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Organization

WHO Pharmaceuticals NEWSLETTER

2023

No. 3

WHO Vision for Safety of Medicinal Products

***No country left behind:
worldwide pharmacovigilance
for safer medicinal products,
safer patients***

*The aim of the Newsletter is
to disseminate regulatory
information on the safety of
medicinal products,*

*based on communications
received from our network of
national pharmacovigilance centres
and other sources such as
specialized bulletins and journals,
as well as partners in WHO.*

*The information is produced in
the form of résumés in English,
full texts of which may be obtained
on request from:*

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*This Newsletter is also available at:
[https://www.who.int/teams/regula
tion-prequalification](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 issue of the newsletter includes a brief overview of the [Vaccine Safety Net](#) (VSN), a global network of websites established by WHO to provide reliable information on the safety of vaccines.

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Antitubercular agents

Potential risk of paradoxical drug reaction

Japan. The Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA) have announced that the product information for antitubercular agents (all products marketed in Japan as listed in the [link](#)) should be revised to include a warning of the potential risk of paradoxical drug reaction.

Paradoxical drug reaction in the tuberculosis (TB) treatment refers to events such as increased shadows on chest radiographs, appearance of new shadows, pleural effusions and swollen or enlarged mediastinal or cervical lymph nodes after starting treatment, despite the reduction or negativity of TB bacteria in the sputum.

The review by the MHLW and PMDA was triggered by the revision of the Prescribing Information for some of the antitubercular agents in the US. In ICSRs reported in Japan, there were in total 39 case reports where a causal relationship between several antitubercular agents and an adverse event was reasonably possible. The mechanism of the event is attributed to allergy to a bacterial cell of *Mycobacterium tuberculosis*; therefore, the

event may occur irrespective of the types of antitubercular agents. Taking into account the situation in Japan where health-care professionals who have experienced TB treatments will decrease due to low prevalence, it was concluded that such warnings for all the antitubercular agents are necessary.

Health-care professionals are advised that if worsening of existing tuberculosis or new onset of tuberculosis symptoms is observed after initiating the treatment, the decision to continue administration should be determined based on drug susceptibility tests or other measures.

Reference:

Revision of Precautions, MHLW/PMDA, 23 March 2023 ([link](#) to the source within www.pmda.go.jp/english/)

Bosutinib

Risk of interstitial lung disease

Europe. The Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) has recommended a change to the product information for bosutinib to include the risk of interstitial lung disease (ILD).

The PRAC has considered the available evidence from clinical studies, post-marketing cases, literature reports and the already known association of ILD

with other drugs within the tyrosine kinase inhibitors (TKIs) class (dasatinib, imatinib, and nilotinib), and has agreed that a causal relationship between bosutinib use and occurrence of ILD is plausible. The MAH should amend the product's information to include this risk.

Reference:

PRAC recommendations on signals, EMA, 6 March 2023 ([link](#) to the source within www.ema.europa.eu)

Cephalosporins

Risk of neurotoxicity

New Zealand. The Medsafe has announced that it is working with the sponsors of cephalosporin products to update the data sheets to include the risk of neurotoxicity.

Cephalosporins are broad-spectrum beta-lactam antibiotics used in primary and secondary care to treat a range of infections. Cephalosporins are grouped into five generations based on their antibacterial properties and their discovery.

Case report and case series reviews found that compared with other cephalosporins, cefepime was associated with the most reports of neurotoxicity internationally. However, neurotoxicity has been reported with all generations of cephalosporins. Reports of neurotoxicity with cephalosporins are mainly

characterized by encephalopathy, myoclonus and/or seizures. Risk factors include older age groups, renal impairment, underlying central nervous system disorders and if intravenous route of administration is used.

The New Zealand Medicines Adverse Reaction Committee (MARC) recommended that health professionals should consider cephalosporin-induced neurotoxicity in patients with the above risk factors and an unexplained, new onset neurological condition. In such cases, withdrawal of the medicine may be appropriate.

Reference:
Prescriber Update, Medsafe, 23 March 2023 ([link](#) to the source within www.medsafe.govt.nz)

COVID-19 vaccine Janssen (Ad26.COV2-S)

Potential risks of myocarditis and pericarditis, and facial paralysis

United States. The US Food and Drug Administration (FDA) has announced that the product information for COVID-19 vaccine Janssen (Ad26.COV2-S) was revised to include a Warning conveying that adverse events following use of the vaccine reported suggest increased risks of myocarditis and pericarditis, particularly within the period 0 through 7 days following

vaccination.

An additional revision to the product information includes facial paralysis (including Bell's Palsy) that have been reported during post-authorization use.

Reference:
US FDA Roundup: March 14, 2023 ([link1](#) and [link2](#) to the source within www.fda.gov)

Diazoxide

Risk of pericardial effusion

Canada. Health Canada has announced the update of the Canadian Product Monographs (CPM) to include the risk of pericardial effusion with the use of diazoxide (Proglycem®).

