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Regulatory Authority

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COMMUNICATION TO STAKEHOLDERS

Issue No.: PV08-2023/24

27 July 2025

Summary of Medicine Safety Regulatory Decisions

INTRODUCTION

This document provides an overview of the medicines safety regulatory decisions made by the South African Health Products Regulatory Authority (SAHPRA) during January – March 2024. This includes decisions where safety concerns were reviewed and concluded, as well as those safety concerns that remain unresolved but warrant immediate action, while SAHPRA continues to monitor and review the safety issue(s). Safety concerns are triggered by any potential safety problem linked to a medicine. This includes known safety problems, changes in the reporting pattern of known problems, new problems and coincidental events.

Regulatory decisions made following review of safety concerns may include:

- changes to the Professional Information and Patient Information Leaflets (PI/PILs)
- changes to scheduling of medicines
- changes to distribution of medicines
- a need for a study to monitor the performance of the implicated medicine on the market
- issuing of public health advisories
- issuing of a DHCPL/Press statement
- removal of the product from the market

SAHPRA's regulatory decisions are actionable by the relevant stakeholders, including pharmaceutical companies. Even though a regulatory decision has been issued, it doesn't necessarily mean a product is unsafe.

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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 harmful patient outcome that seems to be associated with treatment, including there being no effect at all.

Applicant is anyone who has submitted any 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's) 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 the 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 recurrence of similar signs and symptoms upon reintroduction of a medicine.

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 Swiss 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 (US-FDA) 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.

REGULATORY SAFETY DECISIONS

1. Update of professional information (PI) and Patient Information Leaflet (PIL)

1.1 Pseudoephedrine – Risk of Posterior Reversible Encephalopathy Syndrome (PRES) and Reversible Cerebral Vasoconstriction Syndrome (RCVS)

a) Background

SAHPRA became aware of the European Medicines Agency's (EMA's) conclusion that pseudoephedrine is associated with the risks of Posterior Reversible Encephalopathy Syndrome (PRES) and Reversible Cerebral Vasoconstriction Syndrome (RCVS), following review of all available evidence by the Pharmacovigilance Risk Assessment Committee (PRAC). The PRAC has recommended that medicines containing pseudoephedrine should not be used in patients with severe or uncontrolled high blood pressure, or with severe acute or chronic kidney disease/failure. In addition, Healthcare Professionals (HCPs) should advise patients to stop using these medicines immediately and seek treatment if they develop symptoms of PRES or RCVS. They have also recommended updates to the product information for all pseudoephedrine-containing medicines to include the risks of PRES and RCVS. Finally, they recommended the distribution of a Dear Healthcare Professional Letter (DHCPL) to inform HCPs about the risk minimisation measures for PRES and RCVS associated with these medicines.

It was noted that in view of the seriousness of the risk of PRES and RVCS and the PRAC's recommendations to minimise the risks, consider additional risk minimisation measures to curb unsupervised use of pseudoephedrine-containing medicines by the public.

Decision

- SAHPRA took a regulatory decision to adopt EMA's recommendation and request that all applicants of pseudoephedrine-containing medicines:
    - To update the PI/PIL of their medicines to include a warning regarding the risks of PRES and RVCS.
    - To distribute a DHCPL regarding the risk of PRES and RCVS.
- SAHPRA considers the benefit-risk profile of pseudoephedrine-containing medicines favourable, provided the applicants effect the recommended changes.

1.2 Acyclovir/Valacyclovir – Risk of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

a) Background

SAHPRA was made aware of the safety signal that emanated from regulatory actions taken by Health Canada and EMA requesting an update to the product information for valacyclovir-containing medicines to include the risk of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS).

The evaluation of the signal revealed that valacyclovir and acyclovir have similar chemical structures, sharing a 2-aminopurine core. This provides a possibility of cross-hypersensitivity between valacyclovir and acyclovir. However, based on the available data, there have been more reports of hypersensitivity to valacyclovir compared to those reported on acyclovir.

b) Decision

- SAHPRA took a regulatory decision to adopt Health Canada and EMA's decision and requested all applicants/HCRs of acyclovir/valacyclovir medicines to align with the recommendations by amending the PI/PIL to include the risk of DRESS, and to issue a Dear Healthcare Professional letter (DHCPL).
- SAHPRA considers the benefit-risk profile of acyclovir/valacyclovir-containing medicines favourable, provided the applicants effect the recommended changes.

