WHO Vision for Safety of Medicinal Products

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

The aim of the Newsletter is to disseminate regulatory information on the safety of medicinal products, based on communications received from our network of national pharmacovigilance centres and other sources such as specialized bulletins and journals, as well as partners in WHO.

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

Pharmacovigilance,
MHP/RPQ,
World Health Organization,
1211 Geneva 27, Switzerland,

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 the recommendations from the Pharmacovigilance Meeting of the Members of the WHO Programme for International Drug Monitoring (PIDM) and Partners in Africa, March 2023.

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Regulatory Matters

Bupropion

Risk of Brugada syndrome

South Africa. The South African Health Products Regulatory Authority (SAHPRA) will update the professional information (PI) and patient information leaflet (PIL) for bupropion to include the risk of Brugada syndrome associated with the use of bupropion-containing medicines.

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.

Brugada syndrome is a rare but potentially life-threatening heart rhythm condition (arrhythmia) that is sometimes inherited. People with Brugada syndrome have an increased risk of irregular heart rhythms beginning in the lower chambers of the heart (ventricles).

Symptoms of Brugada syndrome range from absence of any symptoms to sudden cardiac death that typically occurs during sleep, possibly secondary to increased vagal tone. Brugada syndrome is associated with ventricular tachycardia or ventricular fibrillation, syncope, palpitations and dizziness. Although Brugada syndrome is uncommon, its association with sudden cardiac death, due to ventricular fibrillation. It requires that health-care professionals are informed of this side effect, its ECG presentation and modulating factors that may underlie a Brugada pattern, and be able to recognize, identify and promptly take corrective measures.

Physicians need to be cautious when treating patients with a family history of cardiac arrest or sudden death.

Reference:
Vigilance communication to health care professional, SAHPRA, 22 May 2023 (link to the source within www.sahpra.org.za)
(See also WHO Pharmaceuticals Newsletter No.1, 2023 Bupropion and Potential risk of cardiac arrest or sudden death through unmasking of Brugada syndrome)

Cefazolin sodium hydrate and cefazolin sodium

Risk of acute coronary syndrome accompanying allergic 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 cefazolin sodium hydrate and cefazolin sodium will be updated to include the risk of acute coronary syndrome accompanying allergic reaction.

Cefazolin sodium hydrate and cefazolin sodium are indicated for sepsis, infective endocarditis, superficial skin infections, deep-seated skin infections, lymphangitis/lymphadenitis, chronic pyoderma, secondary infections following trauma, thermal burn, etc.

The MHLW and the PMDA assessed 7 cases involving acute coronary syndrome accompanying allergic reaction in Japan, and concluded that a causal relationship between cefazolin and acute coronary syndrome accompanying allergic reaction was reasonably possible.

Reference:
Safety Information, MHLW/PMDA, 29 August 2023 (link to the source within www.pmda.go.jp/english/)

Dabigatran etexilate methanesulfonate

Risk of oesophageal ulcer, oesophagitis

Japan. The MHLW and the PMDA have announced that the product information for dabigatran etexilate methanesulfonate will be updated to include the risk of oesophageal ulcer and oesophagitis.

Dabigatran etexilate methanesulfonate is indicated for reduction in the risk of ischaemic stroke and systemic embolism in patients with non-valvular atrial fibrillation.

The MHLW and the PMDA assessed 49 cases involving oesophageal ulcer or oesophagitis in Japan, and concluded that a causal relationship between dabigatran etexilate methanesulfonate and oesophageal ulcer or oesophagitis was reasonably possible.

Reference:
Safety Information,
Dexibuprofen (oral)

Risk of DRESS syndrome

Republic of Korea. The Ministry of Food and Drug Safety (MFDS) has updated the drug label for oral dexibuprofen products to include the risk of drug reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome, a severe adverse drug reaction characterized by an extensive skin rash in association with visceral organ involvement, lymphadenopathy, eosinophilia, and atypical lymphocytosis.

Dexibuprofen is a non-steroidal anti-inflammatory drug (NSAID) commonly used for the reduction of pain, inflammation and fever.

The Korea Institute of Drug safety and Risk Management (KIDS) conducted a review of the report, which suggested a causal link between oral dexibuprofen products and DRESS syndrome. The KIDS also gathered information from foreign regulatory authorities and sought advice from medical experts regarding the causal relationship between them.

Health-care professionals should be aware of the signs and symptoms of DRESS syndrome to allow early diagnosis and prompt treatment. Patients are advised to seek immediate medical attention if they experience these severe cutaneous symptoms.

Reference:
Based on the communication from KIDS and Drug Safety Update, MFDS/KIDS, 28 June 2023 (link to the source within nedrug.mfds.go.kr/index)

Domperidone

Potential risk of psychiatric withdrawal events when used for lactation stimulation

Canada. Health Canada has announced that the product information for domperidone is to be updated to include the potential risk of psychiatric withdrawal events when used for lactation stimulation.

Domperidone is authorized for sale in Canada to treat symptoms of slowed stomach emptying seen with certain gastrointestinal conditions, and to prevent symptoms, such as nausea and vomiting, caused by some drugs used to treat Parkinson’s disease. Domperidone is not authorized in Canada to promote lactation, but data derived from Canadian sources indicate that it has been prescribed for this off-label use.

Triggered by published cases in the scientific literature concerning this risk and the off-label use of domperidone for lactation stimulation, Health Canada reviewed information from the Canada Vigilance database and published literature. Health Canada reviewed 9 cases (4 Canadian and 5 international) of psychiatric withdrawal events following sudden discontinuation or tapering of domperidone when used for lactation stimulation. Of the 9 cases, 7 (4 Canadian) were found to be probably linked to the use of domperidone and 2 were found to be possibly linked. The total daily dose of domperidone used in 8 of the 9 cases was reported to be higher than 30 mg. In all cases, the duration of domperidone use prior to the initial discontinuation or tapering attempt was longer than 4 weeks.

Health Canada also reviewed articles published in the scientific literature, which identified potential biological mechanisms that may explain how sudden discontinuation or tapering of domperidone, when used to stimulate lactation, could lead to psychiatric withdrawal events.

Reference:
Health Product InfoWatch, Health Canada, 30 August 2023 (link to the source within www.hc-sc.gc.ca)

Finasteride

Risk of suicide-related events

Japan. The MHLW and the PMDA have announced that the product information for finasteride will be updated to include the risk of suicide-related events.

Finasteride is indicated for the treatment of androgenetic alopecia (male pattern hair loss).

The MHLW and the PMDA have not identified any cases of suicide-related events for which a causal relationship with finasteride
was reasonably possible as adverse reactions in Japan. However, IC\textsubscript{025} in a disproportionality analysis performed by the PMDA using the dataset of VigiBase as of May 28, 2023 showed the following:

- Suicidal depression 3.5;
- Suicidal ideation 3.3;
- Completed suicide 1.6;
- Suicidal behaviour 1.3;
- Suicidal ideation 0.5;
- Suicide attempt 0.4. Thus, the analysis showed that the number of adverse reactions of these events reported for finasteride was significantly higher than would be expected for the entire database.

Published articles also suggested an association between finasteride and suicide related events.

Reference:
Safety Information, MHLW/PMDA, 29 August 2023 (link to the source within www.pmda.go.jp/english/)

(See also WHO Pharmaceuticals Newsletter No. 4, 2022: Finasteride and Potential risk of suicidal ideation)

**Nivolumab**

**Risk of cytokine release syndrome**

**Europe.** The Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) has recommended updating the product information for nivolumab (Opdivo®) to add the risk of cytokine release syndrome (a form of systemic inflammatory response syndrome (SIRS) that can be triggered by a variety of factors) as a case of infusion related reaction, which is already mentioned in the product information.

Nivolumab is an immune checkpoint inhibitor used in the treatment of various cancers.

The PRAC reviewed the available evidence including from the cumulative review performed by the Marketing Authorisation Holder (MAH) and agreed the recommendation.

Reference:
PRAC recommendations on signals, EMA, 3 July 2023 (link to the source within www.ema.europa.eu)

(See also WHO Pharmaceuticals Newsletter No. 3, 2021: Nivolumab and potential risk of certain blood disorders and cytokine release and tumour lysis syndromes)

**Olaparib**

**Risk of hepatotoxicity**

**Europe.** The PRAC of the EMA has recommended updating the product information for olaparib (Lynparza®) to add the risk of hepatotoxicity including hepatobiliary disorders, drug-induced liver injury (DILI) and transaminases increased.

Olaparib is indicated for the treatment of BRCA-mutated advanced ovarian cancer in adults.

The PRAC reviewed the available evidence including from EudraVigilance and agreed the recommendation.

Health-care professionals are advised that if clinical symptoms or signs suggestive of hepatotoxicity develop, prompt clinical evaluation of the patient and measurement of liver function tests should be performed. In case of suspected DILI, treatment should be interrupted. In case of severe DILI treatment discontinuation should be considered as clinically appropriate.

Reference:
PRAC recommendations on signals, EMA, 31 July 2023 (link to the source within www.ema.europa.eu)

**Peficitinib hydrobromide**

**Risk of venous thromboembolism**

**Japan.** The MHLW and the PMDA have announced that the product information for peficitinib hydrobromide will be updated to include the risk of venous thromboembolism.

Peficitinib hydrobromide is indicated for rheumatoid arthritis in patients who have had an inadequate response to conventional treatments (including the prevention of structural joint damage).

The MHLW and the PMDA assessed five cases involving venous thromboembolism in Japan, and concluded that a causal relationship between peficitinib hydrobromide and venous thromboembolism was reasonably possible.

Reference:
Safety Information, MHLW/PMDA, 29 August 2023 (link to the source within www.pmda.go.jp/english/)
**Regulatory Matters**

### Pembrolizumab and atezolizumab

#### Potential risk of aplastic anaemia

**Canada.** Health Canada has announced that the product information for pembrolizumab (Keytruda®) and atezolizumab (Tecentriq®) is to be updated to include the potential risk of aplastic anaemia, as well as for the other products in the immune checkpoint inhibitors (ICIs) drug class that are not currently labelled for this risk (Bavencio®, Imfinzi®, Jemperli® and Libtayo®), to include the risk of aplastic anaemia.