Diazoxide is authorized to manage low blood sugar (hypoglycaemia) in infants, children and adults caused by a higher-than-normal amount of insulin in the blood (hyperinsulinism) associated with specific tumours, surgeries, maternal or foetal medical conditions, delivery-related complications, or genetic conditions, when other medical therapy or surgical management have been unsuccessful or are not feasible.

The safety review was triggered by published cases in the scientific literature. Health Canada reviewed eight international cases of pericardial effusion in patients taking diazoxide from the Canada Vigilance database. Of the eight

cases assessed, six were in infants and children. Of the eight cases, two were found to be probably linked to the use of diazoxide, four were found to be possibly linked and two were unlikely to be linked. It was concluded that there is a possible link between the use of diazoxide and the risk of pericardial effusion.

Health Canada is working with the manufacturer to update the CPM for diazoxide with a warning about cases of pericardial effusion having been observed, including in infants and children.

Reference:
Summary safety review, Health Canada, 24 March 2023 ([link](#) to the source within www.hc-sc.gc.ca)

Janus kinase (JAK) inhibitors

Risks of major cardiovascular events, malignancy, venous thromboembolism, serious infections and increased mortality

United Kingdom. The Medicines and Healthcare Products Regulatory Agency (MHRA) has informed health-care professionals of new risk minimization measures for JAK inhibitors used to treat chronic inflammatory disorders.

Janus kinase (JAK) inhibitors are a class of medicines that include abrocitinib (Cibinqo®), filgotinib (Jyseleca®), baricitinib (Olumiant®),

upadacitinib (Rinvoq®), and tofacitinib (Xeljanz®). They are used in the treatment of chronic inflammatory disorders such as rheumatoid arthritis, psoriatic arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, non-radiographic axial spondyloarthritis, ulcerative colitis, Crohn's disease, atopic dermatitis, and alopecia areata.

This new risk minimization measures are consistent with the measures introduced for tofacitinib (Xeljanz®) in 2020 and 2021. The MHRA's review found that risks of increased incidence of malignancy, major adverse cardiovascular events (MACE), serious infections, venous thromboembolism (VTE) and mortality, are considered class effects across JAK inhibitors used for chronic inflammatory disorders.

Therefore, it is advised to avoid prescribing these medicines unless there are no suitable alternatives in patients with the following risk factors: age 65 years or older; current or past long-time smoking; other risk factors for cardiovascular disease or malignancy.

In addition to the results of studies for tofacitinib and baricitinib which suggested an increased risk of major cardiovascular events, the latest review conducted by the EMA looked at the available mechanistic and safety data for each of the five JAK inhibitors and concluded that the effects could be considered a class effect.

Following the MHRA's review, changes are being made to the product information for all JAK inhibitor medicines authorized for inflammatory diseases to note the updated risk characterization and expanded risk minimization measures. The MHRA has sent a DHPC letter to advise of these changes.

Reference:

Drug Safety Update, MHRA, 26 April 2023 ([link](#) to the source within www.gov.uk/mhra)

(See also WHO Pharmaceuticals Newsletter [No. 1, 2023](#): Janus kinase (JAK) inhibitors and Risks of cardiovascular conditions, blood clots, cancer, serious infections in Europe and Singapore)

Losartan

Risk of muscle spasm

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 losartan to include muscle spasm as an adverse drug reaction.

Losartan is indicated for the treatment of mild to moderate hypertension.

The NCC-PvPI, IPC reviewed 10 Individual Case Safety Reports (ICSRs) of losartan associated muscle spasm and a causal relationship between them was found.

Reference:

Based on the communication from IPC, India, April 2023 ([link](#) to the source within ipc.gov.in)

Nirmatrelvir-ritonavir and immunosuppressants

Risk of adverse events from drug-drug interaction

Canada. Health Canada has announced that the product information for nirmatrelvir-ritonavir (Paxlovid®) has been updated to include the risk of drug-drug interaction with immunosuppressants (including cyclosporine, everolimus, sirolimus and tacrolimus).

Nirmatrelvir-ritonavir is indicated for the treatment of COVID-19 and is an inhibitor of cytochrome P450 (CYP) 3A. Tacrolimus is metabolized by CYP3A and has a narrow therapeutic index.

Canadian cases of serious adverse events following a drug-drug interaction between nirmatrelvir-ritonavir and tacrolimus have been reported. In some cases, the tacrolimus levels were observed to go up rapidly and to very high levels, which can lead to adverse effects such as acute kidney injury and increased susceptibility to severe infections due to over-immunosuppression. Cases have also been reported in the literature from other countries.

Health-care professionals

are advised to avoid use of nirmatrelvir-ritonavir in patients taking immunosuppressants when close monitoring of immunosuppressant concentrations is not feasible. If co-administered, dose adjustment, monitoring of concentrations and adverse reactions for levels of immunosuppressants are recommended.

Reference:

Health Product InfoWatch: March 2023, Health Canada, ([link](#) to the source within www.hc-sc.gc.ca)

Opioids

New safety label changes

United States. The US FDA is requiring several updates to the prescribing information for immediate-release (IR) and extended-release/long-acting (ER/LA) opioid analgesics.

