.

Gadoteric acid is a gadolinium-based contrast agent indicated for intravenous use with magnetic resonance imaging (MRI).

Two cases of cardiac arrest following administration of gadoteric acid were reported domestically. One patient had a medical history of hypertension, diabetes, IHD (CABG), tetracycline hypersensitivity and underwent stent placement surgeries. Another patient was anesthetized prior to performing MRI due to claustrophobia.

Health-care professionals are advised that in patients with severe cardiovascular disease, gadoteric acid should only be administrated after careful benefit-risk assessment because only limited data are available so far.

Reference:
Newsletter, EDA, December 2022 *(link to the source within www.edaegypt.gov.eg)*

Ibrutinib

Risk of serious cardiac events

Europe. The EMA has published direct health-care professional communication (DHPC) following PRAC discussions on the increased risk of fatal and serious cardiac arrhythmias, and cardiac failure with the use of ibrutinib (Imbruvica®).

Ibrutinib is indicated for the treatment of mantle cell lymphoma, chronic lymphocytic leukaemia (CLL) and Waldenström's macroglobulinaemia.

The DHPC provides the following advice:

- Patients with advanced age, Eastern Cooperative Oncology Group (ECOG) performance status ≥2, or cardiac co-morbidities may be at greater risk of cardiac events including sudden fatal cardiac events.
- Prior to initiating ibrutinib, clinical evaluation of cardiac history and function should be performed.
- In patients with risk factors for cardiac events, benefits and risks should be assessed before initiating treatment with Imbruvica; alternative treatment may be considered.
- Patients should be carefully monitored during treatment for signs of deterioration of cardiac function and if this occurs, clinically managed.
- Ibrutinib should be withheld

for any new onset or worsening grade 2 cardiac failure or grade 3 cardiac arrhythmias. Treatment may be resumed as per new dose modification recommendations.

Reference:
Patients and carers, EMA, 30 September 2022 *(link1 and link2 to the source within www.ema.europa.eu)*

Methylphenidate long-acting formulations

Caution if switching between products

United Kingdom. The MHRA has alerted prescribers and dispensers that a caution is needed if switching patients between different long-acting formulations of methylphenidate (Concerta XL®, Medikinet XL®, Equasym XL®, Ritalin LA®, and generics). Different instructions for use (frequency of dosing and administration with food) and different release profiles may affect symptom management.

Methylphenidate is used as part of a comprehensive treatment programme for attention deficit hyperactivity disorder (ADHD). The differing time–action profiles provided by long-acting formulations of methylphenidate allow clinicians to target specific periods of the day that are particularly relevant for a patient. Transferring to another formulation can result in changes in symptom management at key time periods during the day. Unique characteristics of each agent should be matched to the individual needs of the patient. Switching between formulations with differing pharmacokinetics can be also associated with differences in adverse events or patient experiences of 'effectiveness'. Therefore, changes to medication should only be made in the context of individual review and should be communicated to patients, who should be advised to report any changes to their symptoms or development of adverse effects.

Reference:
Drug Safety Update, MHRA, 26 September 2022 *(link to the source within www.gov.uk/mhra)*

Minoxidil

Risk of folliculitis

India. The NCC-PvPI, IPC has recommended the CDSCO to revise the prescribing information leaflet (PIL) for minoxidil to include folliculitis as an adverse drug reaction. The recommendation is under consideration of the CDSCO.

Minoxidil is indicated for the treatment of alopecia (male pattern baldness) in men.

The NCC-PvPI, IPC reviewed 17 ICSRs of minoxidil associated folliculitis and a causal relationship between them was found.

Reference:
Based on the communication from IPC, India, October 2022 *(link to the source within ipc.gov.in)*

Newer antidiabetic medicines used with insulin and/or sulfonylureas

Risk of hypoglycaemia

New Zealand. The Medsafe has alerted health-care professionals on the risk of hypoglycaemia associated with newer antidiabetic medicines (glucagon-like peptide 1 (GLP-1) receptor agonists, sodium-glucose co-transporter 2 (SGLT-2) inhibitors or dipeptidyl peptidase-4 (DPP-4) inhibitors) used concomitantly with insulin and/or sulfonylureas.

