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Regulatory Authority

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COMMUNICATION TO STAKEHOLDERS

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Summary of Medicine Safety Regulatory Decisions

Introduction

This document provides an overview of the safety regulatory decisions taken by the South African Health Products Regulatory Authority (SAHPRA) during April – June 2023. This includes a summary of regulatory decisions, where safety concerns were reviewed and concluded, and those safety concerns that are not concluded but are severe and serious in nature. SAHPRA's decisions are actionable by the concerned stakeholders including applicants or holders of certificate of registration (HCRs). Safety decisions concerning the amendment of professional information and patient information leaflets (PI/PIL) are submitted to the Clinical Evaluations unit to review and ensure appropriate implementation and amendments thereof.

Applicants/ HCRs, in line with Regulation 11 and 12 of the Medicines and Related Substance Act (Act 101 of 1965, as amended, SAHPGL-CEM-03 Guideline for Patient Information Leaflet for Human Medicines (Categories A and D) and SAHPGL-CEM-02 Guideline for Professional Information for Human Medicines (Categories A and D) must ensure that their product information is kept up to date with the current scientific knowledge. Variations are handled according to the variation of human and veterinary medicines guidance document - SAHPGL-HPA-06 Variations Addendum For Human And Veterinary Medicines.

The timeline recommended by SAHPRA for submission of variations following signal assessment is applicable to both innovator and generic products, unless otherwise specified.

Contents

1. Definitions

Adverse Event is any untoward medical occurrence that may present during treatment with a medicine, but which does not necessarily have a causal relationship with this treatment. An adverse event can be any unfavourable and unintended sign, symptom or disease temporarily associated with the use of a medicine, whether considered related to the medicine, or not.

Adverse Event Following Immunisation (AEFI) is defined as any untoward medical occurrence which follows immunisation; does not necessarily have a causal relationship with the usage of the vaccine; may be any unfavourable symptom about which a vaccine recipient complains; and may be an abnormal laboratory finding, sign or disease found by medical staff.

Adverse Effect is a negative or harmful patient outcome that seems to be associated with treatment, including there being no effect at all.

Applicant is anyone who has submitted any kind of application.

Causality assessment is defined as the evaluation of the likelihood that a medicine was the causative agent of an observed adverse drug reaction.

Clinical Trial is a study performed to investigate the safety or efficacy of a medicine. For human medicines, these studies are carried out in human participants.

Committee for Medicinal Products for Human Use (CHMP) is the European Medicines Agency's (EMA) committee responsible for human medicines. It plays a vital role in the authorisation of medicines in the European Union.

Dechallenge means a withdrawal /reduction in dose of a medicine from the patient's therapeutic regimen.

- Negative dechallenge means continued presence of an adverse experience after withdrawal of the medicine.
- Positive dechallenge means partial or complete disappearance of an adverse event after withdrawal of the medicine.

Data lock point (for a periodic safety update report (PSUR), periodic benefit-risk evaluation report (PBRER) or risk management plan (RMP)) is the date designated as the cut-off date for data to be included in a PSUR/PBRER/RMP.

Dear Healthcare Professional (DHCP) Letter is a communication in a form of a letter intended to convey important medicine safety information, distributed by holders of certificate of registration (HCR) directly to individual healthcare professionals and published on both the SAHPRA and the HCR's websites.

European Medicines Agency (EMA) is the European Union (EU) health regulatory authority in charge of the evaluation and supervision of medicinal products.

Holder of Certificate of Registration (HCR) is a person, natural or juristic, in whose name the certificate of registration for a product has been granted and who is responsible for all aspects of the medicine, including quality, safety, effectiveness and compliance with the conditions of registration. The terms "holder of certificate of registration" (holder) and "applicant" are used interchangeably.

Medication error is any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the healthcare professional, patient, or consumer. Such events may be related to professional practice, healthcare products, procedures, and systems including:

- prescribing errors,
- dispensing errors,
- medicine preparation errors,
- administration errors, and
- monitoring errors.

Medicine

a. means any substance or mixture of substances used or purporting to be suitable for use or manufactured or sold for use in -
   i. the diagnosis, treatment, mitigation, modification or prevention of disease, abnormal physical or mental state or the symptoms thereof in humans; or
   ii. restoring, correcting or modifying any somatic or psychic or organic function in humans; and
b. includes any veterinary medicine.

Patient Information Leaflet (PIL) (previously known as a package insert) is a document included in the package of a medicine that provides information to the patient and consumer about that particular medicine and its use. When a potential medicine safety concern arises, reviews are conducted within SAHPRA. Upon completion of reviews, SAHPRA makes regulatory decisions (such as amendment of PI and PIL) which are communicated to HCR for implementation.