1.3 Non-Steroidal Anti-Inflammatory Drugs (NSAIDS) – Risk of Renal Tubular Acidosis (RTA) and Hypokalaemia

a) Background

SAHPRA evaluated the regulatory decision by the EMA-PRAC, where it was recommended that all Marketing Authorisation Holders (MAHs) of the fixed combination codeine/ibuprofen-containing medicines amend the product information. The recommended product information update for codeine with ibuprofen combination medicines included a warning of serious harms, including death, particularly when taken for prolonged periods at higher than recommended doses. This decision was based on the available data and the biological plausibility.

b) Decision

- SAHPRA took a regulatory decision to request all applicants/HCRs amend systemic ibuprofen-containing medicines to the SAHPRA registered PI/PIL to include the risk of renal tubular acidosis (RTA) and hypokalaemia associated with the use of systemic ibuprofen.
- SAHPRA considers the benefit-risk profile of systemic ibuprofen favourable, provided the applicants effect the recommended changes.

1.4 Opioid Agonist Containing Medicines – Risk of Pancreatitis

a) Background

SAHPRA has evaluated the EMA's decision to request all applicants of loperamide and loperamide/simethicone-containing medicines to update the product information to include the risk of pancreatitis. The safety concern was based on the established risk of pancreatitis associated with loperamide in patients who underwent a cholecystectomy. SAHPRA considers all the available data and made the regulatory decisions below.

b) Decision

- SAHPRA recommended that all applicants/HCRs of opioid agonist-containing medicines be requested to update their PI/PIL to include the risk of pancreatitis as a rare ADR.
- SAHPRA considers the benefit-risk profile of opioid agonist-containing medicines favourable, provided the applicants/HCRs effect the recommended changes.

1.5 Cytarabine – Risk of Posterior Reversible Encephalopathy Syndrome (PRES)

a) Background

SAHPRA considered a review of a safety signal regarding the risk of PRES associated with the use of cytarabine. The source of the safety signal was a PSUR assessment report (PSUSA/00000911/202303) for cytarabine by PRAC in December 2023. The PRAC has recommended a warning on PRES to be added to the PI/PIL for cytarabine following a request for the applicant to conduct a review on PRES in their previous PSUR. The SAHPRA-approved PI/PILs and international prescribing information for cytarabine and other chemotherapeutic agents currently do not carry any warning regarding PRES.

b) Decision

- SAHPRA recommended that no regulatory action be taken at this point as there is insufficient evidence to support a causal relationship between PRES and cytarabine.
- The signal should continue to be monitored as there is currently no change to the benefit-risk profile of cytarabine.

1.6 Amoxicillin Trihydrate and Clavulanate Potassium – Drug-Drug Interaction (DDI) with Methotrexate

a) Background

SAHPRAs Pharmacovigilance (PV) unit was made aware of the potential drug-drug interaction (DDI) between amoxicillin trihydrate and methotrexate following the communication from Medsafe - New Zealand. However, the signal was previously reviewed, and it was recommended that all applicants for amoxicillin-clavulanate update their PI/PILs to include the potential risk of DDI with methotrexate.

b) Decision

- SAHPRA PV's Unit requested all HCRs/applicants of amoxicillin/clavulanate potassium to update and align their PI/PILs to include information on the potential interaction with methotrexate.
- The benefit-risk balance of amoxicillin trihydrate/clavulanate potassium remains favourable for its registered indication(s), provided the applicants/HCRs effect the recommended changes.

1.7 Captopril – Cardiogenic Shock

a) Background

SAHPRA became aware of the risk of cardiogenic shock with the use of captopril through the safety notification. The safety issue arose from the Therapeutic Goods Administration's (TGA's) recommendation in November 2023 to include cardiogenic shock as a contraindication for captopril use. SAHPRA's evaluation of the safety signal noted that the safety issue is not addressed by the approved PI/PIL.

b) Decision

- SAHPRA recommended that applicants/HCRs of captopril be requested to align their PI/PIL with the TGA's recommendations to include cardiogenic shock with the use of captopril.
- The benefit-risk balance of captopril remains favourable for its registered indication(s) provided the applicants/HCRs effect the recommended changes.

1.8 Topical Fluorouracil – Ingestion by Pets

a) Background

SAHPRA PV's Unit decided to request the applicants for topical fluorouracil to update their PI/PILs and include a warning on the risk of ingestion by pets. The request was based on information from an applicant, following a product information safety update in November 2023 by the TGA.

The TGA has recommended adding a warning regarding ingestion by pets to the "Warnings and Precautions" section of the PI, of which the SAHPRA-approved PI/PILs do not contain the warning.

b) Decision

- SAHPRA recommended that applicants of topical fluorouracil-containing medicines update the PI/PIL of their medicines in line with the TGA's recommendations.
- The benefit-risk balance of topical fluorouracil-containing medicines remains favourable for its registered indication(s), provided the applicants/HCRs effect the recommended changes.

1.9 Cariprazine – Risk of Severe Cutaneous Adverse Reactions (SCARS)

a) Background

SAHPRA was made aware of the risk of severe cutaneous adverse reactions (SCARS) with the use of cariprazine. The signal originally emerged in 2017; however, EMA considered the available information insufficient to support a SmPC modification and was to review the signal again in the PSUR due for submission in 2024.