Newer antidiabetic medicines are not typically associated with hypoglycaemia when used as monotherapy, although two cases have been reported domestically.

Health-care professionals should monitor for and discuss the risks of hypoglycaemia when prescribing medicines to treat type 2 diabetes mellitus. Patients on concomitant therapy may require a lower dose of insulin or the sulfonylurea to prevent episodes of hypoglycaemia.

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

Tranexamic acid injection

Risk of medication errors resulting in inadvertent intrathecal injection

WHO. WHO is alerting health-care professionals about the

risk of administration errors that can potentially occur with tranexamic acid (TXA) injection. There have been reports of TXA being mistaken for obstetric spinal anaesthesia used for caesarean deliveries resulting in inadvertent intrathecal administration.

In TXA administered intrathecally, potent neurotoxin and neurological sequelae are manifested, with refractory seizures and 50% mortality. The profound toxicity of TXA administered intrathecally was described in 1980. A 2019 review identified 21 reported cases of inadvertent intrathecal injection of TXA since 1988, of which 20 were life-threatening and 10 fatal. Sixteen were reported between 2009 and 2018.

WHO recommends early use of intravenous TXA within 3 hours of birth in addition to standard care for women with clinically diagnosed postpartum haemorrhage (PPH) following vaginal births or caesarean section. TXA should be administered at a fixed dose of 1g in 10 ml (100 mg/ml) IV at 1 ml per minute, with a second dose of 1g IV if bleeding continues after 30 minutes.

TXA is frequently stored in close proximity with other medicines, including injectable local anesthetics indicated for spinal analgesia (e.g., for caesarean section). The presentation of some of the local anesthetics is similar to the TXA presentation (transparent ampoule containing transparent solution), which can erroneously be administered instead of the intended intrathecal anesthetic resulting in serious undesirable adverse effects.

Recently, obstetricians from several countries have reported inadvertent intrathecal TXA administration and related serious neurological injuries.

TXA is a lifesaving medicine; however, this potential clinical risk should be considered and addressed by all operating theatre staff. Reviewing of existing operating theatre drug handling practices are required in order to decrease this risk, such as storage of TXA away from the anaesthetic drug trolley, preferably outside the theatre.

Reference: Medical product alert, WHO, 16 March 2022 *(link to the source within www.who.int)*

Valproate

Risks in pregnancy and potential risks in male patients

United Kingdom. The MHRA has reminded health-care professionals of the risks in pregnancy and the current Pregnancy Prevention Programme (PPP) requirements and provided information about the potential risks of valproate in other patients including male patients. New safety measures for valproate-containing medicines are to be put in place in the coming months.

Valproate is indicated for the treatment of epilepsy and bipolar disorder. As valproate has a high teratogenic potential, it is contraindicated in female children and women of childbearing potential unless other treatments are ineffective or not tolerated and other conditions of PPP are met. PPP was introduced in 2018 to ensure all women and girls are fully informed of the risks and the need to avoid exposure to valproate medicines in pregnancy through annual review and signing a risk acknowledgement form.

In 2022, the Commission on Human Medicines (CHM) considered a review of safety data relating to valproate. This review included prescribing data showing continued use of valproate in female patients and also some use during pregnancy, as well as evolving information about potential risks in male patients. The CHM has recommended a number of regulatory actions to further strengthen safety measures for valproate, which will be introduced over the coming months and include:

- No patients (male or female) under the age of 55 years should be initiated on valproate unless two specialists independently consider and document that there is no other effective or tolerated treatment.
- For patients under 55 years currently receiving valproate, two specialists should independently consider and document that there is no other effective or tolerated treatment or the risks do not apply.
- Further warnings in the product information, improved educational materials, and better monitoring of health-care professionals' compliance with the new measures.

Reference:
Drug Safety Update, MHRA, 29

November 2022 *(link to the source within www.gov.uk/mhra)*
(See also WHO Pharmaceuticals Newsletter No.2, 2022: Antiepileptic drugs and Risk of major congenital malformations and neurodevelopmental disorders in children exposed in-utero in Ireland, No.1, 2021: in UK)

Call for Submissions

We are very keen to make this newsletter even more useful to all our readers. We are calling out to all national medical products regulatory authorities to send us the latest information on safety and regulatory actions on medicinal products from their countries.