Pharmacovigilance Risk Assessment Committee (PRAC) is a scientific committee at the European Medicines Agency that is responsible for the assessment and monitoring of the safety of medicines. This includes the detection, analysis, risk minimisation and communication of adverse reactions.

Periodic Safety Update Report (PSUR)/ Periodic Benefit-Risk Evaluation Report (PBRER) is a report prepared by the holder of certificate of registration describing the worldwide safety experience with a medicine at a defined time (for example, annually) after its registration.

Periodic safety update report single assessments (PSUSAs) referred also as EU PSUR single assessment, is the assessment of PSURs for medicinal products subject to different marketing authorisations containing the same active substance or the same combination of active substances and for which the frequency and dates of submission of PSURs have been harmonised in the list of European (EU) reference dates (referred also as EURD list). These PSURs are jointly assessed and result in one single assessment report, which is shared amongst all the marketing authorisation holders (MAHs) whose medicinal product(s) are part of the PSUR single assessment procedure.

Professional Information (PI) is a technical document (either printed or in a soft copy), prepared by the manufacturer and approved by SAHPRA, providing information for medical professionals about the use and dosing of a medicine, which includes the pharmacokinetics, dosage forms, and other relevant information about a medicine.

Rechallenge means reintroduction of a product suspected of having caused an adverse event following a positive dechallenge:

- Negative rechallenge means failure of the medicine, when reintroduced, to produce signs or symptoms similar to those observed when the medicine was previously introduced.
- Positive rechallenge means reoccurrence of similar signs and symptoms upon reintroduction of a medicine.

Recognised Regulatory Authorities (RRAs) is a term used to refer to the list of regulatory authorities with which SAHPRA aligns itself. RRAs include US FDA, EMA (Centralised and Decentralised Procedures), MHLW (Japan), Health Canada, Swiss Medic, TGA (Australia), and MHRA (UK).

Risk Management Plan (RMP) is a document that describes a set of pharmacovigilance activities and interventions designed to identify, characterise, prevent, or minimise risks related to a specific medicine and the assessment of the effectiveness of those interventions. It reflects both known and emerging safety data and is updated throughout the medicine's life cycle.

Risk minimisation measures (RMMs) are activities and interventions intended to prevent or reduce the occurrence of adverse reactions associated with exposure to a medicine, or to reduce their severity or impact on the patient. Details of risk minimisation measures are documented in the risk management plan and include:

Routine RMMs

- Professional Information
- Patient Information Leaflet
- Packaging and labelling
- Scheduling status

Additional RMMs

- Educational programmes or tools for healthcare providers and/ or patients
- Controlled access programmes
- Dear Healthcare Professional letter (DHCPL)

Safety signal refers to 'reported' information on a possible causal relationship between an adverse event and a medicine, the relationship being unknown or incompletely documented previously. Usually more than a single report is required to generate a signal, depending upon the seriousness of the event and the quality of the information.

Spontaneous report is a communication to a pharmaceutical company, regulatory authority or other organisation that describes a suspected ADR/AEFI in a patient given one or more medicines, and which does not derive from a study.

Swissmedic is the Swiss authority responsible for the authorisation and supervision of therapeutic products. Swissmedic's activities are based on the Law on Therapeutic Products. The agency ensures that only high-quality, safe and effective medical products are available in Switzerland, thus making an important contribution to the protection of human and animal health.

Summary of Product Characteristics (SmPC) is a European legal document approved as part of the marketing authorisation of each medicine that provide information to healthcare professional on how to use the medicine.

United States Food and Drug Administration (USFDA) is a federal agency of the Department of Health and Human Services in the United States of America, responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, food supply, cosmetics, and products that emit radiation.

2. Regulatory Safety Decisions

2.1 Update of Professional Information (PI) and Patient Information Leaflet (PIL)

2.1.1 COVID-19 Vaccine Janssen® - Risk of Myocarditis and Pericarditis

a) Background

SAHPRA conducted a review regarding the risk of myocarditis and pericarditis associated with the administration of COVID-19 Vaccine Janssen® (Adenovirus type 26 encoding the SARS-CoV-2 spike glycoprotein (Ad26.COV2.S). COVID-19 Vaccine Janssen® is used for preventing coronavirus 2019 (COVID-19) infection caused by the SARS-CoV2 virus in adults aged 18 years and older. The vaccine causes the immune system (the body's natural defences) to produce antibodies and specialised white blood cells that work against the virus, to provides protection against COVID-19 infection.