Pembrolizumab (Keytruda®) and atezolizumab (Tecentriq®) are anti-cancer agents belonging to a class of drugs called ICIs. They are authorized for sale to treat different types of cancers.

Triggered by safety information received from the manufacturers and published cases in the scientific literature, Health Canada reviewed information from the Canada Vigilance database and published literature. Health Canada reviewed 12 cases (1 Canadian and 11 international) of aplastic anaemia in patients receiving Keytruda. Of those 12 cases, 1 was found to be probably linked to the use of Keytruda, 9 (1 Canadian) were found to be possibly linked, 1 was unlikely to be linked and 1 could not be assessed. Health Canada reviewed 2 international cases of aplastic anaemia in patients receiving Tecentriq. Both cases were found to be possibly linked to the use of Tecentriq.

Health Canada also reviewed 9 articles published in the scientific literature reporting cases of aplastic anaemia with the use of Keytruda or Tecentriq. The evidence reviewed further supports the link between the risk of aplastic anaemia and the use of Keytruda or Tecentriq.

**Reference:**
Health Product InfoWatch, Health Canada, 17 August 2023 ([link to the source within www.hc-sc.gc.ca](https://www.hc-sc.gc.ca))

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### Rivastigmine

#### Risk of Prolonged QT

**Japan.** The MHLW and the PMDA have announced that the product information for rivastigmine will be updated to include the risk of prolonged QT interval.

Rivastigmine is a cholinesterase inhibitor used to treat mild and moderate Alzheimer's dementia.

The MHLW and the PMDA assessed a total of 11 cases in Japan (including 5 cases for which a causal relationship between the drug and event was reasonably possible). No patient mortalities have been reported in Japan to date. A total of 15 international cases have been reported (including 3 cases for which a causal relationship between the drug and event was considered reasonably possible). No patient mortalities have been reported internationally to date.

**Reference:**
Safety Information, MHLW/PMDA, 29 August 2023 ([link to the source within www.pmda.go.jp/english/](https://www.pmda.go.jp/english/))

(See also WHO Pharmaceuticals Newsletter No. 4, 2022: Cholinesterase inhibitors and risk of QT interval prolongation and torsade de pointes)

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### Tofacitinib

#### Risk of acne

**Europe.** The PRAC of the EMA has recommended updating the product information for tofacitinib (Xeljanz®) to add acne as an undesirable effect with a frequency ‘common’.

Tofacitinib is a medicine used to treat adults with moderate to severe rheumatoid arthritis, active psoriatic arthritis, active ankylosing spondylitis, and moderate to severe ulcerative colitis. It is also approved for patients ages 2 and older with active polyarticular course juvenile idiopathic arthritis.

The PRAC reviewed the available evidence from EudraVigilance, the literature and the MAH’s responses, and has concluded that there is sufficient evidence to establish a causal relationship between treatment with tofacitinib and acne.

**Reference:**
PRAC recommendations on signals, EMA, 3 July 2023 ([link to the source within www.ema.europa.eu](https://www.ema.europa.eu))
Atorvastatin

Risk of erectile dysfunction

Saudi Arabia. The Saudi Food & Drug Authority (SFDA) has released a safety signal concerning atorvastatin and risk of erectile dysfunction. Atorvastatin is a potent, orally available inhibitor of hepatic 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the major rate-limiting enzyme in cholesterol synthesis. The current primary indication for atorvastatin is the treatment of hypercholesterolemia in persons at high risk for coronary, cerebrovascular and peripheral artery disease. Erectile dysfunction is defined as the failure to achieve or maintain a rigid penile erection suitable for satisfactory sexual intercourse.

In 2023, the SFDA has detected a signal of atorvastatin and erectile dysfunction and reviewed all the evidence available on the association between them. The SFDA found four reported local cases in Saudi Arabia, one of them assessed as possible association. The SFDA looked into VigiBase and found 615 ICSRs and extracted the top 30 cases with highest completeness score (1.0) for further evaluation and application of WHO causality assessment criteria. Among them, 24 cases of erectile dysfunction were either probably or possibly linked to atorvastatin. Data mining of this drug/ADR has been estimated using Information Component (IC= 1.9), 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 atorvastatin and erectile dysfunction. This signal needs further investigation to confirm the risk, and health-care professionals should be aware of this potential adverse reaction.

Reference:
Safety Alerts, SFDA, July 2023 (link to the source within www.sfda.gov.sa)

Clomiphene citrate

Risk of serious visual disturbance (blindness)

France. The National Agency for the Safety of Medicines and Health Products (ANSM) is reminding health-care professionals by issuing a Direct Health-care Professional Communication (DHPC) that there are new visual adverse reactions have been reported with the use of clomiphene citrate (Clomid®). This includes optic neuritis, optic ischemic neuropathy, central retinal vein occlusion, retinal detachment and vitreous detachment. These adverse reactions have in some cases resulted in reversible or irreversible visual impairment, partial or total (blindness), including after discontinuation of clomiphene citrate, especially when increasing the dosage or duration of treatment.

Clomiphene citrate is a medication used to treat infertility in women who do not ovulate, including those with polycystic ovary syndrome. The ANSM reminded health-care professionals that at the start of treatment, patients should be warned of the risk of serious visual disturbances, including blindness. If unusual visual disturbances occur, patients should immediately discontinue their clomiphene citrate treatment and notify their doctor. In cases of visual disturbances, a comprehensive ophthalmological examination is necessary. If no cause of visual disturbance other than clomiphene citrate is identified, treatment with clomiphene citrate should be permanently discontinued.

Reference:
Security information, ANSM, 27 June 2023 (link to the source within ansm.sante.fr)

Dipeptidyl Peptidase-4 (DPP-4) Inhibitors
**Risk of pemphigoid**

**Japan.** The MHLW and the PMDA have alerted that appropriate measures should be taken for pemphigoid due to dipeptidyl Peptidase-4 (DPP-4) Inhibitors.

DPP-4 inhibitors are a class of prescription medicines that are used with diet and exercise to control high blood sugar in adults with type 2 diabetes. Medicines in the DPP-4 inhibitor class include sitagliptin, saxagliptin, linagliptin, and alogliptin.

Precaution for pemphigoid has been in place in the Japanese package inserts of DPP-4 inhibitors. However, cases have been reported where pemphigoid, which occurred after the administration of DPP-4 inhibitors, was exacerbated and led to patient’s hospitalization as a result of continuing administration of DPP-4 inhibitors even after skin abnormalities, the initial symptoms of pemphigoid, were observed.

The MHLW and the PMDA alerted that if oedematous erythema accompanied by itching, blister, erosion, etc. are observed, and pemphigoid is suspected during the use of DPP-4 inhibitors, health-care professionals should consult a dermatologist immediately and take appropriate measures, such as discontinuation of administration.

**Reference:**
Alert for Proper Use of Drugs, PMDA, 30 May 2023 (link to the source within www.pmda.go.jp/english)

(See also WHO Pharmaceuticals Newsletter No.2, 2019; Dipeptidyl peptidase-4 (DPP-4) inhibitors and Risk of bullous pemphigoid)

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**Etoposide**

**Risk of electrolyte imbalance**

**Saudi Arabia.** The SFDA has released a safety signal concerning etoposide and risk of electrolyte imbalance.

Etoposide is a semisynthetic analogue of podophyllotoxin that is used as antineoplastic agent in the therapy of several forms of solid tumours, leukaemia and lymphoma, usually in combination with other agents.

In 2023, the SFDA has detected a signal of etoposide and electrolyte imbalance and reviewed all the evidence available on the association between them. The SFDA initiated this investigation following two local case-report of electrolyte imbalance in SFDA vigilance database. The SFDA looked into VigiBase and found 88 ICSRs and extracted cases with completeness score of 0.8 and above (ICSRs = 8) in order to apply the causality assessment criteria on them. As a result, most of the assessed cases provides positive linkage to etoposide (5 possible cases, 1 unlikely case, and 2 not assessable cases).

More evidence found when looked into data mining. The disproportionality analysis showed that this drug/ADR combination has been reported more than expected when compared to other medications in WHO database (IC= 2.4).

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

**Reference:**
Safety Alerts, SFDA, May 2023 (link to the source within www.sfda.gov.sa)

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**Hyoscine hydrobromide patches**

**Risk of anticholinergic side effects, including hyperthermia**

**United Kingdom.** The Medicines and Healthcare Products Regulatory Agency (MHRA) has advised health-care professionals, patients, parents and carers should be aware of serious and life-threatening anticholinergic side effects associated with hyoscine hydrobromide patches, particularly when used outside the licence guidelines.
Hyoscine hydrobromide is a muscarinic acetylcholine receptor antagonist. The licensed indication of a hyoscine hydrobromide patch (Scopoderm 1.5 mg Patch or Scopoderm TTS Patch) is for the prevention of motion or travel sickness symptoms (for example nausea, vomiting and vertigo) in adults and children aged 10 years of age or older. Each patch should be used for 72 hours. There is widespread use of hyoscine hydrobromide patches outside the licence. Usage outside the licence includes: use for indications other than motion or travel sickness, use in children younger than 10 years of age, cutting patches, application of more than one patch at a time, continuous use of patches without a break, and long-term use.

Anticholinergic side effects associated with hyoscine hydrobromide patches include high temperature, ability to urinate, confusion, disorientation, seeing or hearing things that are not there, fits or convulsions, reduced consciousness, and breathing difficulties. If these symptoms occur seek medical help and remove the patch immediately. If there is a high temperature, take immediate action to reduce body heat in addition to seeking medical help and removing the patch.

The MHRA has requested that Marketing Authorisation Holders (MAHs) for hyoscine hydrobromide patches add hyperthermia to both the list of side effects in the Summary of Product Characteristic (SmPC) and the Patient Information Leaflet (PIL).

