SAHPRA
South African
Health Products
Regulatory Authority

SAHPRA Head Office
Building A
Loftus Park
2nd Floor
Kirkness Str
Arcadia
0083

COMMUNICATION TO STAKEHOLDERS

Issue No: PV06-2023/24

15 May 2024

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 July – September 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 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

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 Phosphodiesterase-5 Inhibitors (PDE-5) – Risk of Retinal Detachment

a) Background

SAHPRA conducted a review of the risk of retinal detachment following the use of phosphodiesterase type 5 inhibitors (PDE-5). Phosphodiesterase inhibitors are medicines registered for the treatment of impotence or erectile dysfunction in men such as sildenafil and tadalafil. Some PDE-5 inhibitors are also used for the treatment of pulmonary arterial hypertension (high blood pressure in the blood vessels in the lungs).

The safety signal was based on an increased risk of retinal detachment during regular use of PDE-5 inhibitors described in a large epidemiological study and in various case reports. Based on the available data and study results, Swissmedic (Switzerland medicines regulatory authority) considered the causal link between administration of PDE-5 inhibitors and the occurrence of retinal detachments very probable and therefore recommended an update in the PI/PIL for PDE-5 inhibitors marketed in Switzerland.

It was noted that although the risk of retinal detachment is rare, users of PDE-5 inhibitors are likely to have comorbidities such as cardiovascular diseases, diabetes mellitus, etc, which are also risk factors to retinal detachment. Furthermore, retinal detachment is an emergency and can lead to loss of vision.

b) Decision

- SAHPRA recommended that applicants of PDE-5 inhibitors update the PI/PIL of their medicines to include a warning regarding the risk retinal detachment.
- SAHPRA considers the benefit-risk profile of PDE-5 inhibitors containing medicines favourable, provided the applicants effect the recommended changes.

2.1.2 Carbidopa/ Levodopa – Risk of Urinary Tract Infections

a) Background

SAHPRA became aware of the European Medicines Agency's (EMA's) decision to request all applicants of carbidopa/levodopa containing medicines to update their PI/PIL to include the risk of urinary tract infections under "Undesirable effects" and "Infections and infestations" subsections with "very common" frequency. Carbidopa/levodopa is a combination medicine registered for the treatment of symptoms of Parkinson's disease. Parkinson's disease is a chronic disorder characterised by slow and unsteady movement, muscular stiffness, and tremor.

EMA's decision was based on the Pharmacovigilance Risk Assessment Committee (PRAC)'s assessment of carbidopa/levodopa periodic safety update reports (PSURs) which found that serious cases of urinary tract infections (UTIs) in relation to carbidopa/levodopa use have been reported, including

reports with positive dechallenge and multiple cases with death outcome. In addition, a study from Germany found significantly increased risk of UTIs for carbidopa/levodopa.

b) Decision

- SAHPRA took a regulatory decision to adopt EMA's decision and requested all applicants/HCRs of carbidopa/levodopa medicines to align with EMA's recommendations by amending the PI/PIL in order to raise awareness on the occurrence of UTI in association with carbidopa/levodopa use.
- SAHPRA considers the benefit-risk profile of carbidopa/levodopa-containing medicines favourable, provided the applicants effect the recommended changes.

2.1.3 Liraglutide – Risk of Dizziness and Delayed Gastric Emptying

a) Background

SAHPRA became aware of EMA's decision to request all applicants of liraglutide-containing medicines (tablets and injectables) to update their PI/PIL to include the risk of 'dizziness' and 'delayed gastric emptying'. Liraglutide is an anti-diabetic medicine registered for use as an adjunct to diet and exercise to achieve glycaemic control in patients with type-2 diabetes mellitus, when previous therapy does not provide adequate glycaemic control. It is also registered to prevent Major Adverse Cardiovascular Events (MACE - cardiovascular death, non-fatal myocardial infarction, or nonfatal stroke) in adults with type-2 diabetes mellitus at high cardiovascular risk, as an adjunct to standard of care therapy. It's a once-daily dose therapy used as monotherapy or in combination therapy with one or more oral antidiabetic medicines such as metformin, sulphonylureas, sodium-glucose cotransporter 2 inhibitor (SGLT2i) or a thiazolidinedione.