The risk of myocarditis and pericarditis was assessed and validated by the applicant/ holder of certificate of registration (HCR). Based on the overall available safety data, the applicant/ HCR concluded that there is a reasonable possibility of a causal association between the administration of Adenovirus type 26 encoding the SARS-CoV-2 spike glycoprotein (Ad26.COV2.S) and the increased risk of myocarditis and pericarditis, particularly in males of <40 years and at risk period of 0-7 days.

The reviewed data include Real World Evidence (RWE), a study by Patone, (2022), the USFDA assessment outcome and post marketing data presented in the periodic benefit risk evaluation report (PBRER) (Data Lock Point, 23 February 2023). In view of the severity of these diseases, their potential impact to public health and consistency of data, a decision was taken by the HCR to update the Risk Management Plan (RMP) and the Professional Information (PI) of COVID-19 Vaccine Janssen®, to include the risk of myocarditis and pericarditis.

Decision

- SAHPRA endorsed the proposed action by the applicant/ HCR to include the risk of myocarditis and pericarditis in the RMP and the PI/PIL of COVID-19 Vaccine Janssen®, based on sufficient evidence to support a possible causal association between the administration of COVID-19 Vaccine Janssen® and the occurrence of myocarditis and pericarditis.
- The overall risk-benefit balance of COVID-19 Vaccine Janssen® is considered favourable, provided the applicant/ HCR effect the changes.

2.1.2 Clopidogrel - Risk of Insulin Autoimmune Syndrome

a) Background

SAHPRA conducted a review of a safety signal regarding the risk of insulin autoimmune syndrome (IAS) associated with the use of clopidogrel containing medicines. Clopidogrel is an antiplatelet medicine. Platelets are very small structures in the blood which help form blood clots to slow or stop bleeding and to help wounds heal.

The safety signal emanated from the Japan Ministry of Health, Labor and Welfare (MHLW)/ Pharmaceuticals and Medical Devices Agency's (PMDA's) regulatory decision to request HCRs of clopidogrel to update the product information with the risk of insulin autoimmune syndrome under 'Precautions' section of the PI. MLHW based their decision on number of cases (for which a causal relationship between the drug and event is reasonably possible) collected in the PMDA's database for adverse drug reactions. It was noted that insulin autoimmune syndrome is a rare, and well-established risk associated with the use of clopidogrel-containing medicines.

b) Decision

- SAHPRA recommended that applicants/ HCRs of clopidogrel-containing medicines update the PI/PIL of their products to include the risk of IAS if they have not yet done so.
- SAHPRA considers the benefit-risk profile of clopidogrel-containing medicines favourable, provided the applicants/ HCRs effect the recommended changes.

2.1.3 Levonorgestrel – Revised Recommendations Regarding Insertion of the Intrauterine Device (IUD)

a) Background

SAHPRA became aware of European Medicines Agency (EMA)'s regulatory decision to request applicants of levonorgestrel- containing medicines to amend the product information to improve the existing recommendations regarding insertion of the intrauterine device (IUD), i.e., to avoid insertion after conception in order to prevent the risk of masculinisation of a female foetus if the IUD remains in place during pregnancy.

Levonorgestrel is an emergency contraceptive registered to be used to prevent a pregnancy when taken within 72 hours (3 days) after having unprotected sex, or if the birth control method in place has failed (e.g., a broken condom).

The safety issue was identified during a single assessment (PSUSA) procedure (PSUSA/00010828/202105) of levonorgestrel PSUR by the Pharmacovigilance Risk Assessment Committee (PRAC). In particular, PRAC agreed to the specific product information updates to further emphasise that subject examinations are needed: to be undertaken before IUD insertion; to recommend strict adherence to the existing advice; to insert the IUD within the first seven (7) days from onset of the menstrual cycle; and that in case it is not possible to insert the IUD within seven (7) days from onset of the menstrual cycle, (since immediate contraceptive protection is not reliably

ensured in that case), women should use a barrier contraception for the next seven (7) days after insertion of the IUD to prevent pregnancy.

SAHPRA approved PIs of levonorgestrel containing IUDs do not mention the improved recommendations for insertion of IUD.

b) Decision

- SAHPRA adopted EMA's decision and recommended applicants/ HCRs of levonorgestrel-containing intrauterine devices to update the PI/PIL of their products in line with EMA's PRAC recommendations.
- The benefit-risk balance of levonorgestrel-containing medicines remains favourable for its registered indication.