We also welcome short reports on any recent events or achievements in pharmacovigilance in your country.

All submissions will be reviewed for relevance and subject to the WHO internal selection, editorial review, and clearance process.

Please send your submissions or questions to: pvsupport@who.int

Summary and recommendations from the virtual meeting of the members of the WHO Programme for International Drug Monitoring (PIDM) and other partners

20 October 2022

The WHO Programme for International Drug Monitoring (PIDM) provides a global platform for WHO Member States, territories and areas to exchange safety and regulatory information on medicines and vaccines[3]. Coronavirus disease (COVID-19) has had a significant impact on pharmacovigilance worldwide, with new vaccines and medicines for the prevention and treatment of COVID-19 being implemented on an unprecedented scale, with the associated increase in case safety reports.

WHO convened a virtual meeting to provide an opportunity for PIDM members and other partners to share their pharmacovigilance experiences from the COVID-19 pandemic, discuss the challenges and how these were addressed and to consolidate the collective learnings and gains for establishing pandemic-ready, resilient and functional pharmacovigilance systems and practices.

1. Challenges and learnings at region and global levels

The objective of this session was to summarize what pharmacovigilance infrastructures have been established by the WHO Pharmacovigilance (PVG) Team at HQ and the WHO Regional Offices during the COVID-19 pandemic, what will be preserved in the post-pandemic period and if pharmacovigilance systems are ready for the next pandemic.

(1) WHO PVG Team

Pharmacovigilance guidance and tools developed:

- a safety manual to prepare countries for safety monitoring of COVID-19 vaccines[4];
- list of adverse events of special interest (AESIs) to focus safety surveillance activities;
- pharmacovigilance tools:
  - protocol templates for surveillance studies[5];
  - standardised MedDRA queries to retrieve safety data from databases[6];
  - case definitions for new events that occurred following vaccination, e.g., thrombosis with thrombocytopenia syndrome (TTS)[7];
- global advisory committee for vaccine safety (GACVS) subcommittee established for weekly or monthly real-time review of emerging safety signals[8];
- early warning system (EWS) platform developed to identify and analyse data on social media to detect and prepare for emerging safety signals;
- supported reliance whereby countries could adopt each other's proposals for core risk management plans (RMPs), with a country-specific annex.

Pharmacovigilance infrastructure to be preserved and developed post-COVID-19 pandemic:

- principles of reliance, leveraging networks involving WHO regional offices and safety communication networks established by the PVG team to enhance the safety monitoring of COVID-19 vaccines;
- adaptation of many of the tools developed for use in pharmacovigilance for new and existing vaccines and medicines.

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[3] The WHO Programme for International Drug Monitoring, WHO https://www.who.int/teams/regulation-prequalification/regulation-and-safety/pharmacovigilance/health-professionals-info/pidm

[4] COVID-19 vaccines: safety surveillance manual, WHO https://www.who.int/publications/i/item/9789240032781

[5] Protocol template to be used as template for observational study protocols for cohort event monitoring (CEM) for safety signal detection after vaccination with COVID-19 vaccines, WHO https://www.who.int/publications/i/item/9789240027398

[6] COVID-19 Terms and MedDRA, MedDRA https://www.meddra.org/COVID-19-terms-and-MedDRA

[7] Guidance for clinical case management of thrombosis with thrombocytopenia syndrome (TTS) following vaccination to prevent coronavirus disease (COVID-19), WHO https://www.who.int/publications/i/item/WHO-2019-nCoV-TTS-2021.1

[8] GACVS COVID19 Sub-committee, WHO https://www.who.int/groups/global-advisory-committee-on-vaccine-safety/topics/covid-19-vaccines/subcommittee

Pandemic preparedness
The PVG team are cautiously optimistic that the infrastructures and process developed to respond to the COVID-19 pandemic will help prepare for the next pandemic. However, other challenges are likely and some serious gaps remain, e.g., AESI background rates, exposure data and data for specific subpopulations.