The required safety labelling changes include:

- the risk of overdose increases as the dosage increases for all opioid pain medicines
- IR opioids should not be used for an extended period unless a patient's pain remains severe enough to require them and alternative treatment options continue to be inadequate
- many acute pain conditions treated in the outpatient setting require no more than a few days of an opioid pain medicine
- it is recommended to reserve ER/LA opioid pain medicines for severe and

persistent pain that requires an extended treatment period with a daily opioid pain medicine and for which alternative treatment options are inadequate.

The updates also include a new warning about opioid-induced hyperalgesia (OIH) which is a condition where opioids cause an increase in pain (hyperalgesia) or an increased sensitivity to pain (allodynia).

This action is part of the implementation of FDA Overdose Prevention Framework.

Reference:

CDER Statement, US FDA, 13 April 2023 ([link](#) to the source within www.fda.gov)

Paracetamol

Risk of fixed drug eruption

India. The 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 paracetamol to include fixed drug eruption as an adverse drug reaction.

Paracetamol is indicated for the symptomatic treatment of pain and fever.

The NCC-PvPI, IPC reviewed 480 Individual Case Safety Reports (ICSRs) of paracetamol associated fixed drug eruption and a causal

relationship between them was found.

Reference:

Based on the communication from IPC, India, April 2023 ([link](#) to the source within ipc.gov.in)

Piperacillin

Risk of haemophagocytic lymphohistiocytosis (HLH)

Malaysia. The National Pharmaceutical Regulatory Agency (NPRA) has announced that the product safety information for piperacillin will be updated to include a warning regarding the risk of haemophagocytic lymphohistiocytosis (HLH).

Piperacillin belongs to the β -lactam antibiotics which are active against a range of gram-positive and gram-negative aerobic and anaerobic bacteria and often combined with a β -lactamase inhibitor such as tazobactam to enhance the activity against many of those resistant organisms.

HLH is a life-threatening syndrome caused by pathologic over-activation of the immune system, with clinical features of extreme systemic inflammation, such as fever, skin rashes, hepatosplenomegaly, cytopenias, hyperferritinaemia, hypertriglyceridaemia, hypofibrinogenaemia, and haemophagocytosis.

The NPRA has reviewed the available information on

cases of haemophagocytic lymphohistiocytosis reported internationally as well as relevant scientific literature. HLH has high mortality rates and a delay in diagnosis of HLH is often the greatest barrier to favourable outcomes owing to the rarity of HLH, variety of clinical presentations, and non-specific clinical and laboratory findings. In a published case series, clinical symptoms of HLH in three children were reported to have improved following cessation of piperacillin/tazobactam in combination with corticosteroid therapy (e.g., intravenous prednisolone/methylprednisolone), one of which involved the addition of Intravenous human immunoglobulin (IVIG). Considering the complexity and severity of the condition the NPRA deems it necessary to alert health-care professionals about the potential risk of HLH following the use of piperacillin-containing products.

Health-care professionals are also reminded that early detection of HLH manifestations followed by timely intervention and treatment are crucial for minimising morbidity and mortality.

Reference:

Safety Alert, NPRA, 1 November 2022 ([link](#) to the source within www.npra.gov.my)
(See also WHO Pharmaceuticals Newsletter No.2, 2023: tazobactam and piperacillin risk of haemophagocytic lymphohistiocytosis)

Piroxicam

Risk of fixed drug eruption

India. The 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 piroxicam to include fixed drug eruption as an adverse drug reaction.

Piroxicam is indicated for the treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, cervical spondylitis and other musculoskeletal disorder.

The NCC-PvPI, IPC reviewed 31 Individual Case Safety Reports (ICSRs) of Piroxicam associated fixed drug eruption and a causal relationship between them was found.

Reference:

Based on the communication from IPC, India, April 2023 ([link](#) to the source within ipc.gov.in)

Propofol

Medication errors that could potentially lead to life threatening/fatal cases

Europe. The PRAC of the EMA has recommended that MAHs for propofol containing products should submit a variation to amend the product information of the outer and immediate packaging

to include “For single use in one patient. Risk of sepsis in multiple use” and “Use immediately after opening”. In case of insufficient space on the immediate packaging, the National Competent Authorities may decide to omit parts of the warning on the immediate packaging.

The PRAC has considered the available evidence in EudraVigilance, literature and the responses of the MAHs for this decision.

Reference:

PRAC recommendations on signals, EMA, 11 April 2023 ([link](#) to the source within www.ema.europa.eu)

Terlipressin

Risk of respiratory failure and septic shock

United Kingdom. The MHRA has alerted health-care professionals that in patients with type 1 hepatorenal syndrome terlipressin may cause serious or fatal respiratory failure at a frequency higher than previously known, and that terlipressin increases the risk of sepsis and septic shock.