The safety signal was based on the evaluation of data from all relevant sources by the applicant It was noted that dizziness and delayed gastric emptying are already included in current European (EU) Summary of Product Characteristics (SmPC) for liraglutide, however, the safety signal is not listed on the SAHPRA approved PI/PIL.

b) Decision

- SAHPRA took a regulatory decision to adopt EMA's decision and requested all applicants/HCRs of liraglutide containing medicines to align with EMA's SmPC by amending the PI/PIL of their liraglutide-containing products.
- SAHPRA considers the benefit-risk profile of liraglutide containing medicines favourable, provided the applicants effect the recommended changes.

2.1.4 Valproate Containing Medicines – Risk of Neurodevelopment Disorders

a) Background

SAHPRA conducted a review regarding the risk of neurodevelopment disorders associated with the use of valproate-containing medicines. Valproate is an antiepileptic medicine. Antiepileptics are a group of medicines (e.g., levetiracetam, phenytoin, carbamazepine, valproate, Topiramate, etc.) commonly used in the treatment of epilepsy (seizures).

The safety signal emanated from the results of a large epidemiological study conducted by Bjørk *et al., (2022)*. The study results showed that the risk of autism spectrum disorders and intellectual disability is multiplied by 2.77 and 3.47, respectively, with prenatal exposure to antiepileptic medicines compared to a pregnancy of an epileptic mother without antiepileptic drug exposure.

b) Decision

- SAHPRA recommended that applicants/ HCRs of valproate-containing medicines update the PI/PIL with the current information relating to the risk of neurodevelopment disorders with regards to prenatal exposure to valproate containing medicines.
- SAHPRA considers the benefit-risk profile of valproate-containing medicines favourable, provided the applicants/ HCRs effect the recommended changes.

2.1.5 Bupropion - Risk of Brugada Syndrome

a) Background

SAHPRA conducted a review a safety signal regarding the risk of Brugada syndrome associated with the use of bupropion containing medicines. Bupropion is an antidepressant medicine registered for the treatment of depression and preventing a relapse and recurrence of further depressive episode. Brugada syndrome is a rare but potentially life-threatening inherited disease that predisposes patients to fatal cardiac arrhythmias.

The safety signal was based on the PRAC's Assessment Report of the PSUR(s) for bupropion. In view of available data on Brugada syndrome from spontaneous reports, including two (2) cases with a positive dechallenge, a reasonable time to onset and mechanism of action described in the literature, it was considered that bupropion may unmask Brugada syndrome.

b) Decision

- SAHPRA recommended that the applicants/ HCRs of bupropion-containing medicines update the PI/PIL and RMPs of their products to include the risk of Brugada syndrome.
- SAHPRA considers the benefit-risk profile of bupropion-containing medicines favourable, provided the applicants/ HCRs effect the recommended changes.

2.1.6 Azacitidine – Cutaneous Vasculitis

a) Background

SAHPRA became aware of the risk of cutaneous vasculitis associated with the use of azacitidine-containing medicines. Cutaneous vasculitis is the inflammation of the blood vessels affecting small or medium-sized vessels in the skin and subcutaneous tissue but not the internal organs. The inflammation can cause the walls of the blood vessels to thicken, which reduces the width of the passageway through the vessel, which may lead to restricted blood flow and may result in organ and tissue damage.

Azacitidine is an anti-cancer medicine, registered for use in adults who are not able to have a stem cell transplantation to treat:

- higher-risk myelodysplastic syndromes (MDS) - a group of bone marrow disorders in which the bone marrow does not produce enough healthy blood cells;
- chronic myelomonocytic leukemia (CMML) - a type of cancer of the blood-forming cells of the bone marrow; and
- acute myeloid leukaemia (AML) - a cancer of the blood cells, characterised by the rapid growth of abnormal white blood cells that accumulate in the bone marrow and interfere with the production of normal blood cells.

