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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 January – March 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.

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1. DEFINITIONS

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

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 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.

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.

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.

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.

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 Amlodipine - Risk of Non-Cardiogenic Pulmonary Oedema

a) Background

SAHPRA conducted a review of a safety signal regarding the risk of non-cardiogenic pulmonary oedema following an overdose administration of amlodipine. Amlodipine belongs to a group of medicines called calcium channel blockers and it is registered for the treatment of high blood pressure and angina, alone or in combination with other medication.

The safety signal emanated from the assessment of amlodipine-containing medicines' periodic safety update report (PSUR(s)), conducted by the European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC). Based on the reviewed data from literature, post marketing spontaneous reports and a plausible mechanism of action, PRAC concluded that there is a possible causal relationship between the risk of non-cardiogenic pulmonary oedema and the use of amlodipine -containing medicines.

b) Decision

- SAHPRA recommended that Applicants/ HCRs of amlodipine-containing medicines amend PIs/PILs of their medicines accordingly to include non-cardiogenic pulmonary oedema as an undesirable effect following amlodipine overdose.
- The benefit-risk profile of amlodipine-containing medicines remains favourable, provided the Applicants/ HCRs effect the recommended changes.

2.1.2 Diltiazem Hydrochloride – Risk of Lupus-Like Syndrome, Renal Failure and DDI with Lomitapide

a) Background

SAHPRA learnt of the risk of lupus-like syndrome, acute kidney injury, renal failure, and drug-drug interaction with lomitapide associated with the use of diltiazem-containing medicines. Diltiazem is a calcium-channel blocking medicine registered for the treatment of high blood pressure and angina. The safety concern was based on a PSUR review of diltiazem by EMA's PRAC. Based on the reviewed data from the literature and spontaneous reports including in some cases a close temporal relationship and a positive de-challenge, and a plausible mechanism of action, the risks were considered to be at least a reasonable possibility.

b) Decision

- SAHPRA took a regulatory decision to adopt EMA's decision and recommended that Applicants/ HCRs of diltiazem-containing medicines align with EMA's recommendation to include the risk of lupus-like syndrome, acute kidney injury, renal failure and drug-drug interaction with lomitapide in the PI/PIL of diltiazem.

- SAHPRA considers the benefit-risk profile of diltiazem-containing medicines favourable, provided the Applicants/ HCRs effect the recommended changes.

2.1.3 Filgastrim and Lipegfilgastrim – Risk of myelodyplastic Syndrome (MDS) and Acute Myeloid Leukemia (AML) in Breast and Lung Cancer

a) Background

SAHPRA conducted a review of the risk of a pre-cancerous blood condition known as myelodysplastic syndrome (MDS) and blood cancer called acute myeloid leukaemia (AML) occurring in breast and lung cancer patients associated with the use of filgrastim/ lipegfilgrastim-containing medicines. Filgrastim/ lipegfilgrastim is a white blood cell growth factor (called granulocyte colony stimulating factor [G-CSF]) registered for the reduction of the duration of neutropenia (low white blood cell count) and the occurrence of febrile neutropenia (low white blood cell count with a fever) which can be caused by the use of cytotoxic chemotherapy (medicines that destroy rapidly growing cells). White blood cells are important as they help the body fight infections. MDS and AML are a well-known risk for filgrastim-containing medicines based on the available data from various sources including literature and is documented in some of the SAHPRA approved PIs/PILs of filgrastim-containing medicines.

b) Decision

- SAHPRA recommended that all Applicants/ HCRs of filgrastim/ lipegfilgrastim-containing medicines update their PI/PIL to include the risk of MDS and AML if they have not yet done so.
- SAHPRA considers the benefit-risk profile of filgrastim/ lipegfilgrastim-containing medicines favourable, provided the Applicants/ HCRs effect the recommended changes.

2.1.4 Triazolam - Risk of Neonatal Sedation and Withdrawal Syndrome

a) Background

SAHPRA conducted a review of a safety signal regarding the risk of neonatal sedation and withdrawal syndrome associated with prenatal exposure to triazolam. Triazolam belongs to a group of medicines known as benzodiazepines, used for the short-term management of sleep problems (insomnia).