Terlipressin is a synthetic pituitary hormone. It is authorized for treatment of bleeding from dilated veins in the food pipe leading to the stomach (bleeding oesophageal varices) and for emergency treatment of type 1 hepatorenal syndrome (rapidly progressive renal failure in

patients with liver cirrhosis (scarring of the liver) and ascites (fluid accumulation in the abdomen)). The advice in this article relates only to use of terlipressin for type 1 hepatorenal syndrome.

A recent European review into the benefits and risks of terlipressin treatment, which was triggered by the CONFIRM trial findings, concluded that new measures were required to reduce the risk of respiratory failure and sepsis when terlipressin is used in patients with type 1 hepatorenal syndrome. The Pharmacovigilance Expert Advisory Group of the UK's Commission on Human Medicines agreed with the recommendations, while also highlighting the benefits of terlipressin treatment when an appropriate assessment of the benefits and risks has been made. Changes will be made to the product information for terlipressin medicines authorized for type 1 hepatorenal syndrome to note the individual benefits and risks when initiating terlipressin treatment, especially for those with severe renal or hepatic impairment and monitor all patients closely during terlipressin treatment. A Direct Healthcare Professional Communication letter has also been sent to UK health-care professionals.

Reference:

Drug Safety Update, MHRA, 23 March 2023 ([link](#) to the source within www.gov.uk/mhra)

(See also WHO Pharmaceuticals

Newsletter [No.1, 2023](#): terlipressin and risks of respiratory failure, sepsis in Europe)

Voriconazole

Drug interaction with flucloxacillin leading to subtherapeutic voriconazole levels

Europe. The PRAC of the EMA has recommended a change to the product information for voriconazole to include drug interaction with flucloxacillin leading to subtherapeutic voriconazole levels.

The PRAC has considered the evidence from the literature, the responses from the MAH and has agreed that the MAHs for voriconazole and flucloxacillin-containing medicinal products should submit a variation to amend the product information as described below: Flucloxacillin has been reported to significantly decrease plasma voriconazole concentrations. If concomitant administration of flucloxacillin with voriconazole cannot be avoided, monitor for potential loss of voriconazole effectiveness (e.g., by therapeutic drug monitoring); increasing the dose of voriconazole may be needed.

Patients are advised to inform their doctor if they are taking medicinal products containing voriconazole and flucloxacillin, as a dose adjustment or monitoring

may be required to check that the medicines are still having the desired effect.

Reference:

PRAC recommendations on signals, EMA, 11 April 2023 ([link](#) to the source within www.ema.europa.eu)

Amlodipine

Potential risk of Hyperkalaemia

Saudi Arabia. The Saudi Food & Drug Authority (SFDA) has released a safety signal concerning amlodipine and risk of hyperkalaemia.

Amlodipine is an antihypertensive drug belonging to the group of drugs called dihydropyridine calcium channel blockers. Hyperkalemia is defined as a serum or plasma potassium level above the upper limits of normal.

In 2023, the SFDA has detected a signal of Amlodipine and hyperkalaemia and reviewed all the evidence available on the association between them. The SFDA found one local case and 225 international cases in VigiBase (the WHO global database of ICSRs) and applied WHO-UMC causality assessment criteria on thirty cases with highest completeness score. It resulted in two probable cases, sixteen possible cases, six unlikely case and six cases not assessable. Data mining of this drug/ADR has been estimated using Information component (IC= 1) which revealed a positive statistical association. Furthermore, a case report was found in the literature that support the association.

The SFDA's investigation concluded that the current available evidence from

causality assessment of the reported cases and literature might support a relationship between Amlodipine and hyperkalaemia. This signal needs further investigation to confirm the risk, and health-care professionals should be aware of this potential adverse reaction.

Reference:

Safety Alert, SFDA, 16 May 2023 ([link](#) to the source within www.sfda.gov.sa)

Folic acid

Potential risk of constipation

Saudi Arabia. The SFDA has released a safety signal concerning folic acid and the risk of constipation.

Folic acid or Folate (vitamin B-9) is important in red blood cell formation and for healthy cell growth and function. The nutrient is crucial during early pregnancy to reduce the risk of birth defects of the brain and spine. Constipation is generally described as having fewer than three bowel movements a week. The SFDA detected a domestic case-report of constipation and 157 international cases in VigiBase and extracted the top 30 cases from VigiLyze that have completeness score of 1.0 in order to apply the WHO causality assessment criteria on them. As a result, majority of the cases were possibly linked to Folic acid (21 cases were possible and the other nine cases were

unlikely). Additionally, the data mining for this drug/ADR combination provided positive statistical association (IC=1.1) at that point of time.

The SFDA's investigation concluded that the current available evidence from assessment of the ICSRs and data mining might support a relationship between folic acid and constipation. This signal needs further investigation to confirm the risk, however, health-care professionals should be aware of this potential adverse reaction.

Reference:

Safety Alert, SFDA, 1 March 2023 ([link](#) to the source within www.sfda.gov.sa)

Ibuprofen

Potential risk of renal tubular acidosis

Saudi Arabia. The SFDA has released a safety signal concerning ibuprofen and its potential risk of renal tubular acidosis.