Reference:
Drug Safety Update, MHRA, 24 July 2023 (link to the source within www.gov.uk/mhra)

Ketamine

Risk of prolonged use leads to severe liver and uro-nephrological damage

France. The ANSM is reminding health-care professionals by issuing a Direct Health-care Professional Communication (DHPC) that there is an increase in the number of hepatobiliary (cholestasis or cholangitis) and uro-nephrological (non-infectious cystitis, interstitial cystitis, acute renal failure, hydronephrosis), most often serious, after prolonged or repeated use of ketamine. Ketamine is a narcotic whose prescription is limited to 28 days.

The ANSM reminded health-care professional to respect the recommended dosages of ketamine and to limit exposure over time, and monitor liver function, renal function and urinary cytology closely if taken repeatedly or over prolonged time.

Reference:
Security information, ANSM, 30 August 2023 (link to the source within ansm.sante.fr)

Levothyroxine

Risk of vertigo

Saudi Arabia. The SFDA has released a safety signal concerning levothyroxine and risk of vertigo.

Oral levothyroxine is primarily indicated for treating primary, secondary, and tertiary hypothyroidism. Vertigo is an abnormal sensation of motion. It can occur in the absence of motion or when a motion is sensed inaccurately.

In 2023, the SFDA has detected a signal of levothyroxine and vertigo and reviewed all the evidence available on the association between them. The SFDA initiated this investigation following a local case-report of vertigo in SFDA vigilance database. The SFDA looked into VigiBase and found 12,678 ICSRs and extracted the top 30 global 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 levothyroxine (6 probable cases, 21 possible cases and 3 unlikely cases). Disproportionality analysis also provides positive relation between drug and adverse reaction. The information component tool shows positive statistical relationship IC=4.4.

The SFDA’s investigation concluded that the current
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<table>
<thead>
<tr>
<th>Available evidence from assessment of the ICSRs and disproportionality analysis might support a relationship between levothyroxine and vertigo. This signal needs further investigation to confirm the risk, and health-care professionals should be aware of this potential adverse reaction.</th>
</tr>
</thead>
</table>

**Medicines containing turmeric or curcumin**

#### Risk of liver injury

**Australia.** The Therapeutic Goods Administration (TGA) has advised consumers and health professionals that medicines and herbal supplements containing the herb Curcuma longa (turmeric) and/or curcumin may cause liver injury in rare cases. This risk also relates to other ingredients from the Curcuma species as they contain naturally occurring curcumin: Curcuma aromatica, Curcuma zanthorrhiza and Curcuma zedoaria.

Curcuma longa (turmeric) is a plant that has been used as a food spice for over 4,000 years, as well for medicinal purposes in traditional Indian (Ayurvedic) and Chinese medicines. Curcumin is a naturally occurring component in Curcuma longa (turmeric) and can be isolated and used as an active ingredient in medicines. Medicines and herbal supplements containing these Curcuma species and/or curcumin can be bought in supermarkets, health food shops and pharmacies without a prescription and without the advice of a health professional. There are over 600 listed medicines included in the Australian Register of Therapeutic Goods (ARTG) that contain these Curcuma species and/or curcumin.

The TGA has received 18 reports of liver problems experienced by consumers taking products containing Curcuma longa (turmeric) and/or curcumin up to 29 June 2023. Nine of these reports had enough information to suggest a liver injury that may have been caused by the Curcuma longa (turmeric) or curcumin product. Of these, in 4 cases there were no other ingredients likely to have contributed to the liver injury. Two of these cases were severe, including one that had a fatal outcome. The other 5 cases involved products that contained other ingredients that may have contributed to liver injury. In addition to these cases, there have been several Australian and overseas case reports in the scientific literature, and multiple cases reported to regulators in other countries.

The TGA has completed a safety investigation of the ingredients Curcuma longa (turmeric) and curcumin and the risk of liver injury. Available evidence shows that there is a rare risk of liver injury from taking Curcuma longa (turmeric) and/or curcumin in medicinal dosage forms. The risk may be higher for products with enhanced absorption or bioavailability and/or higher doses. People with existing or previous liver problems may be more likely to develop this rare adverse event. However, there is not enough information at this time to conclusively identify which medicines are higher risk. The TGA will continue to monitor this issue and is currently considering further regulatory action.

**Reference:**
Safety updates, TGA, 15 August 2023 ([link](https://www.tga.gov.au) to the source within [www.tga.gov.au](http://www.tga.gov.au))

### Methotrexate

#### Risk of photosensitivity reactions

**United Kingdom.** The MHRA has advised patients to take precautions when exposed to the sun to avoid photosensitivity reactions when taking methotrexate treatment. Photosensitivity reactions (which include phototoxicity, where a drug is activated by exposure to UV light and causes damage to the skin that can look and feel like a sunburn or a rash) can occur with both low-dose and high-dose treatment.
Methotrexate is an immunosuppressant medicine that is used to treat inflammatory conditions such as rheumatoid arthritis, psoriasis, and Crohn’s disease. It is also used as a cancer treatment.

Photosensitivity reactions are established side effects of methotrexate treatment and are currently listed in the product information, including the Patient Information Leaflet. However, the Pharmacovigilance Expert Advisory Group (PEAG) of the MHRA was concerned that it is not a well-known side effect and many patients may not be aware of the additional risks of sun exposure during methotrexate treatment. Prescribers and pharmacists are reminded to inform patients of the risk of photosensitivity reactions and to advise them to use a product with a high sun protection factor and clothing that covers the skin when in the sun.

The MHRA is working with Marketing Authorisation Holders of methotrexate medicines to provide updates to the product information as appropriate.

Reference:
Drug Safety Update, MHRA, 30 August 2023 (link to the source within www.gov.uk/mhra)

Pralsetinib

Increased risk for tuberculosis

Europe. The EMA is reminding health-care professionals by issuing a Direct Health-care Professional Communication (DHPC) that tuberculosis, mostly extrapulmonary, has been reported in patients receiving pralsetinib (Gavreto®), and patients should be evaluated for active and inactive (“latent”) tuberculosis before starting treatment as per local recommendations, and in patients with active or latent tuberculosis. Standard antymycobacterial therapy should be initiated before treatment with pralsetinib is started.

Pralsetinib in the European Union is indicated as monotherapy for the treatment of adult patients with rearranged during transfection (RET) fusion-positive advanced non-small cell lung cancer (NSCLC) not previously treated with a RET inhibitor.

An investigation of global safety data for Gavreto identified 9 cases of tuberculosis in pralsetinib treated patients, of which the majority (7/9) occurred in tuberculosis-endemic regions. The events occurred in patients with and without prior known history of tuberculosis. In most cases, extrapulmonary tuberculosis such as lymph node tuberculosis, peritoneal tuberculosis, or renal tuberculosis was reported.

Co-administration of pralsetinib with strong CYP3A4 inducers such as rifabutin, rifampicin can decrease pralsetinib plasma concentrations, which may decrease the efficacy of pralsetinib. Co-administration of pralsetinib with strong CYP3A4 inducers should be avoided. If co-administration cannot be avoided, it is important to increase the pralsetinib dose.

An update to the product information to include the risk of tuberculosis and recommendations for testing and treatment is ongoing.

Reference:
Direct healthcare professional communications, EMA, 16 June 2023 (link to the source within www.ema.europa.eu)

Progesterone

Risk of meningioma

Saudi Arabia. The SFDA has released a safety signal concerning progesterone and risk of meningioma.

Progesterone capsules are an oral dosage form of progesterone, which is chemically identical to Progesterone of ovarian origin. Meningiomas are the most common of benign intracranial tumours. Although the majority of meningiomas are benign, these tumours can grow slowly until they are very large, if left undiscovered, and, in some locations, can be severely disabling and life threatening.
In 2023, the SFDA has detected a signal of progesterone and meningioma and reviewed all the evidence available on an association between them. The SFDA looked into VigiBase and found 67 ICSRs and applied WHO-UMC causality assessment criteria on ICSRs with completeness score 0.8 and above (n=31). Among them, 26 cases of meningioma were possibly linked to progesterone. Data mining of this drug/ADR has been estimated using Information component (IC= 5.1), 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 might support a relationship between progesterone and meningioma. This signal needs further investigation to confirm the risk, and health-care professionals should be aware of this potential adverse reaction.

Reference:
Safety Alerts, SFDA, July 2023 (link to the source within www.sfda.gov.sa)

### Sulphadoxine and pyrimethamine

**Risk of toxic epidermal necrosis**

**Zimbabwe.** The Medicines Control Authority of Zimbabwe (MCAZ) has alerted health-care professionals on the risk of toxic epidermal necrosis with sulphadoxine and pyrimethamine.

Sulphadoxine and pyrimethamine tablets are indicated for the treatment of acute, uncomplicated P. falciparum malaria for those patients in whom chloroquine resistance is suspected and for intermittent prevention of malaria in pregnant women in the malaria-endemic Sub-Saharan region.

The MCAZ reminded health-care professionals that sulphadoxine and pyrimethamine must be discontinued at the first appearance of skin rash or an urticarial reaction, and should not be administered to women receiving cotrimoxazole prophylaxis (e.g. for opportunistic infections) due to an increased risk of adverse effects.

Reference:
Medicine Information Bulletin, MCAZ, August 2023 (link to the source within https://www.mcaz.co.zw)

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**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
A signal is defined by WHO as reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously. Usually more than a single report is required to generate a signal, depending on the seriousness of the event and the quality of the information. A signal is a hypothesis together with data and arguments and it is important to note that a signal is not only uncertain but also preliminary in nature.

The signals in this Newsletter are based on information derived from reports of suspected adverse drug reactions available in the WHO global database of individual case safety reports (ICSRs), VigiBase. The database contains over 36 million reports of suspected adverse drug reactions, submitted by National Pharmacovigilance Centres participating in the WHO Programme for International Drug Monitoring. VigiBase is maintained by the Uppsala Monitoring Centre (UMC) on behalf of WHO and periodic analysis of VigiBase data is performed in accordance with UMC’s current routine signal detection process. International pharmaceutical companies, when identified as uniquely responsible for the drug concerned, are invited to comment on the signal text. Signals are thereafter communicated to National Pharmacovigilance Centres, before being published in this Newsletter. Signal texts from UMC might be edited to some extent by WHO and may differ from the original version. More information regarding the ICSRs, their limitations and proper use, is provided in the UMC caveat document available at the end of Signal (page 32). For information on the UMC Measures of Disproportionate reporting please refer to WHO Pharmaceuticals Newsletter Issue No. 1, 2012.

