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EDITORIAL

Potential Fallouts of Nepal's Graduation from Least Developed Country (LDC) Status on the Pharmaceutical Sector of Nepal

LDCs enjoy several advantages in the realm of patents, aimed at addressing their unique circumstances and fostering their economic development. The TRIPS Agreement acknowledges the special needs of LDCs by granting them extended transition periods for implementing certain provisions and allowing flexibility in adhering to patent-related obligations. LDCs also benefit from the flexibility to produce or import generic versions of patented medicines, crucial for addressing health emergencies. Technology transfer and capacity building initiatives by international organizations support LDCs in utilizing patented technologies. Additionally, they receive assistance in accessing patent information, ensuring innovation and technological development.

Compulsory licensing, as per the article 31bis of TRIPS agreement, allows governments to grant licenses for the production or use of patented pharmaceuticals without the consent of the patent holder, particularly in situations of national emergencies or public health crises. The Doha Declaration reinforces these flexibilities, affirming the priority of public health over strict patent enforcement and promoting access to essential medicines, especially in times of health crises.

As an LDC, Nepal currently benefits from exemptions related to patent protection for pharmaceutical products until January 1, 2033. Additionally, it is not required to implement exclusive marketing rights provisions and mailbox requirements for pharmaceuticals until

the same date. The LDC waiver has allowed Nepal's domestic pharmaceutical sector to produce generic medicines under patent without the need to inform or compensate the innovators. When Nepal is no longer considered a LDC and has to protect patents, it will affect how on-patent drugs are made in the country. To keep making these drugs, the industry will have to get permission from the innovators and might have to pay them a royalty.

Enforcing patent laws in the pharmaceutical sector can affect the availability and accessibility of pharmaceuticals especially those currently under development/clinical trials, such as oncology products, biologicals, anti-infectives, diabetes medications etc. To ensure the readiness of domestic pharmaceutical industries for the implementation of IP laws post-graduation, a comprehensive approach is recommended. This includes initiating capacity building and training programs to enhance professionals' understanding of IP laws, patent filing procedures, and compliance requirements. Strengthening legal frameworks by reviewing and updating national IP laws to align with international standards is crucial. Promoting technology transfer initiatives, encouraging research and development, fostering public-private partnerships, and providing government support and policies are essential for enhancing local production capabilities. Additionally, investing in market research to identify trends, preferences, and growth areas, as well as preparing for trade negotiations by equipping industries with the necessary skills and knowledge, is vital for the strategic development of the pharmaceutical sector.

The imperative for a balanced transition is underscored by the government's responsibility in monitoring drug prices, collaborative global initiatives, and managing the repercussions of patent laws on domestic pharmaceutical industries. Leveraging international assistance and cooperation programs, negotiating waivers, and

strengthening intellectual property infrastructure present opportunities for Nepal in this transformative phase, requiring a delicate balance between enforcing IP regulations and safeguarding public health.

Narayan Prasad Dhakal
(Director General)
Chief Editor

Scope of the Bulletin

- Pharmaceuticals Stability, quality control formulation, biopharmaceutics
- Policy, legislation, and regulatory control
- Availability and supply
- Administration and dosage
- Choice of therapy, indication, contraindications
- Drug interaction
- Pharmacovigilance, Adverse drug reactions
- Essential drugs

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2. REGULATORY NEWS

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 Safety of Medicinal Products 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 Authorization Holders of methotrexate medicines to provide updates to the product information as appropriate.

Source: WHO Pharmaceuticals Newsletter No.1, 2024

D-norpseudoephedrine

Withdrawal of marketing authorization

Mexico. The Federal Commission for Protection against Health Risks (COFEPRIS) has revoked the marketing authorization for two weight-loss products containing D-norpseudoephedrine (Redotex®, Redotex NF®).

The COFEPRIS identified and reviewed 837 reports of adverse events associated with the consumption of those medicines, where various adverse events including heart and pulmonary disorders, as well as anxiety and insomnia were reported.

Health-care professionals are recommended to avoid prescribing the medicines and any other product containing D-norpseudoephedrine, as well as to consider other therapeutic alternatives for obesity patients.

Source: WHO Pharmaceuticals Newsletter No.4, 2023

Mercaptopurine

Potential risk of hypoglycaemia

Canada. Health Canada has announced that the product safety information for mercaptopurine is to be updated to include the potential risk of hypoglycaemia (low blood sugar) in children less than 18 years of age.

Mercaptopurine is indicated for the maintenance therapy for a specific type of cancer of the blood and bone marrow (acute lymphoblastic, lymphocytic leukemia) in combination with other medicines in adults and children.