The safety signal originated from the EMA's PRAC's cumulative review and analysis of cutaneous vasculitis events from all sources (i.e., spontaneous reports, literature, and clinical trials) for azacitidine. Based on the review of available data, PRAC concluded that there is a reasonable possibility of a causal association between azacitidine and cutaneous vasculitis.

b) Decision

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

2.1.7 Proton Pump Inhibitors (PPIs) – Risk of Hypomagnesaemia, Hypocalcaemia and Hypokalaemia

a) Background

SAHPRA became aware of the risk of hypomagnesaemia (lower than normal levels of magnesium in the blood), hypocalcaemia (lower than normal levels of calcium in the blood) and hypokalaemia (lower than normal levels of potassium in the blood) associated with the use of proton pump inhibitors (PPIs). PPIs are a group of medicines such as omeprazole, pantoprazole, lansoprazole etc., that are used to decrease stomach acid production and are registered for use in acid-related disorders. The safety issue was triggered by the regulatory decision taken by the Medicines and Medical Devices Safety Authority of New Zealand to recommend an addition to the PI/PIL of PPIs the risk of hypomagnesaemia, hypocalcaemia and hypokalaemia.

The PI/PILs of PPIs should mention that "*hypomagnesaemia has been reported in patients treated with PPI medicines for at least three months, and in most cases for a year. Hypomagnesaemia may lead to hypocalcaemia and/or hypokalaemia. Severe hypomagnesaemia may result in serious adverse events such as dizziness, fatigue, delirium, tetany, seizures, and potentially also arrhythmias".*

During the review it was noted that the risk of hypomagnesaemia (lower than normal levels of magnesium in the blood), hypocalcaemia (lower than normal levels of calcium in the blood) and hypokalaemia (lower than normal levels of potassium in the blood) is documented in some of the PIs/PILs of PPI medicines registered in South Africa.

b) Decision

- SAHPRA recommended that applicants/ HCRs of proton pump inhibitors align their PI/PIL with those who have already updated with the risk of hypomagnesaemia, hypocalcaemia, and hypokalaemia.
- The benefit-risk balance of PPIs remains unchanged with relative to the risk of hypomagnesaemia, hypocalcaemia, and hypokalaemia, provided the applicants/ HCRs effect the recommended change.

2.1.8 Secukinumab – Risk of Eczematous Eruptions

a) Background

SAHPRA became aware of the risk of eczematous eruptions (an acute inflammatory cutaneous (skin) eruption characterized by itching, redness, papules, vesicles, oedema, serous discharge, dryness, flaking, blistering, cracking, oozing, bleeding and crusting) associated with the use of secukinumab containing medicines. Secukinumab belongs to the 'immunosuppressants' group of medicines and works by weakening part of the immune system, used for the treatment of autoimmune and inflammatory diseases, such as psoriasis, ankylosing spondylitis, and psoriatic arthritis.

The safety issue was noted from the USFDA who recommended the addition of "atopic-dermatitis-like eruptions" and "erythroderma" as adverse drug reactions (ADRs) in the post-marketing section of the USPI, as well as an expansion of the ADRs to eczematous eruptions in the warning section. Eczematous eruption is not listed in the SAHPRA approved PI of secukinumab.

b) Decision

- SAHPRA recommended that applicants of secukinumab-containing medicines update the PI/PIL of their medicines in line with the USFDA recommendations.
- The benefit risk of secukinumab remains unchanged for its registered indication provided the applicants/ HCRs effect the recommended change.

2.1.9 Pegylated Liposomal Doxorubicin – Risk of Interstitial Lung Disease

a) Background

SAHPRA conducted a review of safety signal regarding the risk of interstitial lung disease (ILD) associated with the use of pegylated liposomal doxorubicin. Interstitial lung disease (ILD) is an umbrella term used for a large group of diseases (e.g., asbestosis and hypersensitivity pneumonitis) that cause scarring (fibrosis) of the lungs. The scarring causes stiffness in the lungs which makes it difficult to breathe and get oxygen to the bloodstream. Lung damage from ILDs is often irreversible and gets worse over time.

Pegylated liposomal doxorubicin is an anti-tumour medicine registered to treat cancer of the breast, ovaries, Kaposi's sarcoma (a rare type of skin cancer) in patients with acquired immunodeficiency syndrome and for use in combination with other medicine, bortezomib, to treat multiple myeloma (cancer of the blood).

The safety signal emanated from the EMA's PRAC assessment of pegylated liposomal doxorubicin periodic safety update report (PSUR). Based on the review of data from literature and spontaneous reports, PRAC considered a reasonable association between pegylated liposomal doxorubicin and the risk of interstitial lung disease. The risk of interstitial lung disease is significant and, it's not documented in the SAHPRA approved PI/PIL.

b) Decision

- SAHPRA adopted EMA's regulatory decision and recommended that applicants of pegylated liposomal doxorubicin formulations update PIs/PILs of their medicines in line with EMA's recommendation.
- The benefit-risk balance of pegylated liposomal doxorubicin remains favourable for the registered indication(s) provided the applicants/ HCRs effect the recommended changes.