2.1.4 Ketorolac – Risk of Anastomotic Leakage

a) Background

SAHPRA became aware of EMA's regulatory decision to request all applicants of ketorolac-containing medicines (tablets and injectables) to update the PI/PIL of their products with the risk of anastomotic leakage. Ketorolac belongs to a group of medicines known as non-steroidal anti-inflammatory drugs (NSAIDS) and is registered for use in the short-term management of moderate pain after operations. It also has some properties to reduce redness, swelling and fever.

Anastomotic leak refers to a communication between the hollow organ lumen and the peritoneal cavity at the level of the anastomosis (a surgical connection between two structures), which usually occurs after colorectal surgery. Anastomotic leak is a serious postoperative complication that may be life-threatening.

The EMA's PRAC, based on the available data on anastomotic leakage noted from literature during single assessment (PSUSA) procedure (PSUSA/00001811/202207) of ketorolac PSUR, considered a causal relationship between ketorolac (systemic formulations) and anastomotic leakage to be a reasonable possibility. The SAHPRA approved PIs of ketorolac-containing medicines does not mention the warning on the risk of anastomotic leakage.

b) Decision

- SAHPRA adopted EMA's decision and recommended that applicants/ HCRs of systemic ketorolac containing medicines amend the PI/PIL of their products in line with EMA's PRAC recommendations.
- The benefit-risk balance of ketorolac-containing medicines remain positive for its registered indication(s).

2.1.5 Duloxetine - Risk of Stress Cardiomyopathy/ Takotsubo Syndrome

a) Background

SAHPRA conducted a review of a safety signal regarding the risk of Takotsubo cardiomyopathy (also known as stress cardiomyopathy) associated with the use of duloxetine-containing medicines. Duloxetine is a serotonin and norepinephrine reuptake inhibitor (SNRI) that belongs to a group of medicines called antidepressants and is registered for the treatment of depression and diabetic peripheral neuropathic pain in adult patients. Cardiomyopathy is a disease that causes the heart muscle (myocardium) to stiffen, enlarge or thicken and can cause scar tissue.

The safety signal emanates from Swissmedic's regulatory decision to request HCRs of duloxetine-containing medicines to update the product information with the risk of Takotsubo cardiomyopathy. Swissmedic based their decision on individual case safety reports available from the Swiss Pharmacovigilance System (VOU) national database, case reports on duloxetine identified in the World Health Organization (WHO) pharmacovigilance database, enhanced adrenergic influence of duloxetine and information on Takotsubo cardiomyopathy documented in the American prescribing information on Cymbalta® (duloxetine) under 'Other Adverse Reactions Observed During the Clinical Trial Evaluation of Cymbalta® in adults' section.

Literature showed an association between increase levels of catecholamines and the risk of Takotsubo cardiomyopathy, suggesting that inhibition of androgen receptors by duloxetine results in increased catecholamines levels and consequently cardiomyopathy. Takotsubo cardiomyopathy is reversible upon discontinuation of the causative agent and appropriate treatment. The risk of Takotsubo cardiomyopathy could be a class effect for all SNRIs due to their mechanism of action.

b) Decision

- SAHPRA recommended that all applicants/ HCRs of serotonin and norepinephrine reuptake inhibitor containing medicines update the PI/PIL of their products to include the risk of Takotsubo cardiomyopathy.
- The benefit-risk balance of SNRI-containing medicines with regards to this risk remains positive for its registered indications provided applicants/ HCRs effect the recommended changes.

2.1.6 Cabergoline - Risk of Cardiac, Neurologic and Psychiatric Disorders

a) Background

SAHPRA conducted a review of a safety signal regarding the risks of cardiovascular, neurologic, and psychiatric disorders associated with the use of cabergoline-containing medicines. Cabergoline is a dopamine agonist registered to stop breast milk production (lactation) soon after childbirth, stillbirth, abortion or miscarriage, or voluntary cessation of breastfeeding.

The safety signal emanated from the EMA's PRAC recommendation requiring an update of the European Summary of Product Characteristics (SmPC) for cabergoline to include information on the

risks of cardiovascular, neurologic, and psychiatric disorders. PRAC considered a plausible causal relationship between cardiovascular, neurologic, and psychiatric disorders in post-partum women treated with cabergoline reasonable following their assessment of the periodic safety update report (PSUR) for cabergoline. PRAC identified adverse events of cardiac disorders, vascular disorders, posterior reversible encephalopathy syndrome and central nervous system vascular disorders through a cumulative search of the EU sponsor's safety database for all cabergoline cases with the indication of lactation suppression.

b) Decision

- SAHPRA recommended that applicants/ HCRs of cabergoline-containing medicines update the PI/PIL of their product in line with EMA's PRAC's recommendations.
- The benefit-risk balance of cabergoline-containing medicines with regards to the new risks remains favourable for its registered indication, provided the applicants/ HCRs effect the recommended changes.