The safety signal emanates from the U.S. Food and Drug Administration's (USFDA) regulatory decision to request marketing authorisation holders to update PIs of triazolam medicines with the risk of neonatal sedation and withdrawal syndrome under 'Overdosage', 'Pregnancy and lactation' and 'Warnings and precautions' sections. It was noted that the SAHPRA approved PI of triazolam contraindicate triazolam use in pregnant women, women at risk of pregnancy and breastfeeding mothers.

b) Decision

- SAHPRA recommended that all Applicants/ HCRs of triazolam-containing medicines update their PI/PIL to include the risk of neonatal sedation and withdrawal syndrome associated with prenatal exposure to triazolam.

- SAHPRA considers the benefit-risk profile of triazolam-containing medicines favourable, provided the Applicants/ HCRs effect the recommended changes.

2.1.5 Ustekinumab - Risk of Opportunistic Infections and Lupus-related Conditions

a) Background

SAHPRA conducted a review regarding the potential risk of opportunistic infections and lupus related conditions following the use of ustekinumab-containing medicines. Ustekinumab belongs to a group of medicines called 'immunosuppressants' and is used for the treatment of inflammatory diseases - Crohn's disease and ulcerative colitis in adults.

The safety signals emanated from a periodic safety update report (PSUR) review of ustekinumab by EMA's PRAC. Based on post marketing data, PRAC recommended an update to the European Summary of Product Characteristics (SmPC) to include the risk of lupus related conditions and opportunistic infections (illnesses that occur more frequently and are more severe in people with weakened immune system) which include bacterial infections such as atypical mycobacterial infection, listeria meningitis, pneumonia legionella, and nocardiosis; opportunistic fungal infections; opportunistic viral infections such as encephalitis caused by herpes simplex 2; and parasitic infections such as ocular toxoplasmosis.

b) Decision

- SAHPRA recommended that Applicants/ HCRs of ustekinumab-containing medicines update the PI/PIL of their medicines in line with EMA's recommendations.
- The benefit-risk balance of ustekinumab is considered favourable provided the Applicants/ HCRs effect the recommended changes.

2.1.6 Statin-Containing Medicines - Risk of Myasthenia Gravis and Ocular Myasthenia

a) Background

SAHPRA conducted a review of a safety signal regarding the risk of myasthenia gravis and ocular myasthenia associated with the use of statin containing medicines. Statins are medicines used to lower levels of total "bad" cholesterol, in the blood and raise 'good' cholesterol level. They are used to treat raised cholesterol level in the blood (primary hypercholesterolaemia) or elevated fat levels in the blood (mixed hyperlipidaemia).

The safety signal was based on the assessment by EMA's PRAC. Based on the reviewed data, PRAC noted that numerous literature studies suggest a causal link between statins and myasthenia gravis, however few cases were reported in the databases, suggesting that the risk of developing myasthenia gravis is rare with the use of statins. In view of the review of all the available information including comments provided by Applicants, EMA took a regulatory decision to request Applicants/ HCRs of statin-containing medicines to update the PI/PIL of their products to include the risk of myasthenia gravis and ocular myasthenia.

b) Decision

- SAHPRA recommended that Applicants/ HCRs of statin-containing medicines update the PI/PIL of their medicines to include the risk of myasthenia gravis and ocular myasthenia.
- The benefit-risk balance of statins-containing medicines remain positive for their registered indications, provided the Applicants/ HCRs effect the recommended changes.

2.1.7 Cephalosporin-Containing Medicines – Risk of Neurotoxicity

a) Background

SAHPRA conducted a review of the risk of neurotoxicity (a damage, destruction, or impairment to the functioning of the central and/ or peripheral nervous system caused by a synthetic or naturally occurring substances) associated with the use of cephalosporin-containing medicines. Cephalosporins are a group of antibiotics-containing medicines used to treat infections in different parts of the body caused by bacteria.