UMC, a WHO Collaborating Centre, is an independent foundation and a centre for international service and scientific research within the field of pharmacovigilance. For more information, on the UMC Measures of Disproportionate Reporting etc., visit www.who-umc.org. To leave a comment regarding the signals in this Newsletter, please contact: the Uppsala Monitoring Centre, Box 1051, SE-751 40 Uppsala, Sweden. E-mail: signals@who-umc.org

A review of Delamanid and paediatric sleep disorders and hallucinations

Foreword

In October 2021, the WHO Advisory Committee on Safety of Medicinal Products (ACSoMP) discussed the signal of hallucinations in children treated with delamanid and recommended that the signal should be evaluated further with a specialist in childhood psychology and sleep disorders. The ACSoMP recommended that UMC in collaboration with other relevant experts should do an in-depth investigation. This report is an outcome of the evaluation by UMC, which was presented to the ACSoMP meeting in December 2022 for its discussion.

Summary

Tuberculosis (TB) is a global challenge for public health, including multidrug-resistant TB (MDR-TB) and rifampicin-resistant TB (RR-TB). Delamanid is indicated for the treatment of MDR-TB or RR-TB in adults and children (weighing at least three kilograms). According to the WHO recommendations on the treatment of drug resistant TB, delamanid may be included in the treatment of MDR/RR-TB in pediatric patients of all ages. VigiBase, the WHO global database of reported potential side effects of medicinal products, was utilized to analyse cases of sleep disorders and hallucinations in children and adolescents in combination with delamanid, following the recommendation from ACSoMP as described in the foreword. In total, 16 cases with an age range between 3 to 13 years old were identified and 15 (94%) of the cases were described as serious. Nine reports (56%) were part of a clinical trial. Eight cases (50%) received delamanid as prophylaxis and five (42%) received delamanid as treatment. Sleep disorders are common in children and difficult to distinguish from the side effects of medicines. In the analysed case series, the
Signal association between sleep disorders (but not isolated hallucinations) and the use of delamanid indicates a possible relationship.

Introduction

Tuberculosis (TB) is an infectious disease caused by Mycobacterium tuberculosis and can present clinically as either TB infection or TB disease. TB is a global health issue and a leading cause of infectious death with an estimated mortality in 2021 of 1.6 million. Further, of the worldwide estimated TB incidence of 10.6 million people, 11% occurred in children. Moreover, a decline in TB notifications was seen between 2019 and 2020 due to the COVID-19 pandemic.

TB is a global challenge for public health, including multidrug-resistant tuberculosis (MDR-TB). Between 25,000 and 32,000 children are estimated to develop MDR-TB annually. The mortality among children with MDR-TB has been estimated to be 21%.

Delamanid is a bicyclic nitroimidazole and a mycolytic acid biosynthesis inhibitor, and was initially approved by the European Medicines Agency (EMA) in 2014 for treatment of MDR-TB. Delamanid is indicated for treatment of MDR-TB or rifampicin-resistant TB (RR-TB) in adults and children weighing at least three kilograms. In the WHO recommendations on the treatment of drug resistant TB, delamanid may be included in treatment of MDR/RR-TB paediatric patients of all ages. Moreover, in a modelling study tuberculosis prophylaxis with delamanid for children younger than 15 years living with a person newly diagnosed with MDR-TB or RR-TB increased the effect in terms of reduced incidence and mortality compared with levofloxacin. (Delamanid use for prevention of MDR-TB is being researched in a clinical trial but not yet recommended by WHO.)

In May-June 2021 WHO convened a Guideline Development Group (GDG) meeting on the management of TB in children and adolescents. Among the data reviewed was information from the manufacturer (Otsuka Pharmaceuticals) on a safety signal of hallucinations and sleep disorders (night terrors or nightmares).

Hallucinations among children and adolescents are not uncommon and can be a developmentally healthy phenomenon or a psychopathology related phenomena. Night terrors or nightmares are also common in children. Detailed information on hallucinations and night terrors/nightmares in children and adolescents are described in the column below.

Following the identification of signal of hallucinations in children treated with delamanid and the recommendation from the WHO ACSoMP as referred in Foreword of this article, the cases of sleep disorders and hallucinations in children and adolescents in combination with delamanid in VigiBase, the WHO global database of reported potential side effects of medicinal products of medicinal products, are analysed here.

Clinical presence of hallucinations and night terrors/nightmares in children and adolescents

Generally, hallucinations are sensory perceptions that occur in the absence of an actual external stimulus, not corresponding to what is happening in reality. Even though hallucinations in young populations are mostly transient, they can cause substantial distress. Hallucinations may include visual, auditory, tactile, gustatory or olfactory perceptions. Hallucinations have been reported in children as young as 5 years old and are more commonly reported as transient, however become more associated with psychopathology during later adolescence.
Moreover, sleep related hallucinations which occur immediately before falling asleep (hypnagogic) and during the transition from sleep to waking up (hypnopompic) have been reported as a phenomenon in the general population. Hypnagogic hallucinations also commonly occur in patients with narcolepsy. Hypnopompic hallucinations, in particular, are usually visual and auditory perceptions that occur on awakening and in a state that falls somewhere between dreaming and being fully awake.

For most people they are considered normal and are not a cause for concern. They generally don’t indicate an underlying mental or physical illness, though they may be more common in people with certain sleep disorders. Ohayon et al. reported an overall prevalence of 12.5% and it was also shown that patients with insomnia and excessive daytime sleepiness were more likely to experience this kind of hallucinations. Hypnopompic hallucinations are frequently associated with narcolepsy and are included in the diagnostic criteria for the disorder, although they are only reported by 25–30% of narcoleptics and also occur in people who don’t have narcolepsy.

Night terrors or nightmares are also common in children, and sometimes it is difficult to distinguish between hypnopompic hallucinations and night terrors or nightmares that awaken the child in the middle of the night. Hypnopompic hallucinations differ from nightmares in that they happen as the individual is waking up in the morning, while nightmares tend to occur during rapid eye movement (REM) sleep.

Also, hypnopompic hallucinations usually consist of simple images, sounds, or sensations. Nightmares, on the other hand, tend to be more complex dreams with storylines. Hypnopompic hallucinations can occasionally be alarming, but they do not normally provoke strong emotions, their content is usually rather benign. For example, a hypnopompic hallucination might involve images that look similar to those you would see in a kaleidoscope, or background sounds like a ringing phone or doorbell. While the frightening feeling of nightmares might linger, people usually forget about hypnopompic hallucinations quickly.

Sometimes, sleep-related hallucinations present as complex nocturnal visual hallucinations, occurring after full awakening (in wakefulness after arousal from sleep), without remembering a specific dream, and perceiving complex vivid visual images (multicolour), usually of people or animals, that are relatively immobile and may be distorted. Although patients realize that they are awake, the hallucinations can be very frightening. Sleep-related hallucinations are difficult to differentiate from sleep-onset or sleep-termination dreaming.

Many children have nightmares and night terrors, and although most grow out of them, they can be experienced in adulthood. Night terrors and nightmares are different and happen at different stages of sleep. During a night terror the person may talk and move about but is asleep; it is rare to remember having a night terror. Nightmares are bad dreams that wake the person up and can be remembered. Night terrors are most common in children between the ages of 3 and 8, while nightmares can affect both children and adults. An overview of several differential diagnoses for parasomnias are shown in Table S1.

Methods

VigiBase search

Using MedDRA, within the System Organ Class of “Psychiatric disorders”, the higher level group term (HLGT) “Sleep disorders and disturbances”, and the higher level term (HLT) “Hallucinations (excluding sleep-
related)" were identified as search terms to identify reports. The reporting of these terms combined are referred to as “sleep disorders and hallucinations” hereinafter.

A search of VigiBase, the WHO global database of reported suspected adverse reactions of medicinal products, was performed on 29 August 2022, the inclusion criteria of the search being delamanid marked as a suspected or interacting medication and “sleep disorders and hallucinations” as the adverse reaction. The reports in “sleep disorders and hallucinations” were reviewed by their respective HLT and HLGT as well. To identify paediatric cases, a criterion of patient age being 17 years or younger was applied to the search before in-depth clinical review.

Time to onset (TTO) of symptoms was calculated from the information available, and where more than one date was given for the TTO the earliest date was used. For the duration of symptoms and length of time to positive dechallenge, the latest date reported was used in the calculations.

Disproportionality

Disproportionality calculations of reported preferred terms (PTs) using IC analysis were performed without restriction by patient age. The $IC_{0.025}$ is the lower end of the 95% credibility interval and a positive $IC_{0.025}$ represents positive statistically significant disproportionate reporting. Further analysis after stratification by age was undertaken to study the paediatric population, here the $IC_{0.0005}$ is calculated, showing the lower end of the 99% credibility interval, to indicate statistical significance. Disproportionality was also calculated for the HLGT “Sleep disorders and disturbances” and the HLT “Hallucinations (excluding sleep-related)" and their respective PTs.

De-duplication

Prior to the search and disproportionality calculations, automated de-duplication was applied using vigiMatch. Further manual de-duplication was performed during in-depth clinical review, although no further duplicates were identified.

Results

Summary of reported cases regarding children and adolescents

A total of 16 reports were identified where patient age ranged from 3 to 13 years, as shown in Figure 1, and most were female ($n=13$, 81%). Time to onset was available in all cases, with a median of 7.5 days (interquartile range, 2.5 to 11.5 days). Symptom duration was available in 10 cases, with a median of 13.5 days (interquartile range, three to 26 days). Case narratives were available in all cases, although the level of information varied greatly between individual cases. Nine cases (56%) were part of a clinical trial. Eight patients (50%) received delamanid as prophylaxis, and five (42%) received delamanid as treatment, as displayed in Figure 2, in combination with body weight. Summarized case information is shown in Table 4.