2.1.7 Lurasidone and Clarithromycin – Drug/ Drug Interactions

a) Background

SAHPRA conducted a review of a safety signal regarding the risk of drug-drug interactions between lurasidone and clarithromycin. The safety signal emanated from the United States food and Drug Administration (USFDA) based on published literature. Clarithromycin is an antibiotic that belongs to the macrolides group and works by stopping the growth of certain bacteria which cause infections. Lurasidone is an antipsychotic medicine, not registered in South Africa (SA), however, other medications (cariprazine, quetiapine and aripiprazole) in the same class are registered (in SA) for the treatment of schizophrenia (a disease with symptoms such as hallucinations, strange and frightening thoughts, changes in behaviour, feeling alone and confused) and illnesses that affect the mood.

The concomitant use of lurasidone with strong CYP3A4 inducers and inhibitors, such as clarithromycin, is contraindicated. Clarithromycin has the potential for the same serious risk of drug interaction with lurasidone. Reviewed data from literature provided sufficient evidence (regarding CYP3A4 metabolism of these medicines) to support a biological plausibility of the drug interactions between atypical antipsychotics and macrolides (clarithromycin).

A review of SAHPRA approved PIs of atypical antipsychotics revealed that drug-drug interactions with inhibitors of CYP3A4 including clarithromycin or the class of macrolide anti-infective agents is documented. However, the PIs of clarithromycin does not mention any interaction with atypical antipsychotics.

b) Decision

- SAHPRA recommended that applicants/ HCRs of clarithromycin-containing medicines update the PI/PIL of their products to include the risk of drug-drug interactions with atypical antipsychotics that are predominantly metabolised by the CYP3A4 with quetiapine, cariprazine, and lurasidone, as examples.

- The benefit risk balance of clarithromycin-containing medicines remains favourable, provided the applicants/ HCRs effect the recommended changes.

2.1.8 Co-Trimoxazole – Risk of Fixed Drug Eruption

a) Background

SAHPRA conducted a review of a safety signal regarding the risk of fixed drug eruption associated with the use of co-trimoxazole containing medicines. Co-trimoxazole contains two different antibiotics, sulfamethoxazole and trimethoprim, and is registered for the treatment of infections caused by certain bacteria.

The safety signal emanated from clinical assessment of a single co-trimoxazole case conducted by SAHPRA. The case report involved a 38-year-old male who developed a skin reaction, diagnosed as bullous fixed drug reaction, five days after the commencement of co-trimoxazole (two tablets daily). During the assessment of the case, it was noted that fixed drug eruption is not listed in the approved SAHPRA PIs of cotrimoxazole, however, it is listed in the approved PIs of the recognised regulatory authorities (RRAs).

Data from VigiBase® (a World Health Organization's global Individual Case Safety Report (ICSR) database that contains ICSRs submitted by the participating member states enrolled under WHO's international drug monitoring programme), literature and PIs of SAHPRA's recognised regulatory authorities (RRAs) support a plausible relationship between co-trimoxazole use and the risk of fixed drug eruptions. Although fixed drug eruptions are usually self-limiting, the mainstay of treatment involves identification and withdrawal of the culprit agent. It is important for healthcare professionals and patients to be able to identify the culprit agent based on the information made available on the PI/PIL.

b) Decision

- SAHPRA recommended that applicants/ HCRs of co-trimoxazole-containing medicines update the PI/PIL under 'Undesirable effects' section to include the risk of fixed drug eruption.
- The benefit-risk profile of co-trimoxazole-containing medicines, remains favourable, provided the applicants/ HCRs effect the recommended changes.

2.1.9 Fexofenadine - Risk of Blurred Vision and Drug-Drug Interaction with Apalutamide

a) Background

SAHPRA conducted a review of safety signals regarding the risk of blurred vision and drug-drug interactions with apalutamide following the use of fexofenadine-containing medicines. Fexofenadine is an antihistamine and is registered for the treatment of symptoms associated with seasonal allergic rhinitis (allergies) and symptoms associated with chronic hives (chronic idiopathic urticaria).