(2) WHO Regional Office for Africa (AFRO)
Pharmacovigilance guidance and tools developed:

- safety surveillance manual developed and training provided at subnational levels, with support from local partners which resulted in:
  - an unprecedented number of adverse events following immunization (AEFIs) being reported;
  - committees for causality assessment actively reporting outcomes and communicating clearly:
  - significant improvement in the quality of AEFI reporting;
- African Advisory Committee on Vaccine Safety (AACVS) was set up.

Pharmacovigilance infrastructure to be preserved and developed post-COVID-19 pandemic
Despite the progress made, there is room for improvement and many challenges remain. The AACVS will continue to provide advice and support vaccine safety efforts in the region.

Pandemic preparedness
It is unlikely that the African region will be fully prepared for the next pandemic but notable progress has been made.

(3) WHO Regional Office for Europe (EURO)
Pharmacovigilance guidance and tools developed:

- regional vaccine safety working group established to prepare countries for COVID-19 vaccination;
- web-based monitoring framework implemented to help countries work in a targeted manner;
- VigiBase actively used to monitor AEFI reporting performance and to identify potential safety signals:
  - eight new countries reported AEFIs to VigiBase and one became a PIDM member;
- regional office helped countries to develop their National Deployment Vaccination Plans (NDVPs);
- subregional and national webinars and country-specific training for hundreds of participants;
- AEFI crisis management support provided;
- regional resources and hands-on tools developed and translated to local languages.

Pharmacovigilance infrastructure to be preserved and developed post-COVID-19 pandemic:

- organization and governance for vaccine safety:
  - strengthening policies and procedures and improving resource allocation;
  - reinforcing injury compensation.
- strengthening collaboration between expanded programmes for immunization (EPIs) and national regulatory authorities (NRAs) and other partners.

Pandemic preparedness
Much has been achieved and learnt, but much remains to be done to build and maintain trust and to build resilient systems to be prepared for the next pandemic. Some of the key areas for response include continuous process improvement, coordination and collaboration, improved networking and reliance and access to data. Country-specific contexts need to be understood to provide tailored solutions. Transparency and communication must continue to be improved.

(4) WHO Regional Office for South-East Asia (SEARO)
Pharmacovigilance guidance and tools developed:

- national vaccine pharmacovigilance systems strengthened;
- feedback on NDVPs and plans for enhancing AEFI reporting, investigation, causality assessment and communication:
  - development of web-based system for AEFI detection and reporting;
  - AEFI data management with an Excel-based tool for weekly reporting of vaccination and AEFI data;
  - active promotion of AEFI reporting to VigiBase;
  - review National Immunization Technical Advisory Group (NITAG) reports containing AEFI data from electronic Joint Reporting Forms (eJRFs);

- workshops and sharing of WHO guidelines, tools and regulatory updates to provide regional guidance;
- expert advice provided on vaccine safety signals after implementation of COVID-19 vaccination programme and vaccine safety expert employed in the region.

Pharmacovigilance infrastructure to be preserved and developed post-COVID-19 pandemic:

- web-based system for AEFI detection and reporting now used in five countries and use in other countries is planned;
- training healthcare workers to improve AEFI reporting;
- Excel-based tool for AEFI data management for weekly reporting of vaccination and AEFI data;
- AEFI reporting to VigiBase has been adopted by four new countries;
- continued review of data in National Immunization Technical Advisory Group (NITAG) reports;
- expanded membership of national vaccine AEs committees.

Pandemic preparedness

The region is not completely ready for future pandemics. This will depend on using lessons learnt from the COVID-19 pandemic for strengthening and sustaining AEFI surveillance systems continuously. Direct consumer reporting should be developed and feedback mechanisms strengthened. Closer collaboration with medical associations would improve preparedness. Mechanisms for timely sharing of data on serious AEFIs between vaccine manufacturers, NRAs and EPIs need to be reinforced. Communication and social sciences experts should be systematically included in AEFI committees. AESI surveillance and specific active surveillance studies need to be extended to include more countries.

(5) WHO Regional Office for the Western Pacific (WPRO)

Pharmacovigilance guidance and tools developed:

- regional and country networks implemented to provide training workshops and webinars, technical documents and tools and used to prioritize training needs;
- weekly reporting from countries to the Regional Office that provided updates on COVID-19 vaccination and AEFIs, using eJRFs;
- creation of collaborative network between regional NRAs and national immunization centres (NICs).