Prompted by a USFDA update to the product information to include the risk of hypoglycaemia in children, as well as Canadian and international cases reported, Health Canada reviewed information provided by the manufacturer, and from the Canada Vigilance and published literature. Health Canada reviewed 23 cases (one domestic, 22 international), of which 22 cases were reported in children under 18 years of age and 12 cases were in children under six years of age. Of the 23 cases, six were found to be probably linked to the use of mercaptopurine, 15 (one domestic) were found to be possibly linked and two were unlikely to be linked. The review concluded that there may be a link between the use of mercaptopurine and the potential risk of hypoglycaemia in children.

Source: **WHO Pharmaceuticals Newsletter No.4, 2023**

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.

Source: WHO Pharmaceuticals Newsletter No.1, 2024

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 stablish a causal relationship between treatment with tofacitinib and acne.

Source: **WHO Pharmaceuticals Newsletter No.1, 2024**

Opioids

New safety label changes

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

The required safety labelling changes include:

• the risk of overdose increases as the dosage increases for all opioid pain medicines

• IR opioids should not be used for an extended period unless a patient's pain remains severe enough to require them and alternative treatment options continue to be inadequate

• many acute pain conditions treated in the outpatient setting require no more

than a few days of an opioid pain medicine

• it is recommended to reserve ER/LA opioid pain medicines for severe and persistent pain that requires an extended treatment period with a daily opioid pain medicine and for which alternative treatment options are inadequate.

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

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

Source: WHO Pharmaceuticals Newsletter No.3, 2023

Zinc acetate

Risk of gastric ulcer

Japan. The MHLW and the PMDA have announced that the product information for zinc acetate will be updated to include the risk of gastric ulcer.

Zinc acetate is indicated for the treatment of Wilson's disease and hypozincaemia.

The MHLW and the PMDA assessed a total of 13 reported cases involving zinc acetate and peptic ulcer, and in the seven cases a causal relationship between the medicine and event was reasonably possible. Based on the sites of ulceration in the reports, gastric ulcer, rather than peptic ulcer, was considered as more appropriate term for precaution and added in the product information as clinically significant adverse reaction**.**

Source: WHO Pharmaceuticals Newsletter No.4, 2023

Propofol

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

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

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

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

Source: WHO Pharmaceuticals Newsletter No.3, 2023

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**.**

Source: WHO Pharmaceuticals Newsletter No.1, 2024

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.

Source: WHO Pharmaceuticals Newsletter No.1, 2024

3.SAFETY OF MEDICINES

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.

Source: WHO Pharmaceuticals Newsletter No.1, 2024

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 tumors. 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 Safety of Medicinal Products 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.

Source: **WHO Pharmaceuticals Newsletter No.1, 2024**

Valproate

New study on potential risk of neurodevelopmental disorders (NDDs) in children after paternal exposure

1.Europe. The PRAC of the EMA is reviewing data on the potential risk of neurodevelopmental disorders (NDDs) in children conceived when fathers were taking valproate at the time of conception. The review is focussing on

data from a retrospective observational study conducted by companies using multiple registry databases in Denmark, Norway and Sweden. Initial results of the study may indicate an increased risk of NDDs in children born to men taking valproate up to three months before conception. However, the PRAC has identified important limitations with the data from the study. In particular, the PRAC had questions about the definition of NDDs used in the study and the specific type of epilepsy the patients had. The latter is important because valproate may be prescribed more often for some types of epilepsy which are associated with NDDs. In addition, the companies informed the PRAC about errors in the Norwegian database; the impact of these errors is not yet known. The PRAC has therefore requested companies to provide analyses of corrected data and will review the required data as they become available. Male patients being treated with valproate should not stop taking their medicine without consulting their doctor, as their epilepsy or bipolar disorder could become worse. Patients who have any questions about their treatment should seek advice from their health-care professional.

2.United Kingdom. The MHRA has announced that it has been informed by Sanofi (MAH of Epilim®) of errors that may impact the results of study on outcomes in children whose fathers took valproate at the time of conception. As a result, the researchers from the original study are conducting a full re-analysis before any final conclusions can be drawn. The Commission on Human Medicines (CHM) has advised that further guidance in respect of risks in children of men taking valproate should be based upon data that are accurate and complete. As soon as the revised study analysis is available, it will be re-assessed by the MHRA. The MHRA advice that no action is currently needed for patients, and that no one should stop taking valproate without advice from their health-care professional.