The safety signal emanated from the EMA's PRAC recommendations for applicants/ HCRs to update fexofenadine-containing medicines' SmPC with the two identified risks. PRAC found the available data

from fexofenadine PSUR assessment, a clinical trial published in the literature and the plausible mechanism of action, sufficient to support the association on drug-drug interactions between fexofenadine and apalutamide. Furthermore, available data on blurred vision from spontaneous reports including many cases with a close temporal relationship, a positive dechallenge and/ or rechallenge, was also considered. The causal relationship between fexofenadine and blurred vision was found reasonably possible.

b) Decision

- SAHPRA recommended that applicants/ HCRs of fexofenadine-containing medicines update the PI/PIL of their products in line with EMA's PRAC's recommendations.
- The benefit-risk balance of fexofenadine-containing medicines remains favourable for its registered indication(s).

2.1.10 Piperacillin – Hemophagocytic Lymphohistiocytosis (HLH)

a) Background

SAHPRA conducted a review of a safety signal regarding the risk of hemophagocytic lymphohistiocytosis (HLH) associated with the use of piperacillin-containing medicines. Piperacillin is an antibacterial medicine registered for treatment of moderate to severe infections caused by certain bacteria.

The safety signal emanated from the Japan Ministry of Health, Labor and Welfare (MHLW)/ PMDA's request for applicants/ HCRs of piperacillin-containing medicines to revise the precautions section in their product's label to include the risk of HLH. PMDA based their decision on the assessment of cases involving HLH reported in Japan and overseas.

Furthermore, the EMA's PRAC reviewed a published case series that described cases of HLH observed in patients following treatment with piperacillin/ tazobactam or piperacillin single component for longer than 10 days. Clinical symptoms of HLH in three (3) children were reported to have improved following cessation of piperacillin/ tazobactam in combination with corticosteroid therapy (e.g., intravenous prednisolone/ methylprednisolone), one of which involved the addition of Intravenous human immunoglobulin (IVIG).

HLH is an immune deficiency disorder where part of the immune system is missing or defective and this means that the body can't fight infections as it should. HLH has high mortality rates and a delay in diagnosis of HLH is often the greatest barrier to favourable outcomes owing to the rarity of the disease, variety of clinical presentations, and confounding factors such as underlying diseases/ conditions. Early detection and timely treatment of piperacillin induced HLH are critical for improving clinical outcomes while minimising morbidity and mortality.

b) Decision

- SAHPRA recommended that applicants/ HCRs of piperacillin-containing medicines update their PI/PIL to include the risk of HLH in line with the EMA's PRAC recommendations.

- The benefit-risk balance of piperacillin-containing medicines with regard to HLH remains unchanged provided applicants/ HCRs effect the recommended changes.

2.1.11 Metoclopramide - Dystonic Side Effects in Children and Young Adults

a) Background

SAHPRA conducted a review of a safety signal regarding an increased risk of dystonic side effects in children and young adults associated with the use of metoclopramide. Metoclopramide is an anti-emetic registered for prevention of nausea and vomiting. Dystonia is a movement disorder that involves uncontrolled muscle contractions, which can cause abnormal whole-body movements such as repetitive patterned movements (continuous or intermittent) or parts of the body twisting in unusual ways.

The safety signal emanated from New Zealand Medsafe's regulatory decision to request applicants/ HCRs to update the PIs of metoclopramide containing medicines with the increased risk of dystonic side effects in children and young adults and to restrict metoclopramide use in children and young adults (aged 1 to 19 years, inclusive) due to the risk of dystonic side effects.

The available data indicates that dystonic side effects in children and young adults are well known. However, inconsistencies in the SAHPRA approved PI of metoclopramide-containing medicines were noted. The increased risk of extrapyramidal side effects, including dystonia is sufficiently addressed in the innovator's most recent SAHPRA approved PI.

b) Decision

- SAHPRA recommended that applicants/ HCRs of metoclopramide-containing medicines update the PI/PIL of their medicines in line with the innovator PI regarding the increased risk of extrapyramidal side effects.
- The benefit-risk balance of metoclopramide-containing medicines remains favourable provided applicants/ HCRs effect the recommended changes.

2.1.12 Lopinavir/Ritonavir - Drug-Drug Interactions with Direct Acting Oral Anticoagulants

a) Background

SAHPRA conducted a review of a safety signal regarding the risk of drug-drug interactions (DDI) between lopinavir/ ritonavir and direct acting oral anticoagulants (DOACs). Lopinavir/ ritonavir is an antiviral registered for the suppression of HIV infection. The safety signal emanated from a regulatory decision taken by EMA's PRAC for the applicants/ HCRs to update the PI of lopinavir/ ritonavir (LPV/r) on drug-drug interaction with direct oral anticoagulants (medicines as dabigatran and edoxaban that help to prevent formation of blood clots. They are used in the prevention of stroke specifically for people with abnormal heart rhythm or arrhythmia).

b) Decision

- SAHPRA recommended that applicants/ HCRs of dabigatran-containing medicines include interactions with protease inhibitors such as ritonavir in the PI/PIL and further adopt EMA's recommended wording regarding clinical monitoring and/ or dose reduction of the DOACs.
- The benefit-risk balance of both protease inhibitors and DOACs remains favourable provided applicants/ HCRs effect the recommended changes.