Pharmacovigilance infrastructure to be preserved and developed post-COVID-19 pandemic:

- continued development of monitoring, responding and communicating about product safety;
- enhanced vaccine and immunization safety monitoring and response capacities will be adopted for routine immunization programmes;
- continue collaboration between NRAs and NICs to optimize response to safety-related events and issues.

Pandemic preparedness

Readiness for future pandemics will require further development of capacity to integrate real-world data and evidence into policy guidance on post-marketing safety surveillance for investigational products being used in emergency situations. Open access training on reporting, investigation and causality assessment of AEFIs should be made available to all healthcare workers. The training should aim to enhance the quality and capacity for timely investigation, causality assessment and risk communications about serious AEs at all levels. In addition, a legal framework and mechanisms for assessment of causality and vaccine injury claims are needed.

2. Breakout sessions: Challenges and learnings at the country level

The meeting then split into three break-out rooms with speakers from two regions in each who presented experiences in their country during the COVID-19 pandemic, based on the following questions:

- How did the COVID-19 pandemic impact your programme?
- Did your programme develop any new pandemic?
- How did your programme improve pharmacovigilance systems, methods of working, tools or processes during the COVID-19?
- What lessons have been learnt for the next pandemic?
- How do we leverage what we have learnt and maintain momentum?

(1) Breakout session 1: Eritrea (AFRO) and Iran (EMRO)

Key highlights from presentations and discussion

- In Eritrea, measures taken to mitigate the negative impact of the pandemic resulted in a dramatic decrease in AEFI reports.
- Eritrean pharmacovigilance system was decentralized and zonal regulatory affairs offices and facility-based vigilance systems were established.
- challenges encountered in Iran included shortage of vaccines, fragmented pharmacovigilance system, lack of data linkage, difficulties to access some hospitals.
- implementation of the cohort event monitoring (CEM) protocol for safety signal detection after COVID-19 vaccination in Iran was facilitated by the well-designed protocol, a group of motivated experts involved and the use of electronic tools.

Summary of recommendations

- decentralization of national pharmacovigilance functions is recommended in pandemic situations;
- capacity to anticipate and forecast and resolve potential or emerging issues to be improved;
- important to be flexible and modify strategy and adapt plans, as needed;
- develop national and international emergency plans for future pandemics, based on the lessons learnt from the COVID-19 pandemic;
- reassess existing systems to identify key areas of fragility and implement mitigation strategies to improve preparedness for a future pandemic;
- CEM study protocols need to be adapted to each country setting;
- national pharmacovigilance system steering committees should be established;
- web-based data collection and online reporting systems and dashboards are important and practical for CEM studies;
- continuous quality control should be implemented during CEM studies using online, live and interactive dashboards.

(2) Breakout session 2: Georgia (EURO) and Chile (PAHO)

Key highlights from presentations and discussion

- In Georgia, considerable increase of AEFIs compared with pre-pandemic situation:
  - lack of human resources;
  - lack of capacity to evaluate all serious AEs;
  - lack of capacity to report to WHO;
  - impact of media on vaccination and reporting, communication should be prepared.
- Preparation is key for managing workload and communication:
  - plan for additional staff (including technical assistance);
  - training for pharmacovigilance staff and healthcare professionals on available safety data before launch and during vaccination campaigns;
  - have access to experts, if needed;
  - raise awareness about AEFI reporting and ensure that reporting procedures are straightforward and easily accessible;
  - provide continuous information and feedback on AEFI reports to both healthcare professionals and the general public;
  - promote transparency by regularly communicating local safety data statistical reports.

Summary of recommendations to national pharmacovigilance centres

- coordinate work within different areas and regional centres;
- ensure that procedures are clear;
- develop a network of internal or external experts;
- facilitate AEFI reporting by healthcare professionals and the general public;
- ensure that decision-making processes and local safety statistics are transparent
- communication to the general public about new risks should be done in a balanced manner, i.e., presenting the benefit-risk balance of the vaccine.