Disproportionality

Based on the overall reporting of adverse reactions for delamanid and of the adverse reactions of sleep disorders and hallucinations in VigiBase, there were 56 cases in all age groups; the expected number of reports on the combination was 43, but the association was not statistically significant ($IC_{0.025} = -0.02$).

When stratified by age (see Table 1), the age group of 2 to 11-year-olds was positively disproportionately reported with statistical significance (14 observed reports and one expected report). In the other patient age-group of interest with 12 to 17-year-olds, there were two observed and two expected reports.

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However, in general, the numbers in each age group were small and this can increase uncertainty in interpreting the results of disproportionality calculations. A breakdown of the HLGT “Sleep disorders and disturbances”, HLT “Hallucinations (excluding sleep-related)”, and their respective terms are shown in Table 2 and 3, respectively. Regarding the HLGT of “Sleep disorders and disturbances” (Table 2) the PTs “Insomnia”, “Sleep disorder” and “Hypnopompic hallucination” were disproportionally reported with statistical significance, with more observed cases than expected. However, the PT of “Hypnopompic hallucination” is a rather specific entity and may thus generate a higher disproportionality rate due to lower reporting rates of that specific term. There was no reporting of the PT “Sleep Terror”, which includes the lower level term of “Night terrors”. For the HLT of “Hallucinations (excluding sleep-related)” there was a positive disproportionality reported with 13 observed cases and six expected (see Table 3), however none of the PTs were disproportionately reported.

In-depth clinical review is provided in the following sections concerning the 16 reports identified where patient age ranged from 3 to 13 years.

**Reported terms**

The most common MedDRA PT terms reported under the umbrella term “sleep disorders and hallucinations” were:

- “Hypnopompic hallucinations” and “Hallucinations” (both n=5)
- “Insomnia” (n=4)
- “Sleep disorder” (n=3)
- “Hallucination, visual” (n=2)
- “Abnormal dreams”, “Poor quality sleep”, “Hallucination, auditory” and “Hallucination, mixed” (all n=1)

**Seriousness**

There were 15 cases described as serious (94%), 13 of which had the seriousness criteria of “Other medically important condition” and two “Caused/prolonged hospitalization”. Some examples of serious reactions noted in the narratives were children described as waking up in the night or early morning having visual or auditory hallucinations and subsequent problems going back to sleep. A case narrative described an 11-year-old child (case 3, Table 4) who experienced hypnopompic auditory and visual hallucinations of mild intensity starting the same night as the first dose of delamanid. After one week of delamanid they reported vivid nightmares and visual, auditory and tactile hallucinations occurring between 00:00 and 05:00 which made them scared to go back to sleep. The hallucinations stopped three days after delamanid, which affected her subsequent sleep and behaviour in the daytime. These symptoms waned over a week after discontinuation of delamanid.

Another case (case 9, Table 4) described a 7-year-old male child without co-morbidities who experienced vivid reams and visual withholding delamanid. A 13-year-old female (case 8, Table 4) experienced hypnopompic visual and auditory hallucinations, seeing children and hearing them cursing at her, starting 15 days after initiating hallucinations, headache and insomnia starting after eight days of delamanid, with the child waking up for several minutes to an hour. Since changing the schedule of delamanid upon restarting from 12:00 till 16:00 there was no reported recurrence of hallucinations. One 9-year-old female (case 4, Table 4) refused to continue with delamanid after hypnopompic auditory hallucinations and loss of sleep due to fear of doing poorly in school. One seven-year-old female (case 7, Table 4) was described as experiencing insomnia, agitation, anxiety and visual hallucinations at an unknown time of the day and trying to jump out of a closed
window and required calming by her mother.

**Indication**

In half the cases (n=8), it was stated that the indication for delamanid was tuberculosis prophylaxis (which is outside the current WHO recommendation and being researched). Of these eight cases, it was the sole reported medication in six and the other two reported the use of ascorbic acid and zinc combined. Case information where prophylaxis was the indication tended to be more complete than other cases.

In the other eight cases, five were marked with the indication for treatment of tuberculosis, and there was no indication in the other three. All eight of these noted concomitant use of other anti-tuberculosis medication. Six of them mentioned concomitant use of another medicine that has the corresponding reported term listed as an adverse event (cases 6, 12, 13, 14, 15 and 16). The concomitant medications reported with terms related to "sleep disorders and hallucinations" include levofloxacin (insomnia and psychotic symptoms), linezolid (insomnia), cycloserine (psychosis and somnolence), terizidone (psychosis and somnolence), ethambutol (hallucinations), and ethionamide (hallucinations).

**Posology**

The daily dose reported was consistent whether delamanid was used prophylactically or for treatment.

In total, five cases reported the time of day the dose was taken (10:00, 11:00, 11:00, 12:00, 13:00).

In all the cases where a dose time was given, they reported sleep-related hallucinations. One patient (case 3, Table 4) was reported to take delamanid at 11:00 and experienced auditory, visual and tactile hallucinations and nightmares from the day of commencement, approximately five to six hours after consumption. They subsequently changed the time to 18:45 with a continuation of symptoms. In this case, after discontinuation of delamanid there was a positive dechallenge. Another patient (case 9, Table 4) changed the timing of their dose, withholding the drug after three days of visual hallucinations in the hour after waking. They restarted seven days later and took the medicine later in the day (16:00 rather than 12:00). After the discontinuation and subsequent restart, the patient did not experience further symptoms. Another patient (case 9, Table 4) reported that after withholding delamanid the symptoms resolved four days after discontinuation and following a review by a paediatric psychiatrist, delamanid was reinitiated to be taken at 18:00 each day, without a reoccurrence of symptoms. The initial time at which delamanid was taken in this patient was not noted.

**Dechallenge/Rechallenge**

Nine cases reported a dechallenge period (observation of response to withdrawal of the medicine), all of which were positive, with eight of them taking delamanid prophylactically and one taking it as treatment for MDR-TB. The median time to resolution of symptoms following withdrawal of delamanid was four days, with an interquartile range of 0 to seven days.

Two cases reported a rechallenge period (observation of response to re-administration of the medicine after withdrawal), and both were negative, with no reoccurrence of symptoms. The medication was reintroduced seven days after initial withdrawal in both cases, with the time from last event to restart being three and seven days.

In one case (case 15, Table 4), the patient had been on levofloxacin and terizidone for 62 days prior to the addition of delamanid for the treatment of MDR-TB. Four days after adding delamanid the patient began
experiencing visual hallucinations, mainly at night-time, but also during the day. The episodes were described as lasting between five minutes and two hours. The hallucinations continued for 55 days despite the withdrawal of terizidone, nine days after the onset of symptoms, and eventually subsided 18 days after the withdrawal of levofloxacin, with delamanid continued.

Discussion

In the analysed case series, there were 16 observed cases of paediatric “sleep disorders and hallucinations” in association with the use of delamanid. No obvious difference was observed in case demographics and characteristics in the case series when stratified by indication, although the limited case series size did not prohibit any statistical calculation of any differences. There was also limited reporting of the timing of consumption, although no obvious pattern was observed regarding increased or decreased risk with use at different times.

There were 14 cases with a sleep-related disorder and similarly 14 cases reported hallucinations, with nine of these noting sleep-related hallucinations. All cases, bar one, were marked as a serious adverse event.

The median duration of symptoms was 13.5 days, but there was a large variability with an interquartile range of three to 26 days, with the longest duration being 55 days. A meta-analysis published in 2016 stated that adverse events were higher for MDR-TB patients than that of drug-susceptible TB. Psychiatric disorders were a particular cause for concern, with 13.2% of cases experiencing psychiatric adverse events, although this may be multi-factorial, and given the timing of the publication the role of delamanid in this review is unknown.28 Another consideration is that hallucinations are not uncommon in children and adolescents and can be a developmentally healthy phenomenon or a psychopathology related phenomenon. Given the consequences for children and adolescents of sleep disorders and hallucinations – such as poor sleep patterns affecting quality of life and daily activities – it is important to follow up on this topic. However, it is also important to keep in mind the impacts of inadequate MDR-TB treatment, and the changing landscape of TB treatment in children29.

In general, where adequate information is available, these cases can be described as parasomnias. An adequate diagnosis requires, and is not limited to, knowing at what time of night the individual wakes up, a sufficient description of their behaviour at those moments, the degree of autonomic activation, the presence or absence of confusion, and the degree of memory of the dream content. In the usual clinical setting, the parasomnia refers to “undesirable physical events or experiences that occur during entry to sleep, within sleep, or during arousals from sleep”30. One main issue is the classification of cases and whether they should be reported as hypnopompic hallucinations (not categorized in the ICD-10), or as nightmares (ICD-10 F51.5) or sleep terrors (ICD-10 F51.4) with vivid awakenings. The information available in the reports is sufficient to question the sole diagnoses of hypnopompic hallucinations, and it is not clear that any of them should be exclusively classified as such. Hypnopompic hallucinations are symptoms that could be isolated or present in the context of the clinical frame of night terrors or nightmares. In these cases, there are nightmares and/or night terrors that may be associated with the presence of this perceptual disorder (hypnopompic hallucinations). There were nine cases with a positive...
dechallenge, in both patients undergoing treatment and in prophylaxis of tuberculosis. After dechallenge, the median time to resolution of symptoms was four days. This is consistent with the known pharmacokinetics of delamanid in paediatric populations, which are comparable to that of adults, with a half-life of 30 to 38 hours reported\(^6\). Similarly, the median TTO of 7.5 days is plausible, and the TTO noted in these cases are reasonably consistent with most cases reported within the first two weeks of treatment. Interestingly, there were also two documented rechallenges of delamanid. In both cases, resumption was seven days after initial withdrawal and no recurrence was noted, although the follow up post reintroduction was not reported.

Ten cases in the series noted concomitant medications, with most of these for patients with an indication for treatment of tuberculosis, or where the indication was unknown. In six of these cases, the concomitant medications commonly had “sleep disorders and hallucinations” related terms in their SmPC. Whilst the use of concomitants complicates the assessment of these cases, there are also reports of prophylactic use in patients, who took no concomitant medications as another potential causative factor.