3.Singapore. The Health Sciences Authority (HSA) has announced that a Dear Healthcare Professional Letter (DHCPL) has been issued to inform health-care professionals of new safety information regarding a higher risk

of NDDs in children after paternal exposure to valproate as compared to lamotrigine or levetiracetam. Health-care professionals are advised to inform male patients of this potential risk and consider alternative therapeutic options with the patients. In men initiating or remaining on valproate treatment, it is recommended for health-care professionals to discuss with the patient the need for effective contraception

4.New Zealand. The Medsafe has announced that the product information for valproate has been updated to include the potential risk of NDDs in children whose fathers were treated with valproate at the time of the child's conception. Health-care professionals are advised to inform patients of this potential risk and consider alternative treatment options for those wishing to father a child and discuss the need for effective contraception when starting sodium valproate and periodically throughout treatment.

Source: **WHO Pharmaceuticals Newsletter No.4, 2023**

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 available evidence from assessment of the ICSRs and disproportionality analysis might support a relationship between of levothyroxine and vertigo. This signal needs further investigation to confirm the risk, and health-care professionals should be aware of this potential adverse reaction.

Source: WHO Pharmaceuticals Newsletter No.1, 2024

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.

Source: WHO Pharmaceuticals Newsletter No.1, 2024

Aflibercept

Risks of endophthalmitis and vitreous detachment

Egypt. The Egyptian Pharmacovigilance Center (EPVC), Egyptian Drug Authority (EDA) has alerted health-care professionals on the risks of endophthalmitis and vitreous detachment following the administration of aflibercept. Aflibercept is a recombinant fusion for vascular endothelial growth factor-A (VEGF-A) and placental growth factor (PLGF) and is indicated for the treatment of age-related wet macular degeneration and diabetic macular oedema and retinopathy.

The EPVC received eight individual case safety reports (ICSRs) involving endophthalmitis and/or vitreous detachment after receiving aflibercept intravitreal injection.

Health-care professionals are advised about the prevention methods including aseptic technique and patient monitoring. Key signs and symptoms of intravitreal injection related adverse events include endophthalmitis, intraocular inflammation, increased intraocular pressure, retinal pigment epithelial tear and cataract.

Source: WHO Pharmaceuticals Newsletter No.4, 2023

Azithromycin

Risk of fatal heart rhythms

Zimbabwe. The Medicines Control Authority of Zimbabwe (MCAZ) has alerted health-care professionals on the risk of fatal heart rhythms with azithromycin.

Azithromycin is a macrolide antibiotic and is indicated for the treatment of various infectious diseases. The product information contains information on the risks of QT interval prolongation and torsades de pointes as well as the results of a clinical QT study which showed that azithromycin can prolong the QTc interval.

Health-care professionals should consider the risk of fatal heart rhythms with

azithromycin when considering treatment options for patients who are already at risk of cardiovascular events. Alternative medicines in the macrolide class, or non-macrolides such as fluoroquinolones, also have the potential risks of QT prolongation or other significant adverse events that should be considered.

Source: WHO Pharmaceuticals Newsletter No.4, 2023

Folic acid

Potential risk of constipation

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

Folic acid or Folate (vitamin B-9) is important in red blood cell formation and for healthy cell growth and function. The nutrient is crucial during early pregnancy to reduce the risk of birth defects of the brain and spine. Constipation is generally described as having fewer than three bowel movements a week. The SFDA detected a domestic case-report of constipation and 157 international cases in VigiBase and extracted the top 30 cases from VigiLyze that have completeness score of 1.0 in order to apply the WHO causality assessment criteria on them. As a result, majority of the cases were possibly linked to Folic acid (21 cases were possible and the other nine cases were unlikely). Additionally, the data mining for this drug/ADR combination provided positive statistical association (IC=1.1) at that point of time.

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

Source: WHO Pharmaceuticals Newsletter No.3, 2023

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.

Source: WHO Pharmaceuticals Newsletter No.1, 2024

Scopolamine and butylscopolamine

Risk of medication errors resulting in serious adverse reactions

Spain. The Spanish Agency for Medicines and Health Products (AEMPS) is alerting health-care professionals about the risk of medication errors of administration of scopolamine instead of butylscopolamine resulting in serious adverse reactions. The Spanish Pharmacovigilance System (SEFV-H) has received five cases of serious adverse reactions related to the erroneous administration of scopolamine instead of butylscopolamine. The affected patients required medical assistance. The errors detected indicate that confusion may occur in the prescription, dispensing and administration of the drug.

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

barrier and is indicated as a premedication in anesthesia to reduce excessive salivation and secretions from the respiratory tract.