Ibuprofen is a non-steroidal anti-inflammatory medication that indicated for its analgesia and anti-inflammatory effects.

In 2023, the SFDA has detected a signal of ibuprofen and renal tubular acidosis and reviewed all the evidence available on the association between them.

The SFDA reviewed VigiBase and found 116 ICSRs internationally at that point of time. The SFDA has extracted cases

with completeness score of 0.5 (n=10 cases) in order to apply the causality assessment criteria on them. As a result, all the assessable cases of renal tubular acidosis were either probably or possibly linked to ibuprofen. Data mining of this drug/ADR has been estimated using Information component (IC=4.2) which reflect strong positive statistical association.

The SFDA's investigation concluded that the current available evidence from assessment of the ICSRs, class effect and literature might support a relationship between of ibuprofen and renal tubular acidosis. This signal needs further investigation to confirm the risk, and health-care professionals should be aware of this potential adverse reaction.

Reference:

Safety Alert, SFDA, 21 March 2023 ([link](#) to the source within www.sfda.gov.sa)

(See also WHO Pharmaceuticals Newsletter [No.1, 2020](#): *Ibuprofen and Risk of renal toxicity in New Zealand*)

Isotretinoin

Risk of sexual dysfunction

United Kingdom. The MHRA has announced that the Isotretinoin Expert Working Group (IEWG) of the Commission on Human Medicines (CHM) recommended new measures to strengthen the safety of isotretinoin (capsule form, Roaccutane® and

Reticutan®) treatment. Recommendations include the addition of new warnings for the risk of sexual dysfunction, including the possibility of persistence after treatment discontinuation, and advice for health-care professionals to ask patients about symptoms or signs of sexual dysfunction prior to starting treatment with isotretinoin and to monitor patients for the development of new sexual disorders during treatment. Recommendations also include the development of consistent monitoring requirements for potential psychiatric and sexual side effects in all patients throughout treatment. The initiation of treatment in patients younger than 18 years will require two prescribers to agree a patient's acne is severe and that there is no other effective treatment before initiation of isotretinoin therapy.

Isotretinoin is indicated for severe forms of acne (such as nodular or conglobate acne or acne at risk of permanent scarring) resistant to adequate courses of standard therapy with systemic anti-bacterials and topical therapy.

The MHRA has formed an Implementation Advisory Group to advise on the implementation of these recommendations.

The IEWG considered the available information on psychiatric and sexual side effects suspected to be

associated with isotretinoin. This included suspected side effects reported to the MHRA, research into the risks and the biological mechanisms that may explain these events, from published studies about patients taking isotretinoin, information on how isotretinoin safety is managed in other countries, and result of a public call for information.

Reference:

Drug Safety Update, MHRA, 26 April 2023 ([link](#) to the source within www.gov.uk/mhra)

(See also WHO Pharmaceuticals Newsletter [No.5, 2020](#): *isotretinoin and risks of psychiatric reactions and sexual dysfunction in UK*)

Lactulose

Potential risk of Pruritus

Saudi Arabia. The SFDA has released a safety signal concerning lactulose and its potential risk of pruritus.

Lactulose is a synthetic sugar used to treat constipation. It is broken down in the colon into products that pull water out from the body and into the colon resulting in softening the stools. Lactulose is also used to reduce the amount of ammonia in the blood of patients with liver disease.

In 2023, the SFDA has detected a signal of lactulose and pruritus and reviewed all the evidence available on the association between them. The SFDA initiated this investigation following a local case-

report of pruritus. The SFDA looked into the VigiBase and found 340 ICSRs internationally. The SFDA has extracted the top 30 cases with completeness score of 1.0 in order to apply the causality assessment criteria on them. As a result, most of the assessed cases provides positive linkage to Lactulose (14 probable, 11 possible, and five unlikely cases).

The SFDA's investigation concluded that the current available evidence from assessment of the ICSRs might support a relationship between of lactulose and pruritus. This signal needs further investigation to confirm the risk, and health-care professionals should be aware of this potential adverse reaction.

Reference:

Safety Alert, SFDA, 1 March 2023 ([link](#) to the source within www.sfda.gov.sa)

Levofloxacin

Potential risk of dry mouth

Saudi Arabia. The SFDA has released a safety signal concerning levofloxacin and its potential risk of dry mouth.

Levofloxacin is a broad-spectrum, third-generation fluoroquinolone antibiotic used to treat bacterial infections.

In 2023, the SFDA detected a signal of levofloxacin and dry mouth. Furthermore,

the SFDA reviewed all the evidence available on the association between them. The SFDA found one local case and 857 international cases in VigiBase and applied WHO-UMC causality assessment criteria on ICSRs with completeness score 1.0 (n=30). Among them, 29 cases were either probably or possibly associated with levofloxacin. Evidence from literature found that support the signal, as the risk of dry mouth was reported in a published randomized double-blind controlled trial of levofloxacin.