2.1.13 Voriconazole - Drug-Drug Interactions between Voriconazole and Flucloxacillin

a) Background

SAHPRA became aware of EMA's PRAC recommendations regarding drug interactions between voriconazole and flucloxacillin leading to subtherapeutic levels of voriconazole. PRAC recommended that all applicants/ HCRs should update the PI of their voriconazole and flucloxacillin-containing medicines to reflect the drug interactions after consideration of evidence from the literature, and the responses from the applicants/ HCRs for Vfend® (voriconazole). Flucloxacillin is an antibiotic registered for the treatment of bacterial infections caused by bacteria. Voriconazole is an antifungal registered for the treatment of fungal infections.

b) Decision

- SAHPRA took a decision to align with EMA's PRAC recommendations and recommended all applicants/ HCRs of voriconazole and flucloxacillin containing medicines to update their PI/PIL with the risk of drug interactions between voriconazole and flucloxacillin in line with EMA.
- The benefit-risk balance of both voriconazole and flucloxacillin-containing medicines remains favourable provided applicants/ HCRs effect the recommended changes.

2.2 Periodic Safety Update Reports (PSURs)/ Periodic Benefit-Risk Evaluations Reports (PBRER)

2.2.1 Remdesivir – Periodic Safety Update Report (PSUR)

a) Background

SAHPRA conducted a review of the fifth periodic safety update report (PSUR) of Veklury® (remdesivir). Veklury® is an antiviral nucleotide pro-drug that is intracellularly metabolised into an analogue of adenosine triphosphate that inhibits viral RNA polymerases, and it is registered for the treatment of COVID-19 in adults. The six-monthly PSUR (covering the period of 07 November 2022 to 06 May 2023) was submitted as a condition of registration. Veklury® is registered (55/20.2.8/0458) but not marketed in South Africa. However, the applicant allows their voluntary license holders to import the generic version of remdesivir into South Africa via the Section 21 route. There is currently no remdesivir generic registered in South Africa.

With an estimated post-marketing patient exposure to Veklury® of over 4.9 million patients, remdesivir has extensive post-marketing safety experience with no new adverse drug reactions, or

risks identified during the reporting interval. There were updates to Veklury®'s PI made by other regulatory authorities, and these include addition of the risk of anaphylactic shock in the EU SmPC and inclusion of sinus bradycardia in the Japanese PI. The available data continues to support the positive benefit-risk balance for remdesivir in the treatment of COVID-19.

b) Decision

- SAHPRA found the benefit-risk balance of Veklury® favourable for its registered indications and recommended continuous pharmacovigilance monitoring by the applicant/ HCR.

2.2.2 COVID-19 Vaccine Janssen® – Periodic Benefit Risk Evaluation (PBRER)

a) Background

SAHPRA conducted a review of COVID-19 Vaccine Janssen® (Ad26.COV2.S)'s periodic benefit risk evaluation report (PBRER) for the reporting period 01 September 2022 to 28 February 2023. The PBRER was submitted as a condition of registration. COVID-19 Vaccine Janssen® is used for preventing COVID-19 caused by the SARS-CoV2 virus in adults aged 18 years and older. The vaccine causes the immune system (the body's natural defences) to produce antibodies and specialised white blood cells that work against the virus, therefore providing protection against COVID-19.

The review of the PBRER revealed that spontaneous/ solicited post-marketing reporting of adverse events led to the identification of serious adverse events/reactions such as thrombotic thrombocytopenia syndrome, Guillain Barré syndrome, immune thrombocytopenia, and myocarditis/ pericarditis. These risks occur very infrequently, are adequately monitored, and do not outweigh the significant benefits of single dose vaccination with COVID-19 Vaccine Janssen® in controlling the global pandemic.