The safety concern emanated from safety alert published by the USFDA on their website regarding the risk of neurotoxicity, which includes the need to adjust the dosage in patients with renal impairment associated with the use of cephalosporin containing medicines. The USFDA also identified cases of nonconvulsive status epilepticus associated with the use of cephalosporin-containing medicines, from the medical literature and from the USFDA's Adverse Event Reporting System (FAERS) database. These cases usually resolved after discontinuing treatment and/or after haemodialysis. The USFDA requested that marketing authorisation holders (MAHs) revise the 'Warnings and Precautions' and 'Adverse Reactions' sections of the PIs to highlight the risk of seizures with the use of cephalosporins.

The risk of neurotoxicity associated with the use of cephalosporins is well established and is included in some of SAHPRA approved PIs of cephalosporin-containing medicines.

b) Decision

- SAHPRA recommended that Applicants/ HCRs of cephalosporin-containing medicines should update the PI/PIL of their products to include the risk of neurotoxicity if they have not done so.
- The benefit-risk balance of cephalosporins-containing medicines remain positive for its registered indications, provided the Applicants/ HCRs effect the recommended changes.

2.1.8 Carboplatin – Risk of Kounis Syndrome

a) Background

SAHPRA conducted a review of a safety signal regarding the risk of Kounis syndrome associated with the use of carboplatin-containing medicines. Carboplatin belongs to a group of medicines known as alkylating agents. It has anti-tumour properties and is used to treat patients with advanced or recurrent ovarian cancer.

The safety signal was identified by the EMA's PRAC's following the assessment of a single PSUR (PSUSA/00000559/202201) for carboplatin. PRAC further reviewed spontaneous cases, the literature, and biological plausibility, and concluded that there is reasonable evidence to suggest a causal relationship between exposure to carboplatin and the development of Kounis syndrome.

Kounis syndrome is a potential life-threatening adverse reaction of multiple drugs and is defined as cardiovascular symptoms that occur secondary to allergic or hypersensitivity offences. Kounis syndrome is commonly identified as the cause of acute coronary events in patients without previous history of coronary artery disease (CAD). It was noted that warnings on allergic reactions/ hypersensitivity are documented in the SAHPRA approved PIs of carboplatin, however, there is no mention of allergic angina or allergic myocardial infarction.

The reviewed data including published literature and biological plausibility provide sufficient evidence to associate risk of developing Kounis syndrome during the use of carboplatin-containing medicines.

b) Decision

- SAHPRA recommended that Applicants/ HCRs of carboplatin-containing medicines update PIs/PILs of their medicines to include the risk of Kounis syndrome in line with PRAC's recommendations.
- The benefit-risk balance of carboplatin containing medicines remain positive for its registered indications, provided the Applicants/ HCRs effect the recommended changes.

2.1.9 Ciprofloxacin – Risk of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

a) Background

SAHPRA conducted a review of a safety signal regarding the risk of drug reaction with eosinophilia and systemic symptoms (DRESS) associated with the use of ciprofloxacin. Ciprofloxacin is a medicine that belongs to a group of antibiotics called the fluoroquinolones. It kills bacteria by inhibiting certain bacterial enzymes responsible for the replication of the bacteria. Ciprofloxacin is registered for the treatment of adults with severe and/ or complicated bacterial infection of the lungs, bladder, gut, bone, or skin and soft tissues where other antimicrobials used for similar infections were considered not to be an appropriate treatment option, have failed, cannot be used or are not tolerated.

The safety signal was published by the Therapeutic Goods Administration (TGA) (the medicine and therapeutic regulatory agency of the Australian Government.) on their website. The allergic mechanism of fluoroquinolones is mainly immunoglobulin E and T-cell-dependent reactions. Although DRESS syndrome caused by fluoroquinolones is rarely reported, the available post-marketing data including data from published literature suggests that although rare, quinolones are associated with the risk of DRESS.

SAHPRA approved PIs of ciprofloxacin- containing medicines list Toxic epidermal necrolysis (TEN) and Stevens–Johnson syndrome (SJS) under Undesirable effects section. DRESS is a significant risk associated with quinolone-containing medicines. Due to the distinct clinical, biological,

histopathological characteristics, different treatments and prognoses of SJS/TEN and DRESS, DRESS should be listed in the ciprofloxacin PI under warning and precautions and undesirable effects section as severe cutaneous adverse reactions (SCARs).

b) Decision

- SAHPRA recommended that Applicants/ HCRs of all registered quinolone-containing medicines update PI/PIL of their medicines to include DRESS under warnings and special precautions for use and adverse effects section.
- The benefit-risk balance of quinolones-containing medicines remain favourable provided the Applicants/ HCRs effect the recommended changes.