Summary of recommendations to UMC

- develop and support information technology (IT) solutions for sharing reports to Uppsala Monitoring Centre (UMC);
- provide support for implementation of general public reporting;
- continue analyzing data;

- continue training, particularly for communication and data presentation.

Summary of recommendations to WHO
- facilitate collaboration between regional and country offices and WHO collaborating centres for sharing best practices and work experiences;
- advocate for provision of resources and training;
- continue publishing guidelines and technical documents.

(3) Breakout session 3: Bangladesh (SEARO) and Philippines (WPRO)
Key highlights from presentations and discussion
- COVID-19 pandemic has increased general awareness about pharmacovigilance;
- development of rapid responses that required increased collaboration and networking across all stakeholders;
- Bangladesh simplified their reporting system with the introduction of online and email options for notifications and a specific reporting form for non-serious AEFIs;
- Philippines implemented VigiFlow with data sharing between the national Food and Drug Administration (the National Pharmacovigilance Centre), the market authorization holder, PIDM and VigiBase;
- prepare for future pandemics by adapting best practices, based on lessons learnt and experiences.

Summary of recommendations
- continue to encourage and facilitate local and inter-country collaboration;
- prioritize training of pharmacovigilance staff, healthcare workers and the general public;
- implement clear guidelines to guarantee good quality pharmacovigilance activities;
- continue to advocate funding for pharmacovigilance activities to maintain safety surveillance improvements;
- ensure availability of tools, especially integrated electronic systems for data capture and sharing.

3. How to leverage what has been learnt and maintain the momentum

In this session four panellists presented and discussed the regional mechanisms for networking and collaboration between countries which responded to the pandemic.

(1) EU-M4all
EU Medicines for all or EU-M4all (previously Article 58) is a procedure whereby the EMA and WHO provide a scientific opinion for high priority human medicines and vaccines that are intended for use outside the European Union[9]. The procedure is led by EMA's Committee for Medicinal Products for Human Use (CHMP) with involvement of the Pharmacovigilance Risk Assessment Committee (PRAC) who are responsible for the risk management plan (RMP), periodic safety updates reports (PSURs) and non-interventional post-authorization safety studies (PASS). The procedure used is the same as that for drugs and vaccines intended for use in the EU and is based on reliance and trust. Between 2004 and 2021, EMA issued 12 positive opinions under the EUM4all procedure, which resulted in 142 authorizations in 91 countries.

The sponsor (pharmaceutical company, non-governmental organization (NGO) or academics) initiates the procedure. After a positive opinion, the sponsor is responsible for all pharmacovigilance activities required by EMA and NRA. In addition to the usual 6-month PSUR, a monthly safety summary report was submitted for COVID-19 vaccines.

(2) AU-3S
The AU Smart Safety Surveillance (AU-3S) is a 10-year programme, based on a continent-wide approach to patient safety, to ensure that African regulators and patients have confidence in global health product safety by[10]:
- improving safety across priority products' lifecycles;
- enabling African ownership of African data (e.g., AfriVigilance database);

[9] Medicines assessed under the 'EU-M4all' procedure, EMA https://www.ema.europa.eu/en/partners-networks/international-activities/medicines-assessed-under-eu-m4all-procedure
[10] Overview of AU-3S Programme, AUDA-NEPAD https://www.nepad.org/microsite/african-union-smart-safety-surveillance-au-3s

- piloting and implementing digital health tools adapted to LMIC settings;
- strengthening safety expertise and decision-making in Africa;
- collaborating with continental initiatives such as African Medicine Agency (AMA), African Medicines Regulatory Harmonization (AMRH), African Vaccine Regulatory Forum (AVAREF), Africa Centres for Disease Control and Prevention (ACDC).

The COVID-19 pandemic happened while this programme was being set up. A COVID-19 vaccine safety response group, initially involving four countries (Ghana, Nigeria, Ethiopia and South Africa) and other partners was set up. The activities during the pandemic demonstrated that:

- African EPIs and NRAs can collaborate within and across countries;
- technology and work-sharing (reliance) can be used to address resource constraints and limited expertise;
- African regulators can conduct signal detection and validation on their own safety data;
- African regulators can make evidence-based decisions on their own data to protect their populations.