The SFDA's investigation concluded that the current available evidence from assessment of the ICSRs and literature might support a relationship between levofloxacin and dry mouth. This signal needs further investigation to confirm the risk, and health-care professionals should be aware of this potential adverse reaction.

Reference:

Safety Alert, SFDA, 21 March 2023 ([link](#) to the source within www.sfda.gov.sa)

Nitrofurantoin

Risks of pulmonary and hepatic adverse drug reactions

United Kingdom. The MHRA has reminded healthcare professionals that prescribing nitrofurantoin should be alert to the risks of

pulmonary and hepatic adverse drug reactions and advise patients to be vigilant for the signs and symptoms in need of further investigation.

Nitrofurantoin is a broad-spectrum antibacterial agent, which has been available since the 1950s. It is indicated in adults, children and infants over three months old for the treatment and prophylaxis of acute or recurrent uncomplicated urinary tract infections (UTIs) and acute or recurrent uncomplicated pyelitis. The potential for acute pulmonary damage with nitrofurantoin is well-documented in the product information.

The MHRA has advised health-care professionals as follows:

- patients and caregivers to be vigilant for new or worsening respiratory symptoms while taking nitrofurantoin and promptly investigate any symptoms that may indicate a pulmonary adverse reaction.
- immediately discontinue nitrofurantoin on the occurrence of new or worsening symptoms indicative of pulmonary damage.
- be vigilant for symptoms and signs of liver dysfunction in patients taking nitrofurantoin for any duration, but particularly with long-term use, and monitor patients periodically for signs of hepatitis and for changes in biochemical tests that would indicate hepatitis or liver injury.

- use caution when prescribing nitrofurantoin in patients with pulmonary disease or hepatic dysfunction, which may mask the signs and symptoms of adverse reactions.

Reference:

Drug Safety Update, MHRA, 26 April 2023 ([link](#) to the source within www.gov.uk/mhra)

(See also WHO Pharmaceuticals Newsletter No.2, 2020: nitrofurantoin and Risk of pulmonary and hepatic impairment and peripheral neuropathy in New Zealand)

Pneumococcal Polysaccharide Vaccine (23-Valent)

Potential risk of extensive swelling of vaccinated limb

Malaysia. The NPRA has issued a Safety Alert about the potential risk of extensive swelling of vaccinated limb with pneumococcal polysaccharide vaccine (23-valent) or PPV 23.

PPV 23 containing purified capsular polysaccharides of the 23 most prevalent or invasive pneumococcal types of *Streptococcus pneumoniae* is indicated for children from 2 years of age, adolescents, and adults in whom there is an increased risk of pneumococcal disease.

Extensive limb swelling (ELS) is defined as limb swelling that extends at

least to the joints immediately above and below the injection site or that may cross one or more joints. Alternatively, ELS can be defined as swelling of the limb that results in twice the normal size of the limb circumference. Extensive swelling of vaccinated limb is a known adverse event to some other vaccines, such as Comirnaty® (COVID-19 mRNA vaccine) and diphtheria/tetanus toxoids/acellular pertussis vaccine (adsorbed paediatric) (DTaP), while the reporting rate differs substantially among vaccines.

The NPRA has reviewed available information on cases reported internationally for suspected adverse events and data from the scientific literature. The EMA requested that the package insert for all PPV 23 products be updated with the risk of extensive swelling of vaccinated limb in 2022. In the NPRA's view, it is possible that these events may be overlooked due to the regular occurrence of injection site inflammation following immunisation. Besides, extensive swelling of vaccinated limb might be misdiagnosed as cellulitis or erysipelas in the lack of bacteriological information, which could result in unnecessary antibiotic treatment.

Health-care professionals are advised to be aware and inform vaccine recipients about the possible occurrence of

extensive swelling of vaccinated limb within a short period after administration of PPV 23 and to report all suspected ELS events following immunisation with PPV 23.

Reference:

Safety Alert, NPRA, 20 December 2022 ([link](#) to the source within www.npra.gov.my)

Prednisolone

Potential risk of hypomagnesaemia

Saudi Arabia. The SFDA has released a safety signal concerning prednisolone and its potential risk of hypomagnesaemia.

Prednisolone is a corticosteroid used to treat a wide range of health conditions including allergies, blood disorders, skin diseases, inflammation, infections and certain cancers and to prevent organ rejection. Hypomagnesaemia is an electrolyte disturbance caused by a low serum magnesium level in the blood.

In 2023, the SFDA has detected a signal of prednisolone and hypomagnesaemia and reviewed all the evidence available on the association between them. The SFDA found 28 international cases in VigiBase and applied WHO-UMC causality assessment criteria on all cases. Almost half of them (13 cases) were possibly linked to prednisolone (other 13 cases were not

assessable + two cases were unlikely). Data mining of this drug/ADR has been estimated using Information component (IC= 0.6) which showed a positive statistical association for the drug/ADR combination.