2.1.10 Bisphosphonates-Containing Medicines (e.g., Ibandronic Acid) – Risk of Atypical Femur Fractures

a) Background

SAHPRA became aware of inconsistencies in the SAHPRA approved PIs/PILs of bisphosphonate containing medicines regarding the risk of acute femur fracture (AFF) (bone fracture). Bisphosphonates are a group of medicines (e.g., ibandronic acid, alendronate, risedronate, ibandronate, zoledronic acid, etc.) that primarily acts on bone to prevent the breakdown of bone tissue and increase bone density. They are registered for the treatment of osteoporosis (thinning of bone) in women after menopause. They reduce the chances of having a hip or spinal fracture (break). They are also used in the treatment of high blood levels of calcium due to cancer and bone lesions resulting from multiple myeloma (a cancer that originates in bone marrow) in combination with standard therapy for this condition.

The safety issue was identified during SAHPRA's routine adverse drug reaction monitoring activities, where a review revealed that some PI/PILs of bisphosphonate containing medicines (e.g., ibandronic acid (Boniva®)) do not address the risk of AFF. AFF is a well-established risk associated with the use of bisphosphonate containing medicines, highlighted in different sources such as literature, other regulatory authorities' product information and some of the SAHPRA approved PI of bisphosphonates.

b) Decision

- SAHPRA recommended that applicants of bisphosphonates-containing medicines update the PI/PIL of their products to include the risk of AFF if they have not yet done so.
- The benefit risk profile of bisphosphonate containing medicines remain unchanged.

2.1.11 Nirmatrelvir/Ritonavir (Paxlovid®) – Risk of Hypertension in the elderly

a) Background

SAHPRA became aware of the risk of hypertension associated with the use of nirmatrelvir/ritonavir (Paxlovid®). Paxlovid® is an antiviral medicine registered for the treatment of mild-to-moderate coronavirus disease (COVID-19) in adults 18 years of age and older. It is only used in patients who are

at high risk for progression to severe coronavirus disease (COVID-19), including hospitalisation or death.

SAHPRA noted that Recognised Regulatory Authorities (RRAs) (regulatory authorities with which SAHPRA aligns itself such as the EMA, USFDA, etc.) have identified and documented the risk of hypertension in the elderly patients associated with the use of Paxlovid®. The EMA's SmPC indicates that cases of hypertension, generally non-serious and transient, were reported during treatment with Paxlovid®. Therefore, specific attention including regular monitoring of blood pressure is advised particularly to elderly patients since they are at higher risk of experiencing serious complications of hypertension. Moreover, the USPI also documented the occurrence of hypertension during nirmatrelvir/ritonavir-containing medicines use.

b) Decision

- SAHPRA recommended that the applicant of nirmatrelvir/ ritonavir-containing medicine update the PI/PIL of their medicine to include the risk of hypertension in line with EMA.
- The benefit risk profile of nirmatrelvir/ ritonavir-containing medicine remains unchanged provided the applicant effect the recommended changes.

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

2.2.1 Protopic® (Tacrolimus) – Periodic Safety Update Report (PSUR)

a) Background

SAHPRA conducted a review of Protopic® (tacrolimus)'s ointment 35th periodic safety update report (PSUR) covering period 01 April 2021 to 31 March 2023. Protopic® is a calcineurin inhibitor and is registered for the treatment of moderate to severe atopic dermatitis (AD), and for prevention of flares and prolongation of flare-free intervals in patients who respond to treatment with Protopic® ointment, but who are not adequately responsive to or are intolerant of conventional therapies such as topical corticosteroids (TCS). Protopic® ointment is available for topical application in adult and adolescents from 16 years and above (0.1% Protopic® ointment) and children from the age of 2 years (0.03% Protopic® ointment). Protopic® ointment is not registered for use in children less than two (2) years of age.