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

2.2.1 COMIRNATY® (COVID-19 mRNA Vaccine) – Periodic Safety Update Report

a) Background

SAHPRA conducted a review of coronavirus (COVID-19) mRNA vaccine (Comirnaty®)'s 4th periodic safety update report (PSUR) (19 June to 18 December 2022). Comirnaty® is a COVID 19 mRNA vaccine registered for active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 virus in individuals from the age of five (5) years in SA (six (6) months of age and older elsewhere). Cumulatively, over four (4) billion doses of Comirnaty® were distributed for use worldwide, up to the reporting interval. Extensive surveillance activities were conducted globally.

The reviewed data from the PSUR reporting interval, revealed no new safety concerns or changes to the benefit-risk profile of Comirnaty®. No further changes to the product information or additional risk minimisation activities were warranted in addition to those already documented.

b) Decision

- SAHPRA found the overall benefit-risk profile of Comirnaty® favourable and recommended continuous pharmacovigilance monitoring.

2.2.2 Aranesp® (Darbepoetin Alfa) – Periodic Safety Update Report

a) Background

SAHPRA conducted a review of the 38th Aranesp® (darbepoetin alfa) periodic safety update report (PSUR) for the reporting period of 01 November 2021 to 31 October 2022. The PSUR was submitted as a condition of registration for the product. The PSUR contained the required safety data of summarised interval and cumulative benefit-risk information regarding Aranesp®. During the reporting period, evaluation of the safety data revealed no new risks or significant actions taken, or changes made to the Company Core Safety Information (CCSI) for Aranesp®. The overall data received during the reporting period did not indicate a change in the positive benefit-risk profile of Aranesp®.

b) Decision

- SAHPRA found the overall benefit-risk balance of Aranesp® for its approved indications favourable during the reporting period.
- SAHPRA recommended the discontinuation of close monitoring of Aranesp® and continuous pharmacovigilance surveillance which include submission of a PSUR as per the guideline 'SAHPGL-CEM-PV-04 Post Marketing reporting of ADRs for Human Medicines in South Africa.'

2.2.3 Symbicord – Periodic Benefit Risk Evaluation Report (PBRER)

a) Background

SAHPRA conducted a review of budesonide/ formoterol (Symbicord®) turbuhaler's 12th periodic benefit risk evaluations report (PBRER) for the period of 25 August 2021 to 24 August 2022. Symbicord® turbuhaler is a combination of budesonide and formoterol which through different ways (mechanism) treat asthma and Chronic Obstructive Pulmonary Disease (COPD). The PBRER was submitted as a condition of registration for the product. The PBRER review revealed no significant actions related to safety actions taken or proposed during the reporting period. Data received during the reporting period did not indicate a change in the positive benefit-risk profile of Symbicord®.

A clinical development programme - PT009 and an Applicant-sponsored ongoing Symbicord® clinical trial were noted. No important safety findings relevant to the benefit-risk assessment of Symbicord® were identified from both the clinical trial and clinical development programme.

Furthermore, an off-label use of Symbicord® for the treatment of COVID-19 during the reporting period was noted. Data received regarding Symbicord® use during COVID-19 pandemic did not suggest any significant changes in the safety profile of Symbicord® in its registered indication, nor indicate any important unexpected benefit in off-label use.

b) Decision

- SAHPRA found the overall benefit-risk balance of Symbicord® favourable for its approved indications during the reporting period and recommended discontinuation of close monitoring of Symbicord®.
- SAHPRA recommended that Symbicord® should follow the routine pharmacovigilance monitoring as stipulated in the *SAHPGL-CEM-PV-04 Post Marketing reporting of ADRs for Human Medicines in South Africa*, guideline.