The administration by mistake of scopolamine at doses of butylscopolamine involves an overdose that can cause anticholinergic adverse reactions at the level of the central nervous system with serious consequences. Characteristic signs and symptoms of scopolamine overdose are headache, nausea, vomiting, blurred vision, confusion, disorientation, memory loss, and hallucinations.

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

Source: WHO Pharmaceuticals Newsletter No.3, 2023

4. SIGNAL

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.

A review of Delamanid and paediatric sleep disorders and hallucinations

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 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 children1. 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[7]. 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[8,9]. 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[10]. (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[11]. 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[12]. 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[12].

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 population13. Hypnagogic hallucinations also commonly occur in patients with narcolepsy.

Hypnopompic hallucinations, in particular, are usually visual and auditory perceptions that occur on awakening[14] and in a state that falls somewhere between dreaming and being fully awake[15].

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.[16] 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[17] 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[18]. 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[18].

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[19]. 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[19] were performed without restriction by patient age. The IC_{025} is the lower end of the 95% credibility interval and a positive IC_{025} represents positive statistically

significant disproportionate reporting. Further analysis after stratification by age was undertaken to study the paediatric population, here the IC_{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[21]. 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_{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.

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 7year-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)[22], linezolid (insomnia)[23], cycloserine (psychosis and somnolence)[24], terizidone (psychosis and somnolence)[25], ethambutol (hallucinations)[26], and ethionamide (hallucinations)[27].

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 children[29].

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 re introduction 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.

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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

Patient age	Observed cases	Expected cases *	IC0005	IC
2–11 years	14	1	1.4	2.9
12–17 years	2	2	-4.8	0.2
18–44 years	27	24	-0.8	0.2
45–64 years	9	10	-2.1	-0.2
65–74 years	1	2	-8.2	-0.6
≥ 75 years	2	1	-4.5	0.5
Unknown	1	4	-9.0	-1.4

* 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

MedDRA Term		Observed cases	Expected cases*	IC0005	IC
Higher Level Group Term	Sleep disorders and disturbances	47	38	-0. 1	0.3
Preferred	Insomnia	25	14	**0.2**	0.78

Term					
	Sleep disorder	9	4	**0.0**	1.1
	Somnolence	7	14	-2.2	-0.9
	Hypnopompic hallucination	5	0	**1.9**	3.4
	Nightmare	2	2	-2.5	0.1
	Abnormal dreams	1	1	-4.1	-0.3
	Poor quality sleep	1	1	-3.7	0.1
	Sopor	1	0	-2.9	0.9

*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

MedDRA Term		**Observed cases**	**Expected cases***	**IC0005**	**IC**
Higher Level	Hallucinations (excluding sleep-related)	13	6	**0.3**	1.2
Preferred Term	Hallucination	5	4	-1.1	0.3
	Hallucination, auditory	3	1	-0.2	1.8
	Hallucination, visual	3	1	-0.6	1.5
	Formication	2	1	-1.4	1.2
	Hallucinations, mixed	1	0	-2.5	1.3

*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.

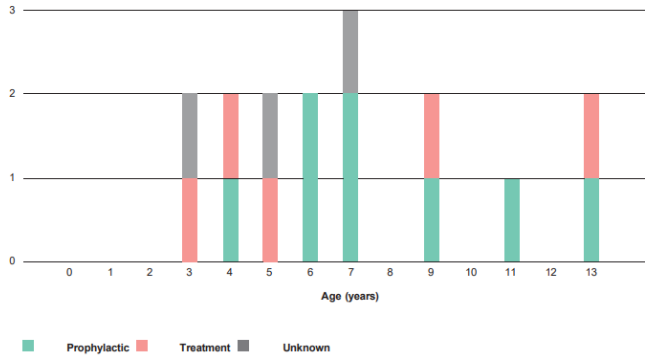

Figure 1. Number of paediatric cases, by age and treatment indication, of "sleep disorders and hallucinations" in combination with delamanid in VigiBase, as of 29/08/22