The PSUR was submitted in compliance with the product's conditions of registration. The PSUR review revealed no potential changes to the benefit-risk profile of Protopic® ointment based on clinical/non-clinical data identified during the reporting interval. However, it was noted that in the latest European (EU) PSUR Assessment report (EMEA/H/C/PSUSA/00002840/202103), PRAC requested LEO Pharma to continue to provide Intercontinental Medical Statistics (IMS) data on use of Protopic® ointment in children less than two (2) years of age, and the use of 0.1% in children aged 2-16 years, and prescriber type in Europe.

b) Decision

- SAHPRA found the benefit-risk balance of Protopic® ointment favourable for its registered indication(s)
- SAHPRA recommended that the applicant/ HCR continue with routine pharmacovigilance monitoring of Protopic® ointment.

2.2.2 Pentasa® (Mesalazine) - Periodic Safety Update Report (PSUR)

a) Background

SAHPRA conducted a review of a periodic safety update report (PSUR) for Pentasa® (mesalazine). The annual PSUR (covering the period of 20 Feb 2022 – 19 Feb 2023) was submitted as a condition of registration. Mesalazine is an intestinal anti-inflammatory agent with the active component of sulfasalazine, used for the treatment of ulcerative colitis (UC) and Crohn's disease (CD). After oral as well as rectal administration, mesalazine has local anti-inflammatory effects on the inflamed intestinal tissue i.e., inhibit leukocyte chemotaxis, decrease cytokine and leukotriene production, and scavenge for free radicals.

No significant new safety concerns regarding the important risks for Pentasa® were identified during the reporting interval.

b) Decision

- SAHPRA found the benefit risk profile for Pentasa® favourable for its registered indications.
- SAHPRA recommended continuous routine pharmacovigilance monitoring of Pentasa®.

2.2.3 Fremanezumab (Ajovy®) – Periodic Safety Update Report (PSUR)

a) Background

SAHPRA conducted a review of the first periodic safety update report (PSUR) of Ajovy® (fremanezumab) (covering from 14 September 2021 to 13 September 2022) submitted as a condition of registration. Fremanezumab is a medicine used to prevent migraine in adults and reduces the frequency of migraine attacks and days. This medicine also decreases the disability associated with migraine and reduces the need for other medicines used to treat migraine attacks.

Ajovy® is not yet marketed in South Africa, therefore, no South Africa-specific annex was submitted. There was no new information on known or potential risks identified during the reporting interval. For missing information, analysis of reported adverse events (AEs) following the use of Ajovy® during pregnancy and in children, provided no safety concerns.

No new significant efficacy or effectiveness information was found. Additionally, the proposed risk minimisation activities as per the approved RMP were found adequate to minimise the risks and to ensure a positive benefit-risk balance of Ajovy®. Data described in the PSUR did not change the benefit-risk balance of Ajovy® and no additional actions for safety reasons were taken during the reporting interval.

b) Decision

- SAHPRA found the benefit risk balance of Ajovy® favourable for its registered indications.
- SAHPRA recommended continuous pharmacovigilance monitoring of Ajovy®.

2.3 Risk Management Plans (RMPs)

2.3.1 Tagrisso® (Osimertinib) - Risk Management Plan (RMP)

a) Background

SAHPRA conducted a review of Tagrisso® (osimertinib) risk management plan (RMP). Osimertinib is classified as an anticancer medicine and is registered for use after complete tumour resection in adult patients with stage IB-IIIA non-small cell lung cancer (NSCLC) whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations.

The RMP for Tagrisso® was submitted as part of an application for an amendment to the therapeutic indications. The RMP included the important identified risks and important potential risks associated with the use of Tagrisso®, which are interstitial lung disease (ILD) and cardiac failure respectively. The pharmacovigilance activities (including an ongoing, multicentre, EU wide, non-interventional post-authorisation study - EU-PASS 242-12-402) and risk minimisation measures (including the educational materials that seeks to reinforce the PI and PIL) were found acceptable.

b) Decision

- SAHPRA found the benefit-risk balance of Tagrisso® favourable for its registered indications.
- SAHPRA recommended that the applicant continue monitoring the benefit-risk profile of Tagrisso® and submit the results of the ongoing studies when they become available.