2.3 Risk Management Plans (RMPs)

2.3.1 Deltyba® (Delamanid) – Risk Management Plan (RMP)

a) Background

SAHPRA conducted a review of Deltyba® (delamanid) risk management plan (RMP) version 4.1 dated 25 May 2022, with a data lock point of 27 April 2021. Delamanid is a medicine that belongs to a group

of antimicrobials, used in the treatment of tuberculosis in the lungs caused by mycobacteria that are not killed by the most commonly used antimicrobials.

Cumulative exposure of 1,377 patients in clinical trials and 45,522 patients from post-marketing data worldwide with South Africa having 4,087 patients and 1,881 patient-treatment years, was noted. The important identified risks, potential identified risks, and missing information outlined in the RMP was reviewed.

There were no new safety concerns or risks identified from the RMP. Safety concerns, including the risk of QT prolongation and the monitoring thereof, were adequately addressed. The review of delamanid RMP found the safety concerns and the planned pharmacovigilance monitoring measures acceptable for its approved indication.

b) Decision

- SAHPRA found delamanid RMP version 4.1 acceptable and recommended continuous monitoring of the benefit-risk profile of delamanid containing medicines.

2.3.2 Fentora® (Fentanyl) – Risk Management Plan

a) Background

SAHPRA conducted a review of Fentora® risk management plan (RMP) submitted as part of a new registration application. Fentora® is a fentanyl-containing medicine that belongs to a group of strong painkillers, which are also called opioids. The RMP described the implementation plan and the risk minimisation measures, which include SAHPRA approved PI and the proposed educational materials for patients/ caregivers, doctors, and pharmacists. The RMP detailed all required information such as the characterisation of safety concerns, pharmacovigilance plan and risk minimisation measures including additional risk minimisation measures (RMMs).

b) Decision

- SAHPRA found the Fentora® RMP acceptable and recommended continuous monitoring of Fentora®'s benefit-risk balance profile.

2.3.3 Imbruvica® (Ibrutinib) – Risk Management Plan (RMP)

a) Background

SAHPRA conducted a review of a risk management plan (RMP) of Imbruvica® (ibrutinib). Imbruvica® is an anticancer medicine used to treat different types of blood cancers (such as Mantle Cell Lymphoma (MCL), Chronic Lymphocytic Leukaemia (CLL) and Waldenström's Macroglobulinaemia (WM)) in adults. The submission of Imbruvica® RMP was requested by SAHPRA for the assessment of the benefit -risk profile of ibrutinib, and the risk minimisation measures in place. The request was triggered by the Applicant's proposal to distribute a dear healthcare professional letter to inform healthcare professionals about cardiovascular risks (Atrial fibrillation, ventricular tachyarrhythmias, cardiac failure, use in patients with severe cardiac disease) associated with the use of ibrutinib.

The routine risk minimisation measures and planned additional pharmacovigilance activities, include targeted follow-up of adverse events (AEs) through a guided questionnaire for each identified safety concern, periodic safety update reports and a dear healthcare professional letter (DHCPL). The DHCPL aimed to increase awareness of important cardiovascular risks associated with the use of ibrutinib and to provide guidance on how to manage these risks.

b) Decision

- SAHPRA found the Imbruvica® RMP acceptable and recommended continuous routine pharmacovigilance monitoring.

2.3.4 Lenalidomide DRL® - Risk Management Plan (RMP)

a) Background

SAHPRA conducted a review of lenalidomide DRL® risk management plan. Lenalidomide belongs to a group of medicines called immunomodulators, which can modify or regulate the functioning of the immune system. Lenalidomide DRL® is used in combination with other medicines in the treatment of adult patients who have previously received treatment for multiple myeloma and to treat adult patients who have been diagnosed with myelodysplastic syndromes.

Lenalidomide DRL® is registered for marketing under a restricted distribution programme called LEN PERM (program for the evaluation of risk and management).

Planned additional pharmacovigilance activities for Lenalidomide DRL® include a Pregnancy Registry. The primary objectives of the Lenalidomide Pregnancy Registry are to determine lenalidomide exposure status for each reported pregnancy and to collect pregnancy outcomes, other pregnancy or delivery complications or abnormalities, abnormal foetal outcomes, neonate/ infant outcomes and infant follow-up for reports of foetal exposure, indeterminate exposure, and/ or breastfeeding exposure (six (6) monthly for one (1) year).