**Literature/Labelling**

Sleep disorders and hallucinations were newly added in the Summary of product characteristics (SmPC) for delamanid during the period of this evaluation\(^6\). In the system organ class psychiatric disorders “Sleep disorders and disturbances” including insomnia is listed as frequency very common and “Hallucination” is listed as frequency common. The reported adverse events in a paediatric population are expected to be the same as that of adults\(^31\). However, in the age-stratified disproportionality analysis of “sleep disorders and hallucinations” shown here, the only age group that showed statistically significant positive disproportionate reporting was 2 to 11 years old, and these comprised the majority of the reports in the case series. Similarly, the reported incidence of hallucination has been reported to be 5.4% of paediatric patients, compared to the 1% incidence seen in adults. Furthermore, in this case series, a high number of reports were from clinical studies, which may have caused stimulated reporting that can impact disproportionality calculations.

**Conclusion**

Sleep disorders are common in children and difficult to distinguish from the side effects of medicines. However, the association between sleep disorders (but not isolated hallucinations) and the use of delamanid indicates a possible relationship, supported by dechallenges, although rechallenges were negative. Disproportionality calculations highlight the 2 to 11-year age group, but interpretation of the disproportionality should be done cautiously with consideration of factors such as concomitant medications, background incidence and stimulated reporting.

**Acknowledgements**

We would like to thank Professors Emilio Sanz and Carlos de las Cuevas Castresana for their hard work and valuable expert input.

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Table 1. Disproportionality analysis of sleep disorders and hallucinations in association with delamanid, in VigiBase as of 29/08/2022, stratified by age

<table>
<thead>
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<th>Patient age</th>
<th>Observed cases</th>
<th>Expected cases*</th>
<th>IC_{9005}</th>
<th>IC</th>
</tr>
</thead>
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<td>1</td>
<td>1.4</td>
<td>2.9</td>
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<td>2</td>
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</tr>
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<td>24</td>
<td>-0.8</td>
<td>0.2</td>
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<td>10</td>
<td>-2.1</td>
<td>-0.2</td>
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<td>65–74 years</td>
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<td>2</td>
<td>-8.2</td>
<td>-0.6</td>
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<td>≥ 75 years</td>
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<td>-4.5</td>
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<tr>
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<td>4</td>
<td>-9.0</td>
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*The number expected is calculated based on the number of reports for the overall reporting for the Preferred Term and medication compared to all reports in VigiBase.

Table 2. Disproportionality analysis of the HLGT “Sleep disorders and disturbances” and the PTs it contains, in association with delamanid, in VigiBase as of 29/08/2022

<table>
<thead>
<tr>
<th>MedDRA Term</th>
<th>Observed cases</th>
<th>Expected cases*</th>
<th>IC_{9005}</th>
<th>IC</th>
</tr>
</thead>
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<td>Higher Level Group Term</td>
<td>Sleep disorders and disturbances</td>
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<td>Preferred Term</td>
<td>Insomnia</td>
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<td>14</td>
<td>0.2</td>
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<td></td>
<td>Sleep disorder</td>
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<td>4</td>
<td>0.0</td>
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<tr>
<td></td>
<td>Somnolence</td>
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<td>14</td>
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<td>Hypnopompic hallucination</td>
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<td>1.9</td>
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<td></td>
<td>Nightmare</td>
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<td>2</td>
<td>-2.5</td>
</tr>
<tr>
<td></td>
<td>Abnormal dreams</td>
<td>1</td>
<td>1</td>
<td>-4.1</td>
</tr>
<tr>
<td></td>
<td>Poor quality sleep</td>
<td>1</td>
<td>1</td>
<td>-3.7</td>
</tr>
<tr>
<td></td>
<td>Sopor</td>
<td>1</td>
<td>0</td>
<td>-2.9</td>
</tr>
</tbody>
</table>

*The number expected is calculated based on the number of reports for the overall reporting for the Preferred Term and medication compared to all reports in VigiBase.
Table 3. Disproportionality analysis of the HLT “Hallucinations (excluding sleep-related)” and the PTs it contains, in association with delamanid, in VigiBase as of 29/08/2022

<table>
<thead>
<tr>
<th>MedDRA Term</th>
<th>Observed cases</th>
<th>Expected cases*</th>
<th>IC\textsubscript{000}</th>
<th>IC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Higher Level Term</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hallucinations</td>
<td>13</td>
<td>6</td>
<td>0.3</td>
<td>1.2</td>
</tr>
<tr>
<td>(excluding sleep-related)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preferred Term</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hallucination</td>
<td>5</td>
<td>4</td>
<td>-1.1</td>
<td>0.3</td>
</tr>
<tr>
<td>Hallucination, auditory</td>
<td>3</td>
<td>1</td>
<td>-0.2</td>
<td>1.8</td>
</tr>
<tr>
<td>Hallucination, visual</td>
<td>3</td>
<td>1</td>
<td>-0.6</td>
<td>1.5</td>
</tr>
<tr>
<td>Formication</td>
<td>2</td>
<td>1</td>
<td>-1.4</td>
<td>1.2</td>
</tr>
<tr>
<td>Hallucinations, mixed</td>
<td>1</td>
<td>0</td>
<td>-2.5</td>
<td>1.3</td>
</tr>
</tbody>
</table>

*The number expected is calculated based on the number of reports for the overall reporting for the Preferred Term and medication compared to all reports in VigiBase.

Figure 1. Number of paediatric cases, by age and treatment indication, of “sleep disorders and hallucinations” in combination with delamanid in VigiBase, as of 29/08/22
Figure 2. Daily dose of delamanid, by weight and treatment indication, of “sleep disorders and hallucinations” in combination with delamanid in VigiBase, as of 29/08/22.

Figure 3. Daily dose of delamanid, by weight in those reporting sleep disorders and/or hallucinations, in combination with delamanid in VigiBase, as of 29/08/22.
<table>
<thead>
<tr>
<th>Case</th>
<th>Age/Sex</th>
<th>Suspected (S) or concomitant (C) drugs</th>
<th>Daily dose (mg)</th>
<th>Use</th>
<th>Reactions (MedDRA preferred terms)</th>
<th>Time to onset (days)</th>
<th>Symptom duration (days)</th>
<th>Dechallenge/ Rechallenge</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4/F</td>
<td>Delamanid (S), Ascorbic acid/ Zinc (C)</td>
<td>50</td>
<td>Prophylaxis</td>
<td>Hypnopompic hallucination</td>
<td>1</td>
<td>3</td>
<td>Positive dechallenge</td>
<td>Recovered</td>
</tr>
<tr>
<td>2</td>
<td>6/M</td>
<td>Delamanid (S)</td>
<td>50</td>
<td>Prophylaxis</td>
<td>Hypnopompic hallucination, Sleep deficit</td>
<td>9</td>
<td>6 – hypnopompic hallucinations and 14 sleep deficit</td>
<td>Positive dechallenge/ Negative rechallenge</td>
<td>Recovered</td>
</tr>
<tr>
<td>3</td>
<td>11/F</td>
<td>Delamanid (S)</td>
<td>150</td>
<td>Prophylaxis</td>
<td>Hallucination</td>
<td>0</td>
<td>26</td>
<td>Positive dechallenge</td>
<td>Recovered</td>
</tr>
<tr>
<td>4</td>
<td>9/F</td>
<td>Delamanid (S)</td>
<td>100</td>
<td>Prophylaxis</td>
<td>Hypnopompic hallucination, Insomnia</td>
<td>2</td>
<td>8 – hypnopompic hallucinations and 13 – insomnia</td>
<td>Positive dechallenge</td>
<td>Recovered</td>
</tr>
<tr>
<td>5</td>
<td>6/F</td>
<td>Delamanid (S)</td>
<td>100</td>
<td>Prophylaxis</td>
<td>Hypnopompic hallucination</td>
<td>19*</td>
<td>26</td>
<td>Positive dechallenge</td>
<td>Recovered</td>
</tr>
<tr>
<td>6</td>
<td>5/F</td>
<td>Delamanid (S), Levofloxacin, Linezolid and Clofazemine (all C)</td>
<td>50</td>
<td>Treatment</td>
<td>Sleep disorder</td>
<td>8</td>
<td>-</td>
<td>-</td>
<td>Recovered</td>
</tr>
<tr>
<td>7</td>
<td>7/F</td>
<td>Delamanid (S)</td>
<td>100</td>
<td>Prophylaxis</td>
<td>Abnormal behaviour, Hallucination, visual, Agitation, Insomnia, Anxiety, Wrong technique in product usage process</td>
<td>3</td>
<td>-</td>
<td>Positive dechallenge</td>
<td>Recovered</td>
</tr>
<tr>
<td>8</td>
<td>13/F</td>
<td>Delamanid (S)</td>
<td>200</td>
<td>Prophylaxis</td>
<td>Hallucination, auditory</td>
<td>14</td>
<td>25</td>
<td>Positive dechallenge</td>
<td>Recovered</td>
</tr>
<tr>
<td>9</td>
<td>7/M</td>
<td>Delamanid (S), Ascorbic acid/ Zinc (C)</td>
<td>100</td>
<td>Prophylaxis</td>
<td>Hallucination, visual, Abnormal dreams, Poor quality sleep, Insomnia, Headache</td>
<td>8</td>
<td>3</td>
<td>Positive dechallenge/ Negative rechallenge</td>
<td>Recovered</td>
</tr>
<tr>
<td>No.</td>
<td>Gender</td>
<td>Medications</td>
<td>Dose (mg)</td>
<td>Duration</td>
<td>MedDRA PTs</td>
<td>Days</td>
<td>Outcome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----</td>
<td>--------</td>
<td>-------------------------------------------------------</td>
<td>-----------</td>
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<td>------------</td>
<td>------</td>
<td>---------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>3/F</td>
<td>Delamanid (S), Bedaquiline fumarate (S)</td>
<td>100</td>
<td>-</td>
<td>Hallucination, Sleep disorder, Nervousness</td>
<td>125</td>
<td>-</td>
<td>Recovering</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>5/F</td>
<td>Delamanid (S), Bedaquiline fumarate, Clofazimine (both C)</td>
<td>25</td>
<td>-</td>
<td>Sleep disorder, Fear, Hallucination</td>
<td>7</td>
<td>-</td>
<td>Recovered</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>7/F</td>
<td>Delamanid (S), Clofazimine, Linezolid, Bedaquiline (all C)</td>
<td>100</td>
<td>-</td>
<td>Hallucination</td>
<td>8</td>
<td>-</td>
<td>Recovered</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>4/M</td>
<td>Delamanid (S), Bedaquiline (S), Clofazimine (S), Cycloserine (S) and Linezolid (S)</td>
<td>100+</td>
<td>Treatment</td>
<td>Product use issue, Insomnia</td>
<td>0</td>
<td>-</td>
<td>Recovered</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>13/F</td>
<td>Delamanid (S), Clofazimine (S), Cycloserine (S) and Linezolid (S)</td>
<td>200</td>
<td>Treatment</td>
<td>Hypnopompic hallucination, Fear, Product use issue, Headache, Nausea</td>
<td>45</td>
<td>2</td>
<td>Recovered</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>3/F</td>
<td>Delamanid (S), Levofloxacin (S), Terizidone (S), Ethambutol, Ethionamide, Aminosalicylic acid, Pyrazinamide, Lidocaine/ Prilocaine, Heparin, Iron (all C)</td>
<td>50</td>
<td>Treatment</td>
<td>Hallucination</td>
<td>4</td>
<td>55</td>
<td>Recovered</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>9/F</td>
<td>Delamanid (S), Pyrazinamide, Ethambutol, Amoxicillin trihydrate/ Clavulanate potassium (all C)</td>
<td>100</td>
<td>Treatment</td>
<td>Hallucinations, mixed</td>
<td>3</td>
<td>7</td>
<td>Positive dechallenge</td>
<td>Recovered</td>
</tr>
</tbody>
</table>