The SFDA's investigation concluded that the current available evidence from assessment of the ICSRs might support a relationship between prednisolone and hypomagnesaemia. This signal needs further investigation to confirm the risk, and health-care professionals should be aware of this potential adverse reaction.

Reference:

Safety Alert, SFDA, 30 April 2023 ([link](#) to the source within www.sfda.gov.sa)

Prednisone

Potential risk of osteonecrosis

Saudi Arabia. The SFDA has released a safety signal concerning prednisone and its potential risk of osteonecrosis.

Prednisone is a synthetic, anti-inflammatory glucocorticoid that derives from cortisone.

Osteonecrosis is the death of bone cells due to decreased blood flow.

In 2023, the SFDA has detected a signal of prednisone and osteonecrosis and reviewed all the evidence available on the association between

them. The SFDA found one local case and 1037 international cases in VigiBase. The SFDA applied WHO-UMC causality assessment criteria on ICSRs with completeness score 1.0 (n=30). Twenty cases provided positive association (one probable and nineteen possible cases). Eight cases were unlikely and two cases were not assessable. Data mining of this drug/ADR was estimated using Information component (IC= 4.0), which showed a strong positive statistical association for the drug/ADR combination.

The SFDA's investigation concluded that the current available evidence from assessment of the ICSRs and data mining might indicate a relationship between prednisone and osteonecrosis. This signal needs further investigation to confirm the risk, and health-care professionals should be aware of this potential adverse reaction.

Reference:

Safety Alert, SFDA, 21 March 2023 ([link](#) to the source within www.sfda.gov.sa)

Scopolamine and butylscopolamine

Risk of medication errors resulting in serious adverse reactions

Spain. The Spanish Agency for Medicines and Health Products (AEMPS) is alerting health-care professionals about the risk

of medication errors of administration of scopolamine instead of butylscopolamine resulting in serious adverse reactions.

The Spanish Pharmacovigilance System (SEFV-H) has received five cases of serious adverse reactions related to the erroneous administration of scopolamine instead of butylscopolamine. The affected patients required medical assistance. The errors detected indicate that confusion may occur in the prescription, dispensing and administration of the drug.

The very similar name of the two active ingredients makes them susceptible to confusion. However, their indications and dosage are very different. Butylscopolamine bromide (formerly called scopolamine butylbromide), because of its chemical structure as a quaternary ammonium salt, does not cross the blood-brain barrier. It is indicated for the treatment of acute spasms of the gastrointestinal, biliary and genitourinary tracts. Scopolamine hydrobromide, on the other hand, has a tertiary amine structure so it crosses the blood-brain barrier and is indicated as a premedication in anesthesia to reduce excessive salivation and secretions from the respiratory tract.

The administration by mistake of scopolamine at doses of butylscopolamine

involves an overdose that can cause anticholinergic adverse reactions at the level of the central nervous system with serious consequences.

Characteristic signs and symptoms of scopolamine overdose are headache, nausea, vomiting, blurred vision, confusion, disorientation, memory loss, and hallucinations.

Health-care professionals are advised to pay detailed attention to the possible confusion between scopolamine and butylscopolamine, both in the prescription and in the dispensing and administration of the medicinal product.

Reference:

Security Notes, AEMPS, 17 April 2023 ([link](#) to the source within www.aemps.gob.es)

Sitagliptin

Potential risk of fatigue

Saudi Arabia. The SFDA has released a safety signal concerning sitagliptin and its potential risk of fatigue.

Sitagliptin is dipeptidyl peptidase-4 (DPP-4) inhibitor indicated for the treatment of patients with T2D.

Fatigue is a term that refers to a general feeling of exhaustion or a lack of energy.

In 2023, the SFDA detected a signal of sitagliptin and fatigue and reviewed all the evidence available on the association between them. The SFDA initiated this

investigation following a local case-report of fatigue. The SFDA looked into VigiBase and found 629 ICSRs and extracted international cases with completeness score of 1.0 (n=19 cases) in order to apply the causality assessment criteria on them. As a result, seven cases of fatigue were either probably or possibly linked to sitagliptin. Literature evidence found supportive in a published article. Additionally, the risk is written in reference safety information of medications from the same class.

The SFDA's investigation concluded that the current available evidence from assessment of the ICSRs, class effect and literature might support a relationship between of sitagliptin and fatigue. This signal needs further investigation to confirm the risk, and health-care professionals should be aware of this potential adverse reaction.

Reference:

Safety Alert, SFDA, 1 March 2023 ([link](#) to the source within www.sfda.gov.sa)

Valproic acid (sodium valproate)

Risks of birth defects and developmental disorders in children

WHO. WHO has issued a safety statement to alert stakeholders to the revised guidance on the use of

valproic acid (and its sodium salt, sodium valproate) for the treatment of epilepsy and bipolar disorder in women and girls of childbearing potential contained in the addendum to the [mhGAP intervention guide \(mhGAP-IG\)](#) and [mhGAP humanitarian intervention guide \(mhGAP-HIG\)](#). The addenda have been issued in advance of an update to the mhGAP guideline for non-specialist health-care providers which is due to be released later this year, and was discussed at the meeting of the WHO Advisory Committee for the Safety of Medicinal products (ACSoMP) on 14 December 2022.