The totality of data supports that vaccination with COVID-19 Vaccine Janssen® remains efficacious against severe/ critical COVID-19, including hospitalisations and deaths related to COVID-19, and against some emerging variants. Data on booster usage (homologous or heterologous) suggests increased effectiveness in protecting against COVID-19 including some variants of concern and variants of interest.

b) Decision

- SAHPRA found the benefit risk balance of COVID-19 Vaccine Janssen® favourable when used as recommended for the currently approved indication(s) and recommended continuous pharmacovigilance monitoring of COVID-19 Vaccine Janssen® by the applicant/ HCR.

2.2.3 Covovax® - Periodic Safety Update Report (PSUR)

a) Background

SAHPRA conducted a review of Covovax® (SARS-CoV-2 rS Protein (COVID-19) recombinant spike protein Nanoparticle Vaccine) periodic safety update report (PSUR). The six-monthly PSUR covering the period of 16 August 2022 to 15 February 2023 was submitted as a condition of registration. Covovax® is registered for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in

individuals 12 years of age and older. The vaccination course consists of two separate doses of 0.5 ml each, with the second dose recommended to be administered three (3) weeks after the first dose.

Cumulative exposure from post-marketing experience for the reporting interval is 9.334 million doses. Covovax® was not marketed in South African post registration. There were no adverse events reported, nor actions taken for safety reasons, or withdrawal nor suspension of marketing authorisation reported for the reporting interval. Furthermore, no clinical trials carried out for the evaluation of the vaccine were suspended or stopped for safety reasons. The overall benefit-risk profile of Covovax® was found positive for its registered indication.

b) Decision

- SAHPRA found the benefit risk balance of Covovax® favourable when used as recommended for the currently approved indication(s) and recommended continuous pharmacovigilance monitoring of Covovax® by the applicant/ HCR.

2.3 Risk Management Plans (RMPs)

2.3.1 Spravato® (Esketamine) – Risk Management Plan (RMP)

a) Background

SAHPRA conducted a review of Spravato® risk management plan (RMP). Spravato® contains the active substance esketamine and is registered as an anti-depressant for the treatment of resistant depression in conjunction with other antidepressants, in adult patients who have not responded adequately to treatment with at least two different antidepressants at adequate doses and duration to treat the current depressive episode. The RMP was assessed to determine the adequacy, applicability to SA settings and implementability of the proposed risk minimisation measures for preventing or minimising risks associated with the use of Spravato® in patients, based on the product's safety characterisation/ profile.

The RMP (European version) contained proposed routine and additional pharmacovigilance activities such as ongoing studies, National Pregnancy Registry for Antidepressants, etc. Routine and additional risk minimisation measures such as Healthcare Professional Checklist, Controlled Access Program, Healthcare Professional Guide and Patient Guide that addresses the important identified risks such as drug abuse, transient dissociative states and perception disorders, disturbances in consciousness, and blood pressure increase. The Controlled Access Program was found unsuitable for the current South African settings due to its restrictive nature. Therefore, the EU RMP of Spravato® was not accepted.

b) Decision

- SAHPRA accepted the HCR's Core RMP of Spravato® which did not include the Controlled Access Program as a risk minimisation measure.
- The benefit-risk profile of Spravato® remains favourable for its registered indication(s).

2.4 Post Authorisation Safety Studies

2.4.1 Delamanid – Risk of QT Prolongation (Pass Results)

a) Background

SAHPRA conducted a review of the results of EU-PASS 242-12-402 which is a multicentre, EU-wide, non-interventional post-authorisation study intended to assess the safety and usage of delamanid in routine medical practice in multidrug-resistant tuberculosis patients. Delamanid is a medicine that belongs to a group of antimicrobials and is registered for the treatment of tuberculosis in the lung caused by mycobacteria that are not killed by the most commonly used antimicrobials to treat tuberculosis.

The study is an additional pharmacovigilance activity, aimed to monitor the usage of delamanid in a real-life setting when prescribed as part of an appropriate combination regimen (ACR) designed by the treating physician.

Safety data presented in the EU PASS study results was found to be in line with the known safety profile of delamanid. QT prolongation (a heart rhythm disorder that can potentially cause fast, chaotic heartbeats) was the most prominent risk related to delamanid use noted from the study. This risk is well known and was managed with frequent electrocardiogram (ECG) (records the electrical signal from the heart to check for different heart conditions) monitoring during the study. All risks are adequately addressed in the SmPC, RMP and PI.

b) Decision

- SAHPRA accepted the results of the EU-PASS 242-12-402 study. The benefit risk profile of delamanid containing medicines was found favourable for its registered indication.
- Continuous pharmacovigilance monitoring by the applicant/ HCR was recommended.

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SIGNIFLOW

Dr Boitumelo Semete-Makokotlela
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20 May 2024