*Initiated treatment 19 days before symptoms, but withheld treatment for 9 days after the second day before restating 7 days before symptoms.

*States dose was reduced to 50 mg per day, but timeline unclear.

MedDRA PTs included in the search for “sleep disorders and hallucinations” are shown in bold.
### Table S1. Overview of differential diagnoses of parasomnias

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Nightmares</th>
<th>Sleep terrors</th>
<th>Sleep related hallucinations</th>
<th>Sleepwalking</th>
<th>Confusional arousal</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Usual sleep stage</strong></td>
<td>REM &gt;&gt; NREM</td>
<td>NREM</td>
<td>Hyponagogic – at sleep onset</td>
<td>NREM</td>
<td>NREM</td>
</tr>
<tr>
<td><strong>Time of night</strong></td>
<td>Late &gt; early</td>
<td>Children – early Adults – early or late</td>
<td>Hypnopompic – on awakening Children – early Adults – early or late</td>
<td>Children – early Adults – early or late</td>
<td></td>
</tr>
<tr>
<td><strong>Sleep stage at start</strong></td>
<td>REM</td>
<td>Children – stage N3 Adults – stages N2 or N3</td>
<td>Complex – after full awakening Children – stage N3 Adults – stages N2 or N3</td>
<td>Children – stage N3 Adults – stages N2 or N3</td>
<td></td>
</tr>
<tr>
<td><strong>Screams</strong></td>
<td>Rare, talking more common</td>
<td>Yes</td>
<td>No – hyponagogic or hypnopompic Yes – complex nocturnal visual hallucinations</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Autonomic activation</strong></td>
<td>Mild</td>
<td>Extreme</td>
<td>No – hyponagogic or hypnopompic Could be – complex nocturnal visual hallucinations</td>
<td>Unusual</td>
<td>Unusual</td>
</tr>
<tr>
<td><strong>Walking</strong></td>
<td>No</td>
<td>No</td>
<td>Could be</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Confusion after episode on awakening</strong></td>
<td>Rare</td>
<td>Usual</td>
<td>Rare</td>
<td>Usual</td>
<td>Usual</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>Child – common Adult – less common</td>
<td>Any age</td>
<td>Child – common Adult – less common</td>
<td>Child – common Adult – less common</td>
<td>Child – common Adult – less common</td>
</tr>
</tbody>
</table>
### Diagnostic criteria

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A.</strong> Recurrent episodes of awakenings from sleep with recall of intensely disturbing dream mentation, usually involving fear or anxiety, but also anger, sadness, disgust, and other dysphoric emotions.</td>
<td><strong>A.</strong> Sudden episode of terror occurs during sleep, usually initiated by a cry or loud scream that is accompanied by autonomic nervous system activation and behavioural manifestations of intense fear.</td>
</tr>
<tr>
<td><strong>B.</strong> Full alertness or awakening, with little confusion or disorientation; recall of sleep mentation is immediate and clear.</td>
<td><strong>B.</strong> At least one of the following is present:</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>C.</strong> At least one of the following associated features is present:</td>
<td><strong>i.</strong> Delayed return to sleep after the episode.</td>
</tr>
<tr>
<td></td>
<td><strong>ii.</strong> Occurrence of episodes in the latter half of the habitual sleep period.</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>A.</strong> The patient experiences hallucinations just prior to sleep onset (hypnagogic) or on awakening during the night or in the morning (hypnopompic).</td>
<td><strong>B.</strong> Persistence of sleep, an altered state of consciousness, or impaired judgment during ambulation is demonstrated by at least one of the following:</td>
</tr>
<tr>
<td><strong>B.</strong> Hallucinations are primarily visual.</td>
<td></td>
</tr>
<tr>
<td><strong>C.</strong> The disturbance is not better explained by another sleep disorder, medical or neurologic disorder, mental disorder, medication use, or substance use disorder.</td>
<td><strong>i.</strong> Difficulty in arousing the person.</td>
</tr>
<tr>
<td><strong>i.</strong> Note: Hypnagogic or hypnopompic hallucinations may be difficult to differentiate from sleep-onset or sleep-termination dreaming. Complex nocturnal visual hallucinations may clearly occur in wakefulness following arousal from sleep.</td>
<td><strong>ii.</strong> Mental confusion when awakened from an episode.</td>
</tr>
<tr>
<td><strong>A.</strong> Ambulation occurs during sleep.</td>
<td></td>
</tr>
<tr>
<td><strong>B.</strong> Routine behaviours that occur at inappropriate times.</td>
<td><strong>iii.</strong> Amnesia (complete or partial) for the episode.</td>
</tr>
<tr>
<td><strong>B.</strong> Persistence of sleep, an altered state of consciousness, or impaired judgment during ambulation is demonstrated by at least one of the following:</td>
<td><strong>iv.</strong> Inappropriate or nonsensical behaviours.</td>
</tr>
<tr>
<td><strong>i.</strong> Difficulty in arousing the person.</td>
<td><strong>vi.</strong> Dangerous or potentially dangerous behaviours.</td>
</tr>
<tr>
<td><strong>ii.</strong> Mental confusion when awakened from an episode.</td>
<td><strong>C.</strong> The disturbance is not better explained by another sleep disorder, medical or neurologic disorder, mental disorder, or substance use disorder.</td>
</tr>
</tbody>
</table>

**Abbreviations:** REM – Rapid Eye Movement; NREM – Non-Rapid Eye Movement (divided into three stages; N1, N2 and N3)
CAVEAT DOCUMENT

Statement of reservations, limitations and conditions relating to data released from VigiBase, the WHO global database of individual case safety reports (ICSRs).

Understanding and accepting the content of this document are formal conditions for the use of VigiBase data.

Uppsala Monitoring Centre (UMC) in its role as the World Health Organization (WHO) Collaborating Centre for International Drug Monitoring receives reports of suspected adverse reactions to medicinal products from National Centres in countries participating in the WHO Programme for International Drug Monitoring. The information is stored in VigiBase, the WHO global database of individual case safety reports (ICSRs). It is important to understand the limitations and qualifications that apply to this information and its use.

Tentative and variable nature of the data
Uncertainty: The reports submitted to UMC generally describe no more than suspicions which have arisen from observation of an unexpected or unwanted event. In most instances it cannot be proven that a specific medicinal product is the cause of an event, rather than, for example, underlying illness or other concomitant medication.

Variability of source: Reports submitted to national centres come from both regulated and voluntary sources. Practice varies: some national centres accept reports only from medical practitioners; others from a broader range of reporters, including patients, some include reports from pharmaceutical companies.

Contingent influences: The volume of reports for a particular medicinal product may be influenced by the extent of use of the product, publicity, the nature of the adverse effects and other factors.

No prevalence data: No information is provided on the number of patients exposed to the product, and only a small part of the reactions occurring are reported.

Time to VigiBase: Some national centres make an assessment of the likelihood that a medicinal product caused the suspected reaction, while others do not. Time from receipt of an ICSR by a national centre until submission to UMC varies from country to country. Information obtained from UMC may therefore differ from that obtained directly from national centres.

For these reasons, interpretations of adverse effect data, and particularly those based on comparisons between medicinal products, may be misleading. The data comes from a variety of sources and the likelihood of a causal relationship varies across reports. Any use of VigiBase data must take these significant variables into account.

Prohibited use of VigiBase Data includes, but is not limited to:
- patient identification or patient targeting
- identification, profiling or targeting of general practitioners or practice

Any publication, in whole or in part, of information obtained from VigiBase must include a statement:

(i) recording ‘VigiBase, the WHO global database of individual case safety reports (ICSRs)’ as the source of the information
(ii) explaining that the information comes from a variety of sources, and the probability that the suspected adverse effect is drug-related is not the same in all cases
(iii) affirming that the information does not represent the opinion of the UMC or the World Health Organization.

Omission of this statement may exclude the responsible person or organization from receiving further information from VigiBase.

UMC may, in its sole discretion, provide further instructions to the user, responsible person and/or organization in addition to those specified in this statement and the user, responsible person and/or organization undertakes to comply with all such instructions.