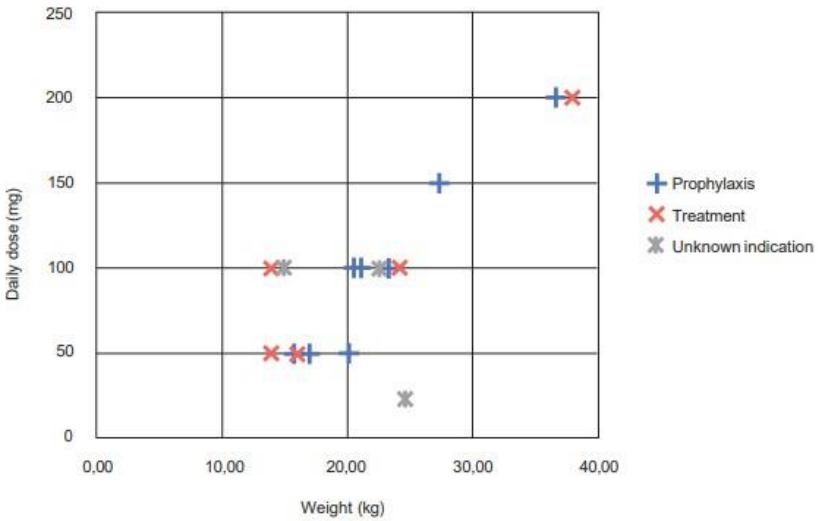

Figure 2. Daily dose of delamanid, by weight and treatment indication, of" sleep disorders and hallucinations" in combination with delamanid in VigiBase, as of 29/08/22

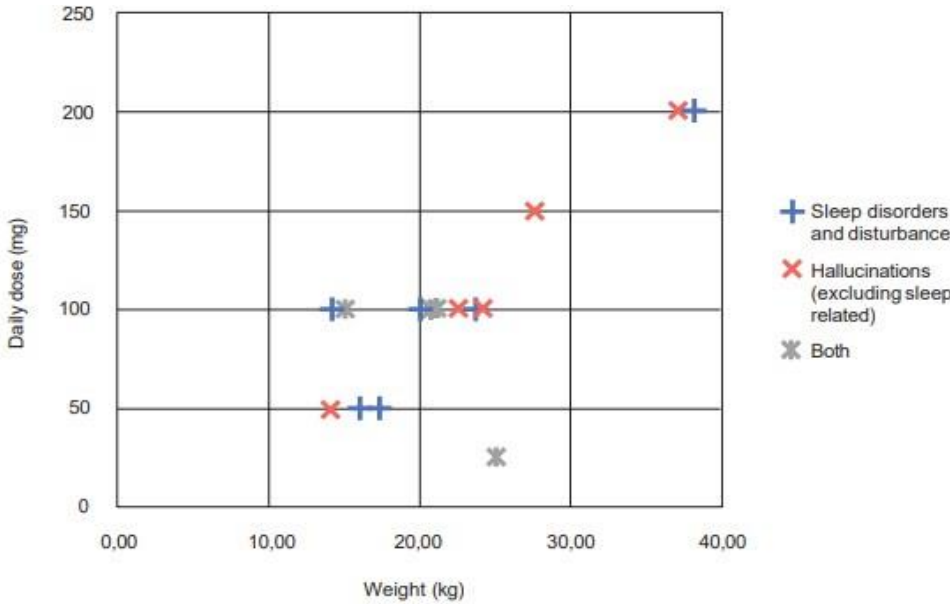

Figure 3. Daily dose of delamanid, by weight in those reporting sleep disorders and/ hallucinations, in combination with delamanid in VigiBase, as of 29/08/22

*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

Characteristic	**Nightmares**	**Sleep terrors**	**Sleep related hallucinations**	**Sleepwalking**	**Confusional arousal**
Usual sleep stage	REM >> NREM	NREM	Hypnagogic – at sleep onset	NREM	NREM
Time of night	Late > early	Children – early Adults – early or late	Hypnopompic – on awakening	Children – early Adults – early or late	Children – early Adults – early or late
Sleep stage at start	REM	Children – stage N3 Adults – stages N2 or N3	Complex – after full awakening	Children – stage N3 Adults – stages N2 or N3	Children – stage N3 Adults – stages N2 or N3
Screams	Rare, talking more common	Yes	No – hypnagogic or hypnopompic	No	No

Characteristic	Nightmares	Sleep terrors	Sleep related hallucinations	Sleepwalking	Confusional arousal
			Yes – complex nocturnal visual hallucinations		
Autonomic activation	Mild	Extreme	No – hypnagogic or hypnopompic Could be – complex nocturnal visual hallucinations	Unusual	Unusual
Walking	No	No	Could be	Yes	No
Confusion after episode on awakening	Rare	Usual	Rare	Usual	Usual

Characteristic	Nightmares	Sleep terrors	Sleep related hallucinations	Sleepwalking	Confusional arousal
Age	Child – common Adult – less common	Any age	Child – common Adult – less common	Child – common Adult – less common	Child – common Adult – less common