2.3.2 Fremanezumab (Ajovy®) – Risk Management Plan (RMP)

a) Background

SAHPRA conducted a review of Ajovy® (fremanezumab) risk management plan that was submitted as a condition of registration. Fremanezumab is a medicine used to prevent migraine in adults and reduces the frequency of migraine attacks and days. This medicine also decreases the disability associated with migraine and it reduces the need for other medicines used to treat migraine attacks.

The pharmacovigilance plan (adverse drug reaction reporting and signal detection) including ongoing post-authorisation safety studies aimed to address potential risks and missing information and risk minimisation measures were noted.

b) Decision

- SAHPRA found the Ajovy® RMP acceptable and recommended continuous pharmacovigilance monitoring of Ajovy®.
- The benefit-risk balance of Ajovy® remains favourable for its registered indications.

2.4 Additional Risk Minimisation Measures (ARMMs)

2.4.1 Deltyba® (Delamanid) – Additional Risk Minimisation Measures (ARMMs)

a) Background

SAHPRA conducted a review of Deltyba® (delamanid) educational materials and a communication plan. 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.

The educational materials and communication plan were submitted as part of the additional risk minimisation measures for the risk of QT interval prolongation (a condition where the heart's electrical system takes longer than usual to recharge between beats) associated with delamanid use. The aim of the educational materials is to educate healthcare professionals (HCPs) and patients involved in prescribing, dispensing and administering delamanid on QT interval prolongation (HCPs), drug resistance (HCPs), drug use during pregnancy (patients) and drug use during breastfeeding (patients).

The aRMMs were found to be acceptable.

b) Decision

- SAHPRA accepted and approved the Deltyba® aRMMs and target audience.
- The benefit-risk balance of Deltyba® remains favourable for its registered indication.

2.4.2 Erivedge® (Vismodegib) – aRMMs

a) Background

SAHPRA conducted a review of Erivedge® (vismodegib)'s additional risk minimisation materials (aRMMs). Vismodegib is a medicine used to treat adults with a type of skin cancer, called basal cell carcinoma, which has spread to other parts of the body or that has come back after surgery or that cannot be treated with surgery or radiation.

The additional risk minimisation measures were intended to address the important identified risk of teratogenicity and congenital malformations of vismodegib, in accordance with the risk management plan. The aRMMs included a letter to healthcare professionals (HCPs), HCP reminder card, patient brochure and patient counselling guidelines. These aRMMs are aimed to convey important information regarding the Pregnancy Prevention Program. The Program's purpose is to minimise the risk of teratogenicity and provide education on the risk of teratogenicity, and the recommended contraceptive measures to prevent foetal exposure.

b) Decision

- SAHPRA approved the Erivedge® aRMMS for distribution to the target audience as planned.
- The overall risk-benefit balance of Erivedge® remains favourable for its registered indication(s). SAHPRA recommended continuous routine and additional pharmacovigilance monitoring.

2.4.3 Hemlibra® (Emicizumab) – additional Risk Minimisation Materials (aRMMs)

a) Background

SAHPRA conducted a review of Hemlibra® (emicizumab) additional risk minimisation materials (aRMMs). Hemlibra® is a humanised monoclonal modified immunoglobulin G4 (IgG4) antibody, registered for routine prophylaxis to prevent bleeding or reduce the frequency of bleeding episodes in adults and children with haemophilia A (congenital factor VIII deficiency) with or without factor VIII inhibitors. Hemlibra® treatment is recommended for initiation under the supervision of a medical practitioner experienced in the treatment of haemophilia and/or bleeding disorders.

Hemlibra® aRMMs include Healthcare Professional Guide, Guide for Patients and Caregivers and Patient Card for distribution to HCPs, caregivers, and patients. The overall content of aRMMs aligned with the PI/PIL and RMP. The aRMMs distribution is planned to be done twice a year via email and face-to-face.

b) Decision

- SAHPRA found Hemlibra® aRMMs acceptable and approved them for distribution provided the applicant addresses all document specific recommendations such as standardisation in grammar and formatting.
- The benefit-risk balance of Hemlibra® remains positive for its registered indication.

2.4.4 Epilim® (Valproate) – Additional Risk Minimisation Measures (aRMMs)

a) Background

SAHPRA conducted a review of additional risk minimisation measures for Epilim® (valproate containing medicine). Epilim® is a valproate containing medicine registered for the treatment of seizure disorders and mental/ mood conditions (such as manic phase of bipolar disorder).