The group was able to confirm the safety of COVID-19 vaccines in Africa with African safety data being very similar to global data. High levels of sponsorship and engagement from NRAs and removing barriers to EPI and NRA collaboration were among the key success factors. Commitment to solutions adapted to country-specific settings development of digital tools for healthcare providers and the public, across products and countries and provision of real-time technical support to countries were also important. AU-3S can be considered as a model for safety responses in future pandemics in LMICs.

(3) SEARN

The South-East Asia Regulatory Network (SEARN), a voluntary association of 11 countries, was initiated in April 2017 in Delhi to enhance information sharing, collaboration and integration of regulatory practices[11]. Their 2022-2023 workplan includes developing strategies to improve AEFI reporting rates, setting up regional pharmacovigilance integration, reviewing NRAs' COVID-19 experience to improve regional preparedness, supporting capacity building for SEARN members and facilitating information sharing and reliance. One challenge for SEARN is dealing with language diversity. Future plans include identifying regional solutions for integration (signal detection), capacity building (signal assessment and PSURs) and reliance (core risk management plans).

(4) PAHO PV network

The Regional Pharmacovigilance Network of the Americas, composed of NRA representatives from 34 countries and other partners, such as UMC, promotes information exchange and sharing of resources and experiences, to strengthen safety surveillance[12]. The network facilitated access to resources for regulatory processes, such as recommendations, guidelines, monthly bulletins with updated information in English, Spanish and Portuguese and a dedicated pharmacovigilance dashboard for COVID-19 vaccine surveillance. A regional AEFI system was developed to collect and report AEFI data following COVID-19 vaccination. A regional network of 28 sentinel hospitals has been established in 12 countries for retrospective and prospective active surveillance of COVID-19 vaccines. The network facilitated the development of regional active surveillance projects for molnupiravir and nirmatrelvir/ritonavir, provided training on AEFI reporting and causality assessment and supported coordination between NRAs and EPIs.

Session Summary

The promotion of efficient and clear mechanisms for networking and collaboration between countries with different regulatory maturity levels can develop regional capacity. Many medicines and vaccines used during the pandemic have emergency use authorizations and therefore potentially have increased risks requiring reinforced surveillance by passive and active surveillance systems.

4. Recommendations and conclusions

Pharmacovigilance activities have greatly increased during the COVID-19 pandemic. It will be important to build on the pharmacovigilance and AEFI surveillance systems that have been implemented and the increased collaboration and networking across all stakeholder levels at national, regional and global levels. Collaboration

[11] South-East Asia Regulatory Network (SEARN), WHO SEARO https://www.who.int/southeastasia/activities/south-east-asia-regulatory-network-(searn)

[12] Pharmacovigilance, WHO PAHO https://www.paho.org/en/topics/pharmacovigilance

between NRAs and EPIs for pharmacovigilance activities should be encouraged. Regional collaboration resulted in the creation of networking, development of tools, information sharing, capacity building and training. Reporting tools were shared to improve passive AEFI reporting and other tools for the implementation of active surveillance and epidemiological studies activities were developed and shared. This was achieved with the involvement of all stakeholders including governmental payers and other funding bodies.

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The meeting received more than 890 online registrations from approximately 140 countries covering all the WHO Regions and was attended online by approximately 500 participants.

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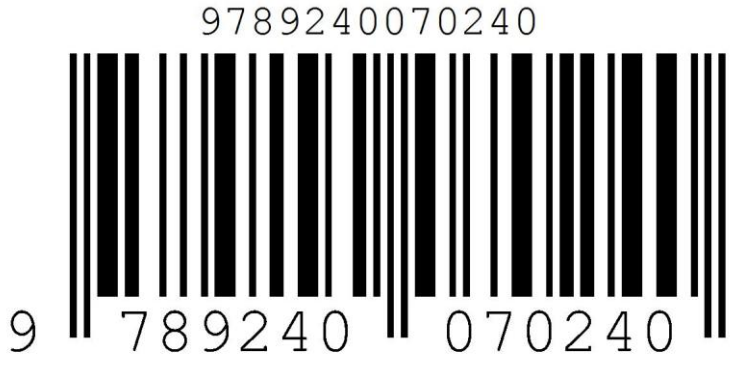
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