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

Source: WHO Pharmaceuticals Newsletter No.1, 2024

5. REGULATORY NOTICES

नेपाल सरकार

स्वास्थ्य तथा जनसंख्या मन्त्रालय

औषधि व्यवस्था विभाग

प्रकाशित मिति: २०८१/८/२५

प्रदेश स्तरमा हुने फार्मेसी (औषधि) पसलको दर्ता नवीकरण तथा व्यवसायी मान्यता प्राप्त कार्डको नविकरण सम्वन्धि जरुरी सूचना।

यस विभागले सालवसाली रुपमा फार्मेसी (औषधि पसल) दर्ता प्रमाणपत्र नवीकरण तथा प्रत्येक पाँच-पाँच वर्षमा व्यवसायी मान्यता प्राप्त कार्डहरुको नवीकरण गर्दै आईरहेको व्यहोरा विदितै छ।

उल्लेखित कार्यलाई चुस्त दुरुस्त राख, सेवाग्राही मैत्रि वनाउन साथै सेवाग्राहीहरुको माग तथा असुविधालाई ध्यानमा राख्दै मिति २०८०/९/१७ मा विभागीय निर्णय वमोजिम फार्मेसी पसलको दर्ता प्रमाणपत्र नविकरण लगायत व्यवसायी मान्यता प्राप्त कार्डको नवीकरण गर्ने कार्यको लागि यस विभागवाट टोली खटिने हुँदा गण्डकी प्रदेश अन्तर्गत संचालनमा रहेका थोक तथा खुद्रा औषधि पसलका संचालक तथा व्यवसायीहरुको जानकारीको लागि यो सूचना प्रकाशन गरिएको छ।

निम्नः

स्थानः सामाजिक विकास तथा स्वास्थ्य मन्त्रालयको कार्यालय गण्डकी प्रदेश, कास्की, पोखरा।

मितिः २०८०/१०/०२ मंगलवार देखि २०८०/१०/०७ आइतवारसम्म।

समयः विहान १० वजे वाट दिउसो ४ वजे (कार्यालय संचालन समयसम्म)।

सम्पर्क नं ९८४३६९८३३०

३/१२

वरिष्ठ औषधि व्यवस्थापक

नेपाल सरकार
स्वास्थ्य तथा जनसंख्या मन्त्रालय
औषधि व्यवस्था विभागको

Comparator Brand/ औषधि सम्बन्धी अत्यन्त जरुरी सूचना

प्रकाशित मितिः २०८०/०९/१३

कुनै औषधिको Comparative Dissolution गर्नुपर्दा वा Bioequivalence अध्ययन गर्नुपर्दा Comparator Brand/ औषधि आवश्यक हुने हुँदा औषधि दर्ता कार्यविधीको बुँदा नं. १.३.२.६ IV को प्रयोजनार्थ देहाय अनुसार गर्न/गराउनु हुन मिति २०८०/०९/११ को विभागीय निर्णयानुसार जानकारी गराइन्छ ।

तपसिलः

१. Comparator brand को सन्दर्भमा उपलब्ध भए सम्म Innovator brand/WHO Listed Comparator सँग Comparative Dissolution गर्नुपर्ने ।

२. Comparative Dissolution अध्ययनको Requirement र Report Format देहायको अनुसूची १ बमोजिम हुनुपर्ने।

३. Innovator brand/ WHO listed Comparator उपलब्ध हुन नसक्ने अवस्थामा देहायको अनुसूची २ बमोजिमको सूचीमा संलग्न औषधिहरुको हकमा तोकिएका Comparator brand सँग Comparative Dissolution गर्नुपर्ने।

४. Innovator उपलब्ध नभएका र विभागको Comparator brand को सूचीमा समेत संलग्न नरहेका वा Comparator brand को सूचीमा उल्लेख भई उपलब्ध हुन नसकेको औषधिहरुको हकमा विभागले अन्य ब्राण्डलाई समेत Comparator brand को मान्यता दिन सक्ने ।

५. विभागको Comparator brand को सूची समय सापेक्ष रुपमा अद्यावधिक भई रहने।

महानिर्देशक

नेपाल सरकार
स्वास्थ्य तथा जनसंख्या मन्त्रालय
औषधि व्यवस्था विभागको

औषधि उत्पादन/विक्री वितरण सम्बन्धि अत्यन्त जरुरी सूचना ।

प्रस्तुत बिषयमा विभागमा Aceclofenac, Linagliptin, Linagliptin & Metformin, Rivaroxaban का औषधिहरु विभिन्न Strengths हरु दर्ता भएकोमा हाल सो औषधिहरुको Stringent Regulatory Authority हरुमा दर्ता रहेका विवरण एवं Safety, Efficacy र Tolerability को हकमा प्राप्त विवरणहरुका आधारमा सो औषधिको देहाय Strengths हरुको नयाँ दर्ता नगर्न भनि औषधि मुल्यांकन समितिबाट प्राप्त प्राविधिक राय बमोजिम विभागको मिति २०८०/०८/११ को निर्णयानुसार सो औषधिहरुको औषधि सल्लाहकार समितिबाट सिफारिस प्राप्त नहुँदा सम्मको लागि नयाँ उत्पादन नगर्न र बजारमा बिक्रि वितरण भइरहेको ब्राण्ड समेत थप उत्पादन नगर्न/ नगराउनुहुन सबैको जानकारीका लागि यो सूचना प्रकाशन गरिएको छ।