The aRMMs were developed in order to educate and guide Healthcare Professionals (HCPs) and to inform patients on the risks of congenital malformations and neurodevelopmental disorders in children exposed to valproate during pregnancy. The aRMMs included an updated PI and PIL, DHCPL, educational materials for HCPs (*Guide for prescribers to provide advice on pregnancy prevention program*) and patients (*Patient information booklet and patient cards (for female children, female adolescents, women who are being prescribed valproate*) and both HCPs and patients (*Annual risk acknowledgement form to ensure that patients are fully aware of and understand the risks related to the use of valproate during pregnancy*).

The Epilim® aRMMs apply to all sodium valproate formulations.

b) Decision

- SAHPRA found Epilim® aRMMs acceptable and approved them for distribution.
- All HCRs of valproate-containing medicines are required to implement similar risk minimisation measures as for Epilim®.

- The benefit-risk balance of valproate-containing medicines remains favourable for its registered indications.

2.5 Other Safety Monitoring Reports

2.5.1 Eltroxin New Formulation® (Levothyroxine) – Six Monthly Monitoring Report

a) Background

SAHPRA conducted a review of Eltroxin New Formulation® (levothyroxine) monitoring report for the period 01 January 2023 to 30 June 2023. Levothyroxine is a synthetic version of thyroxine, which is a naturally produced hormone in the body by the thyroid gland. Eltroxin New Formulation® is registered to treat hypothyroidism, a disease in which the thyroid gland is underactive and does not produce enough thyroxine, a hormone, which is important for controlling metabolism.

SAHPRA requested Aspen to closely monitor Eltroxin New Formulation® following an increase in adverse reactions/ events (ADRs/AEs) complaints received from the consumers after discontinuation of the Eltroxin® old formulation. The report provided a summary of safety data received by the applicant and was prepared to monitor potential clinical risks to patients arising from changes to the finished levothyroxine medicine implemented globally.

The available reviewed data did not reveal any previously unrecognised pattern of adverse events (AEs) or meaningful changes in adverse events occurrence. Moreover, the previously heightened consumer complaints have decreased significantly.

b) Decision

- SAHPRA found the benefit-risk profile of Eltroxin New Formulation® favourable for its registered indications.
- SAHPRA recommended cessation of close monitoring for Eltroxin New Formulation® and continuous routine pharmacovigilance monitoring.

2.5.2 Crizanlizumab (Ryverna®) – Benefit-Risk Review

a) Background

SAHPRA conducted a review of the benefit-risk balance of crizanlizumab. Crizanlizumab is a monoclonal antibody, registered for the prevention of painful episodes (crises) of sickle cell disease (SCD) in patients aged 16 years and over. Sickle cell disease is an inherited blood disorder, causing affected red blood cells to be sickle-shaped and have difficulty passing through small blood vessels. Additionally, in sickle cell disease, the blood vessels are damaged and sticky due to the ongoing chronic inflammation. This leads to blood cells sticking to the blood vessels, causing acute episodes of pain and organ damage (vaso-occlusive crises (VOCs).

The review was triggered by the EMA's Committee for Medicinal Products for Human Use (CHMP) decision to cancel the registration of crizanlizumab in the European market because the preliminary results of a post-marketing study A2301, published in 2022 showed no difference between

crizanlizumab and placebo in annualised rates of vaso-occlusive crises leading to a healthcare visit over the first-year post randomisation.

SAHPRA's review found that the data derived from study A2301 is numerically small, but clinically relevant. Moreover, crizanlizumab does not prevent VOCs but reduces its frequency. The study A2301 did not confirm the benefits of crizanlizumab. Administration of crizanlizumab is associated with adverse events in all studies. A further study may resolve these discrepancies.

The available reviewed data from clinical studies and additional data from post-marketing setting, support a favourable benefit-risk balance of crizanlizumab for use in patients with SCD aged 16 years and older. SCD is a rare condition in South Africa and there could be patients benefiting from this medicine.

b) Decision

- SAHPRA found the benefit-risk balance of crizanlizumab favourable for its registered indication.
- SAHPRA recommended continuous use crizanlizumab in South Africa and continuous routine pharmacovigilance monitoring.

Dr Boitumelo Semete-Makokotlela
SAHPRA Chief Executive Officer

20 May 2024