Uppsala Monitoring Centre (UMC)
Box 1051, SE-751 40 Uppsala, Sweden
Tel: +46-18-65 60 60, E-mail: info@who-umc.org
www.who-umc.org
Established in 1968, the WHO Programme for International Drug Monitoring (PIDM) provides a global platform for the WHO Member States and the territories and areas, to exchange safety and regulatory information on all medicines and vaccines. In 1992, Morocco was one of the first African countries to join the WHO-PIDM. Since 2011, the Centre Anti Poison et de Pharmacovigilance du Maroc (CAPM) in Rabat, Morocco has been appointed as a WHO Collaborating Centre (WHO CC) for Strengthening Pharmacovigilance Practices.

Pharmacovigilance (PV) has had significant progress in Africa, and currently 44 full members and 5 associate members are recognized in the WHO PIDM as of November 2022 in Africa (called the PIDM members in Africa hereafter). The members are under the jurisdiction of either the WHO Regional Office for Africa (AFRO) or the WHO Regional Office for the Eastern Mediterranean (EMRO). The progress has been made thanks to the country’s commitment supported by the WHO, the WHO CCs and core partners with specific innovative approaches for PV strengthening.

The COVID-19 pandemic has imposed significant challenges to PV systems, especially since countries are having to use COVID-19 vaccines (and later, therapeutics) for which there is not enough safety data. The challenges have been more pronounced in the low and middle-income countries (LMICs). While the pandemic has been impacting on public health and economy, it also presented opportunities where core partners could initiate and develop innovative approaches and tools to strengthen PV systems.

The Pharmacovigilance Meeting of the Members of the WHO PIDM and Partners in Africa was held from 2 to 3 March 2023, in Rabat, Morocco. This meeting was hosted by the CAPM.

The objective of the meeting was to bring together stakeholders and key partners to understand the efforts made to support Africa in strengthening PV and how these efforts are being sustained. The meeting aimed to highlight the power of partnership and build bridges between partners to collaborate and leverage efforts done for an efficient, sustainable, and strengthening PV system in Africa. The meeting also aimed to showcase innovative approaches, methods, and tools proposed by key partners during the COVID-19 pandemic to strengthen PV systems and their impact, and how these are placed in routine pharmacovigilance.

One of the most important outcomes from this meeting was the formation of recommendations which would shape the future of PV. Recommendations were made by delegates through group work. The meeting included five working groups (WGs) that discussed various issues in PV. The summary of discussions and the recommendations are described in this article.

**WG 1: PV training**

During this workshop, participants discussed the main challenges existing in the pharmacovigilance training as well as the key attributes to make a training successful.
Pharmacovigilance trainings face several challenges that need to be addressed to improve their effectiveness. One of the main issues is that there are numerous training courses which are not very visible and recognized, making it difficult for trainees to identify the most suitable courses for their needs.

Additionally, the lack of a PV training course available in Portuguese is a significant challenge for Portuguese speakers. Another challenge is PV trainings provided by individuals who do not have experience in clinical practice, which may result in a lack of practical insights into the training. Moreover, the lack of coordination of existing trainings and insufficient funding to effectively and sustainably train PV stakeholders are identified as other pressing concerns. Finally, the involvement of trainees who are not clearly qualified for a training is a challenge as their skill and knowledge levels may vary, affecting their overall learning experience. These challenges must be addressed to improve the quality of PV trainings and ensure that trainees receive adequate trainings to contribute effectively to the duties.

Successful training programs require careful consideration of various criteria. These include duration and topic of training, as well as allocated budget for programs. A variety of learning approaches including a setup of multiple levels (e.g., beginner, intermediate, advanced etc.) and availability in multiple platforms, should be considered to enhance the learning experience. Interactive programs and tailored contents that are relevant to the target audience are also crucial. Assessments are necessary to evaluate progress and ensure effectiveness of a training. A mix between face-to-face and online training, wherever possible, might provide flexibility and convenience. Finally, qualified trainers who are knowledgeable and skilled are essential to deliver successful training programs.

Recommendations:

- A repository of all existing training materials and courses should be standardized and shared;
- All courses (and their documents) should be available in English, French and Portuguese to be able to include all African countries while waiting to develop courses specific in Portuguese (5 African countries are Lusophones). As such, UMC courses should be translated into French and CAPM courses in English;
- Coordinate between the existing trainings (UMC and CAPM for example);
- At a post-training period, provide support from a mentor in order to ensure whether the training is properly implemented;
- Engage only trainers who have necessary qualifications and experiences;
- Need for some forms of certification at the end of a training program;
- Mobilize resources to support existing trainings;
- Introduce new training methods such as games.

**WG 2: Increasing Adverse Events (AE) and Adverse Events Following Immunization (AEFI) African reports in VigiBase**

Despite having a large population, African countries have a comparatively low numbers of reports represented in VigiBase. There are several barriers to collect ADR and AEFI reports in Africa. One of the challenges is a difficulty in identifying Adverse Events as well as the lack of adequate reporting tools, systems, and pharmaceutical regulations. Additionally, private sector’s contribution in reporting is limited. There are also challenges with data sharing both locally and globally, such as a difficulty in connecting local databases to VigiBase and problems with interoperability between different databases due to different regulations. These challenges highlighted the need of concerted efforts to improve AE reporting systems in Africa and enhance global data sharing mechanisms.

The goal of WG was to come up with recommendations to enhance reporting tools and resources to ensure that the most accurate and up-to-date information on drugs and vaccines safety in Africa are available.

a) Recommendations for WHO-HQ and regional offices
- Support countries to get free access to VigiFlow and other electronic reporting tools
- Transfer of knowledge on how to use these reporting tools
- Create interoperability between VigiFlow and other local databases
- Strengthen capacity of NRAs

b) Recommendations for WHO-CC
Feature

- Support evaluation of PV systems in countries
- Training of national PV centres
  c) Recommendations for PV centres
  - Contact WHO to allow VigiFlow access
  - Harmonization of databases
  - Extend training to lower levels
  - Provide feedback on reports
  - Reinforce regulations
  - Sensitize patients, HCPs for AE reporting
  - Put a PV focal point in each public health programme

WG 3: Harmonizing methods between PV and EPI (causality assessment and investigation)

The analysis of AE related to health products presents many crucial issues during the PV process. The choice of methods to be implemented depends more on the affinities of the different operators and profiles of pharmacovigilance teams from different countries. It seems to be important to try to harmonize methods between PV and EPI in order to develop a common standard PV case analysis method to be used for all health products by committees. The group discussed need the need to harmonize methods based on presentations of the 3 causality methods: the French method for drug safety, the WHO method for drug safety and the WHO method for AEFI causality assessment. The discussion highlighted strengths of the methods as well as their limitations and the discussion continued regarding a possibility of using the vaccine method for drugs. The discussion resulted in general recommendations to start working on this topic.

Recommendations:

- Create an international working group on harmonization.
- Analyse similarities between methods.
- Collect investigation reporting forms to propose harmonization.
- Conduct a literature review comparing different methods.
- Conduct a survey in National PV Centres in different countries to assess the relevance of the final vaccine classification for medicines.
- Set up an international working group to re-work on the translation and harmonization of terminology:
  - between methods
  - between translations
- Create a WhatsApp group to follow-up on the recommendations.

WG 4: Better collaboration between NRA and NIP in PV

Various points were discussed to define the best way of collaboration between NRA and NIP and to identify the challenges they might face. This working group invited participants to look back on their learnings and experiences, and to leverage the efforts done for a sustainable pharmacovigilance with efficient collaboration.

Following a discussion, relevant recommendations were made on how to make this collaboration successful for African countries:

a) Recommendations for countries
- Promote establishment of a centralized safety review committee
- Clarification of roles and responsibilities of NRA and NIP
- Overlap or missing roles often due to weak legal framework
- Establishment of a mechanism for collaboration
- Through regular meetings, procedures, and chat to discuss progress and identify any potential issues that need to be addressed
- Use of VigiFlow as a platform to decentralize vigilance activities, giving access to NIP
- Train PV focal points in NIP

b) Recommendations for WHO
- Advocate with donors and partners for better coordinated vigilance activities
Feature

- In a WHO region, establish a regional network for information and learning sharing
- Advocate with Ministry of Health (MoH) for better PV activities and better collaboration

c) Recommendations for partners
- Advocate with donors and partners for better coordinated vigilance activities
- Integrate PV into curriculum
- Support development of harmonized tools for data sharing

d) Recommendations for others
- Advocate to promote harmonization of PV system
- Capitalize the COVID-19 experiences and use existing structure to respond to our needs
- Have a Memorandum of Understanding (MoU) about the ideal collaboration to give structure
- Have an integrated annual plan

WG 5: Place of Active Surveillance

The participants listed the main active surveillance studies conducted in their countries and discussed the challenges for implementing such studies. Lack of resources, regulatory framework, awareness and collaboration and involvement between stakeholders and across countries etc were identified as the main challenges.

The participants also discussed about how to leverage from previous experiences on active surveillance in Africa and recommendations to design an adapted guidance at regional and national level of implementing active surveillance. The group provided recommendations to WHO HQ and regional offices, WHO-CCs and national PV centres in order to develop generic protocols on active surveillance.

a) Recommendations for WHO-HQ and regional offices
- Trainings on conducting active surveillance
- Information platform
- Adapt existing tools for active surveillance
- Help countries to collaborate and contribute
- Increase funding
- Advocacy for enforcement of regulations and laws for active surveillance
- Engage Marketing Authorization Holders (MAHs) in active surveillance planning
- Guidelines on protocol and increasing public awareness on importance of active surveillance
- Provide technical assistance

b) Recommendations for WHO-CC
- Advocacy for collaboration with different countries
- Training on how to conduct active surveillance
- Guidelines on protocol/increasing public awareness on importance of active surveillance
- Adaptation of generic protocols

c) Recommendations for PV centres
- Work on enactment of laws for countries
- Capacity building
- Implementation of ethical supervision in collaboration with regulatory bodies
- Increase awareness of public for active surveillance
- Collaboration with Public Health Programme (PHP) and MOH/ Ministry of Labour to train practitioners in conducting active surveillance
- Collaboration with academia for integration of active surveillance in curriculum
- Mapping active surveillance happening in the country
- Timely interim analysis of data by an expert committee