तपसिलः

सि.नं	औषधिको नाम
1.	Linagliptin 2.5 mg tablet
2.	Linagliptin 10 mg tablet
3.	Rivaroxaban 5 mg tablet
4.	Acelofenac 200mg Immediate Release tablet
5.	Acelofenac 300mg Dispersible/Immediate Release/Controlled Release/Extended Release/Sustained Release tablet
6.	Linagliptin 2.5mg and Metformin 500 mg (Extended Release / Sustained Release tablet)
7.	Linagliptin 2.5 and Metformin 850mg (Extended Release / Sustained Release tablet)
9.	Linaglptin 5mg and Metformin 500 mg, Immediate Release tablet
10.	Linaglptin 5mg and Metformin 850 mg, Immediate Release tablet

नेपाल सरकार
स्वास्थ्य तथा जनसंख्या मन्त्रालय
औषधि व्यवस्था विभागको

प्रेस्क्रिप्सनका आधारमा औषधि विक्री-वितरण गर्नुपर्ने सम्बन्धी अत्यन्त जरुरी सूचना

प्रकाशित मितिः २०८०/०८/१४

औषधि ऐन २०३५ को दफा (१७) को उपदफा (२) मा चिकित्सकको प्रेस्क्रिप्सन बिना बिक्रि-वितरण गर्न नहुने भनि समूहकृत गरिएको औषधि (समूह "क" र समूह "ख" का औषधिहरु) चिकित्सकको प्रेस्क्रिप्सन बिना विक्री-वितरण गर्न नहुने व्यवस्था रहेको सबैलाई विदितै छ।

यस विभागबाट नियमित रुपमा हुने गरेको औषधि पसलहरुको निरीक्षणको क्रममा प्रेस्क्रिप्सनका आधारमा विक्री-वितरण हुनुपर्ने औषधि बिना प्रेस्क्रिप्सन नै विक्री-वितरण भएको पाइएको एवं प्रतिजैविक औषधिहरु समेत बिना प्रेस्क्रिप्सन विक्री-वितरण भएको र सो औषधिहरुको व्यापक प्रयोगले रोग प्रतिरोध क्षमता अभिवृद्धि भै कतिपय अवस्थामा औषधिले काम नगरेको अवस्था छ।

यी लगायत समूह क र समूह ख का विभिन्न औषधिहरु अनिवार्य रुपमा प्रेस्क्रिप्सनका आधारमा मात्र विक्री-वितरण गर्नुहुन सम्बन्धित सरोकारवालाहरुलाई जानकारीका लागि यो सूचना प्रकाशित गरिएको छ। साथै, औषधि ऐन २०३५ को दफा (१७) विपरितका त्यस्ता काम/कारवाहीहरु गरेको पाइएमा सोही ऐन बमोजिम कारवाही हुने व्यहोरा यसै मार्फत सूचित गरिन्छ।

त्यस्तै, सर्वसाधारणहरुले औषधि खरिद गर्नुपूर्व चिकित्सकको सल्लाह लिई प्रेस्क्रिप्सन आवश्यक पर्ने औषधिको अनिवार्य प्रेस्क्रिप्सन सहित औषधि पसलबाट मात्र औषधिको खरिद गर्नुहुन समेत यसै मार्फत सूचित गरिन्छ।

०८०।८।१४

नेपाल सरकार
स्वास्थ्य तथा जनसंख्या मन्त्रालय
औषधि व्यवस्था विभागको

कुशल भण्डारण तथा वितरण अभ्यास (Good Storage & Distribution Practice GSDP) सम्बन्धि
"क्षमता अभिवृद्धि तालिम", बारेमा सूचना
प्रकाशित मिति: २०८०/०७/२४