Prescription of valproic acid (sodium valproate) for women and girls of childbearing potential:

- Valproic acid (sodium valproate) should not be prescribed because of the high risk of birth defects and developmental disorders in children exposed to valproic acid (sodium valproate) in the womb.
- Lamotrigine or levetiracetam should be offered as first line monotherapy for both generalized onset seizures and focal onset seizures.
- For women and girls of childbearing potential currently prescribed valproic acid (sodium valproate):
- Advice should be provided on use of effective contraception, without interruption, during the entire duration of treatment.

Information must be provided on risks associated with valproic acid (sodium valproate) use during pregnancy, pregnancy prevention and refer for contraceptive advice if they are not using effective contraception.

- Individual circumstances should be evaluated in each case when choosing the contraception method and involving the woman in shared decision making.
- If a woman is planning to become pregnant, a person trained in the management of epilepsy/bipolar disorder in pregnant

women should consider alternative treatment options. Women should be advised to consult their physician as soon as they are planning pregnancy and the need to urgently consult their physician in case of pregnancy.

- Every effort should be made to switch to appropriate alternative treatment prior to conception. If switching is not possible, the woman should receive further counselling regarding the risks of valproic acid (sodium valproate) for the unborn child to support her informed decision-making.

- A specialist should periodically review whether valproic acid (sodium valproate) is the most suitable treatment for the person.

Reference:

Safety alert, WHO, 2 May 2023 ([link](#) to the source within www.who.int)

(See also WHO Pharmaceuticals Newsletter [No.1, 2023](#): Valproate and risks in pregnancy and potential risks in male patients in UK and [No.2, 2023](#): summary of ACSoMP meeting on 14 December 2022)

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

National Regulatory Authorities welcome to join Vaccine Safety Net

Background information

The [Vaccine Safety Net](#) (VSN) is a global network of websites, established by the World Health Organization, that provide reliable information on vaccine safety.

Due to the success of immunization, some diseases are no longer perceived as a threat. Certain groups have even questioned the utility of vaccination despite its proven success in controlling disease. In recent years, several websites providing unbalanced, misleading and alarming vaccine safety information have been established, which can lead to undue fears, particularly among parents and patients.

Acknowledging the above-mentioned issues and urged by governments, key non-governmental organizations and the United Nations Children's Fund (UNICEF), WHO initiated, in 2003, the Vaccine Safety Net Project (VSN).

A key player in the Project is the Global Advisory Committee on Vaccine Safety (GACVS), established by WHO in 1999, to respond promptly, efficiently, and with scientific rigor to vaccine safety issues of potential global importance.

VSN criteria

GACVS developed four categories of criteria for good information practices - regarding credibility, content, accessibility and design to which digital resources providing information on vaccine safety should adhere. The WHO Pharmacovigilance (PVG) team uses the criteria to evaluate candidate websites and to re-evaluate existing VSN member websites. There are 44 formal assessment criteria, divided into 4 broad categories. Each category is designated as mandatory or desired. The criteria are grouped as follows:

- credibility (25 mandatory criteria);
- content (quality and quantity) (7 mandatory and 1 desired criteria);
- accessibility (2 mandatory and 4 desired criteria);
- design (2 mandatory and 3 desired criteria).

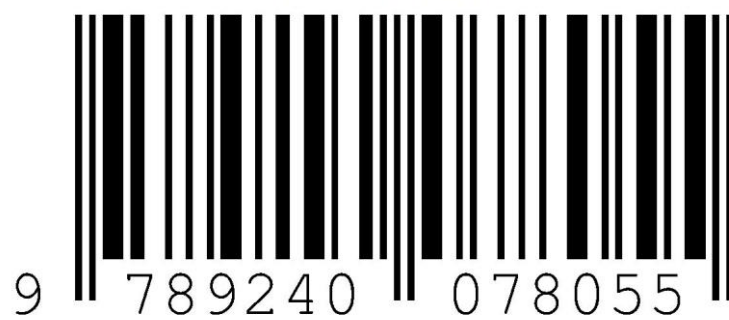
You can find detailed [VSN criteria](#) on the WHO website.

The network is continuously expanding. To date, 104 websites, from 44 countries provide information in 36 languages.

National Regulatory Authorities (NRAs)' websites are welcome to apply for VSN membership to ensure that reliable, understandable, evidence-based information on the safety of vaccines is available to the public.

If you feel that your site meets the GACVS criteria outlined above, please kindly send a request for a site evaluation to pvsupport@who.int. The WHO PVG team will then conduct an assessment of your website and will send you feedback regarding any areas that require clarification or improvements in order to meet the GACVS criteria as well as a set of recommendations to assist you in meeting these criteria. Once the identified issues have been addressed to the satisfaction of the evaluators, WHO will add your website to the [list of VSN members](#).

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