Routine pharmacovigilance activities, routine risk minimisation activities and additional risk minimisation activities were found to be appropriate for the important identified and potential risks.

b) Decision

- SAHPRA found the RMP of lenalidomide DRL® acceptable and recommended continuous pharmacovigilance monitoring of the benefit-risk balance of lenalidomide DRL®.

2.4 Additional Risk Minimisation Measures (aRMMs)

2.4.1 Roaccutane® (Isotretinoin) – Additional Risk Minimisation Measures

a) Background

SAHPRA conducted a review of isotretinoin additional Risk Minimisation Materials (aRMMs). Roaccutane is a medicine that contains isotretinoin which is a substance related to vitamin A, and one of a group of medicines called retinoids. Roaccutane is used to treat severe forms of acne (such as nodular or conglobate acne, or acne that is at risk of causing permanent scarring) in adults and adolescents (older than 12 years of age).

The reviewed aRMMs include a letter to HCPs, physician checklist/ acknowledgement form, pharmacist checklist and patient reminder card regarding the important identified risk of teratogenicity and congenital malformations following the use of isotretinoin. The Applicant planned to disseminate the aRMMs on an annual basis, through physical distribution using wholesalers and via email using Medpages (targeting 167 Dermatologists, 8275 General Practitioners and 4159 Pharmacies).

The aRMMs are aligned with the RMP in addressing the important identified risk of teratogenicity and congenital malformations with the use of isotretinoin. Moreover, it was noted that the SAHPRA approved PI includes a boxed warning of teratogenicity and states that the doctor should provide the material to reinforce the warnings and the need for contraception in women of childbearing age as part of the Pregnancy Prevention Programme.

b) Decision

- SAHPRA accepted and approved the aRMMs of isotretinoin for implementation and recommended continuous pharmacovigilance monitoring of the benefit-risk balance of isotretinoin-containing medicines.

2.5 Cancellation and Withdrawal of Registration of Medicines

2.5.1 Pholcodine – Increased Risk of Anaphylactic Reaction during General Anaesthesia with Neuromuscular Blocking Agents (NMBAs) Post Pholcodine Use

a) Background

SAHPRA conducted a review of a safety signal regarding increased risk of anaphylactic reaction during general anaesthesia with neuromuscular blocking agents (NMBAs) associated with the use of pholcodine-containing medicines. The safety concern emanated from the EMA's PRAC's recommendation to withdraw pholcodine-containing medicines from the European markets due to its association with anaphylactic reaction (sudden, severe, and life-threatening allergic reactions) occurring during surgery with the use NMBAs.

Pholcodine is a medicine registered for the treatment of non-productive (dry) cough and is available in a number of non-prescription medicines, either as a single active ingredient or in combination with other medicines. NMBAs are used as muscle relaxants during surgery.

Reviewed available data including the results of the Allergy to Neuromuscular Blocking Agents and Pholcodine Exposure (ALPHO) study carried out to assess the relationship between pholcodine exposure and NMBA-related anaphylaxis suggested that exposure to pholcodine up to 12 months before an anaesthesia procedure significantly increases the risk of having an NMBA-related anaphylaxis, which confirms a link between pholcodine exposure and NMBA-related anaphylaxis.

Effective measures to minimise this risk and risk factors for NMBA-related anaphylaxis could not be identified because surgery is not always a planned procedure, and any person exposed to pholcodine is at risk should they require a NMBA during surgery within 12 months of pholcodine use. Moreover, the decision to use a NMBA during anaesthesia and the choice of NMBA is based on clinical necessity regardless of history of pholcodine use, the availability of the NMBA, patient factors, co-morbidities, type of procedure being performed, and the clinical indication.

b) Decision

- In consideration of the available data and the significance of the risk associated with pholcodine use, SAHPRA found the benefit-risk profile of pholcodine unfavourable and took a regulatory decision to withdraw pholcodine-containing medicines from the South African market.

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