उपरोक्त सम्बन्धमा फार्मेसीहरुबाट प्रवाह हुने सेवालाई चुस्त/दुरुस्त तथा थप गुणस्तरिय बनाई समग्र फार्मेसी अभ्यासलाई सुधार गरि कुशल फार्मेसी तथा कुशल भण्डारण तथा वितरण अभ्यासहरुलाई प्रचलनमा ल्याउने अभिप्रायले फार्मेसी (खुद्रा/थोक) सञ्चालन गर्दै आएका फार्मासिष्ट/सहायक फार्मासिष्ट/व्यवसायीहरुलाई **"क्षमता अभिवृद्धि तालिम"** को आयोजना भएकोमा **कुशल भण्डारण तथा वितरण अभ्यास (GSDP)** सम्बन्धि तालिममा आवेदनहरु पर्याप्त प्राप्त नभएकोले अर्को अवसरको रुपमा सो पहिलो चरणको तालिममा सहभागी हुन् छुट भएका इच्छुक **थोक औषधि पसल (आयातकर्ता समेत)** सञ्चालन गर्दै आएका फार्मासिष्ट/सहायक फार्मासिष्ट/व्यवसायीहरुका लागि **कुशल भण्डारण तथा वितरण अभ्यास (Good Storage & Distribution Practice , GSDP)** तालिम देहाय स्थान र मितिमा दोस्रो चरणमा संचालन हुने भएकोले देहाय ढाँचामा विवरणहरु सहित यस सूचना प्रकाशन भएको मितिले सात (७) दिन भित्र विभागको आधिकारिक email info@dda.gov.np मा पत्राचार गर्नुहुनका लागि यो सूचना प्रकाशित गरिएको छः

सि.नं.	तालिम केन्द्र र तालिम मिति	इच्छाएको तालिम केन्द्र	थोक(आयातकर्ता समेत) औषधि पसलको नाम र ठेगाना	र.प.नं.	पसल दर्ता प्रमाणपत्रको नवीकरण म्याद	थोक पसल दर्ता प्रमाणपत्रमा उल्लेखित फार्मासिष्ट/ सहायक फार्मासिष्ट/ व्यवसायीको नाम, सम्पर्क नं., इमेलः	फार्मेसी परिषद दर्ता नं./ व्यवसायी मान्यता प्रमाणपत्र नं.
१.	भरतपुर, **Bharatpur Garden Resort,** २०८०/०८/०५ र ०६ गते	उल्लेखित तिन तालिम केन्द्र मध्ये कुनै एक					
२.	विराटनगर, **Hotel Eastern star,** २०८०/०८/०५ र ०६ गते						
३.	काठमाडौं, **Indreni Complex** २०८०/०८/०७ र ०८ गते						

द्रष्टव्यः आवेदकले आवेदन दिँदा उल्लेखित ढाँचामा **Word/Excel Format** मा आफ्नो औषधि पसल दर्ता प्रमाणपत्रको प्रतिलिपी समेत संलग्न गरि आवेदन दिनुहुन अनुरोध गरिन्छ।

०८/०६/२४
महानिर्देशक

औषधि प्रयोग गर्दा ध्यान दिनुपर्ने कुराहरू:

- मान्यता प्राप्त स्वास्थ्यकर्मीको पूर्जामा मात्र औषधि प्रयोग गर्ने ।
- औषधिको प्रयोग सम्बन्धि पूर्ण जानकारी लिने ।
- औषधिको सेवन तोकिएको समयमा, तोकिए बमोजिमको फरकमा, तोकिएको समयसम्म प्रयोग गर्ने ।
- औषधि बालबच्चाको पहुँचबाट टाढा राख्ने ।
- यदि कुनै औषधि सेवन गर्न भूलेमा सम्झने बित्तिक्कै सेवन गर्ने तर अर्को मात्रा सेवन गर्ने समय नजिक भएमा सेवन नगरी अर्को मात्रा सेवन गर्ने ।
- आफू गर्भवती भएमा सो बारे स्वास्थ्यकर्मीलाई जानकारी दिने ।
- औषधि प्रयोग गर्दा जिउ चिलाएमा, छालामा डाबरहरु आएका, स्वास फेर्न गाह्रो भएमा वा यस्तै अन्य लक्षण देखा परेमा तुरुन्त औषधि प्रयोग गर्न छाडी स्वास्थ्यकर्मीलाई सम्पर्क राख्ने ।

एण्टिबायोटिक औषधि प्रयोग गर्दा मान्यता प्राप्त स्वास्थ्यकर्मीको सल्लाहमा तोकिएको अवधि र समयभित्र प्रयोग गरौं र गराऔं ।

औषधि सम्बन्धि थप जानकरीका लागि तल उल्लेखित ठेगानामा सम्पर्क राख्नुहोला ।

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