Based on the US-FDA product monograph and the intention by the applicant to update the TGA product information, it was recommended that the applicant update their PI/PIL in line with the US monograph for Vraylar (cariprazine containing medicine).

The following adverse reaction has been identified with unknown frequency during post-approval use of cariprazine:

- *Skin and subcutaneous Tissue Disorders – Stevens-Johnson Syndrome.*

b) Decision

- SAHPRA recommended that the applicant update their PI/PIL for cariprazine using their proposed wording as it sufficiently addresses the risk.
- The benefit-risk balance of cariprazine remains favourable for its registered indication(s) provided the applicants/HCRs effect the recommended changes.

1.10 Hepatitis-B Surface Antigen Recombinant Vaccine – Risk of Myelitis (including Transverse Myelitis)

a) Background

SAHPRA became aware of the risk of myelitis associated with the hepatitis-B surface antigen recombinant vaccine. This followed a safety communication from the TGA. Based on the cumulative weight of evidence supporting a plausible temporal association between hepatitis-B surface antigen recombinant vaccine and myelitis, the TGA have requested that the PI for Engerix-B vaccine to be updated to include the risks of myelitis, including transverse myelitis, in Section 4.8 “Adverse Events”.

SAHPRA further noted that the EMA and the US-FDA have updated PIs which include information on myelitis, including transverse myelitis, as possible adverse events. Additionally, the risk of myelitis is not currently listed in the SAHPRA-approved product information (PI).

b) Decision

- The applicant is to align with the recommendations from the TGA and update their local PI/PIL.
- Other applicants for hepatitis-B plasma-derived and recombinant vaccines should also align for consistency.

- The benefit-risk balance of hepatitis B surface antigen recombinant vaccine remains favourable for its registered indication(s), provided the applicants/HCRs effect the recommended changes.

1.11 Levetiracetam and Clobazam – Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

a) Background

SAHPRA was notified about the risk of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) associated with levetiracetam and clobazam based on a Drug Safety Communication issued by the US-FDA in November 2023. The US-FDA reviewed worldwide cases of DRESS associated with levetiracetam and clobazam and requested manufacturers of these medicines to add new warnings about DRESS to the prescribing information.

Most SAHPRA-approved PIs for levetiracetam already list DRESS as an uncommon undesirable effect. However, there is no description of symptoms as requested by the US-FDA. In the SAHPRA-approved PI for clobazam, DRESS is not listed as an adverse event. Some symptoms related to this risk are described more generally in other sections of the clobazam PI. Although there is limited literature to support the association between DRESS and clobazam and levetiracetam, the association is possible based on the global case reports and suggested mechanisms associated with antiepileptic drugs.

b) Decision

SAHPRA recommended that applicants should align with the US-FDA recommendations as follows:

- The applicants for levetiracetam-containing products should add a new warning in the "Warnings and Precautions" section of the Professional Information (PI)/Patient Information Leaflet (PIL), which describes the most serious and significant potential safety issues, if they have not done so.
- The applicants for clobazam-containing products should add a new warning specifically about DRESS to the PI/PIL.
- For both levetiracetam and clobazam, the PI/PIL should include a warning which states that early symptoms of DRESS such as fever or swollen lymph nodes can be present even when a rash cannot be seen.

The benefit-risk balance of levetiracetam and clobazam remain favourable for its registered indication(s) provided the applicants/HCRs effect the recommended changes.

1.12 Vildagliptin (Galvus®) – Risk of Cholecystitis

a) Background

SAHPRA's PV Unit was notified about the risk of cholecystitis associated with the use of vildagliptin-containing medicines. The signal was based on a regulatory action taken by the TGA, Australia, to add cholecystitis as an adverse drug reaction (ADR) in the product information of vildagliptin-containing medicines. It was noted that there is sufficient evidence from literature, biological plausibility and actions by other regulatory authorities to support the association of the risk of cholecystitis as a class effect of DPP-4 inhibitors.

b) Decision

SAHPRA's PV Unit recommends that:

- Applicants of vildagliptin-containing medicines be requested to update PI/PIL of their medicines to include the risk of cholecystitis as an ADR.
- Applicants of other DDP-4 inhibitor medicines (saxagliptin, linagliptin, and sitagliptin) be requested to comment on the risk of cholecystitis associated with these products.
- The benefit-risk balance of vildagliptin remain favourable for its registered indication(s) provided the applicants/HCRs effect the recommended changes.

1.13 Brolucizumab – Risk of Scleritis

a) Background

SAHPRA's PV Unit was notified about the class effect of the risk of scleritis associated with the use of brolucizumab. This was based on the EMA PRAC's process of evaluating a signal regarding brolucizumab and the risk of scleritis as part of a PSUR single assessment (PSUSA) for the reporting period from October 7, 2022, to October 6, 2023. Additionally, EMA PRAC had requested that concerned HCRs/applicants submit a cumulative review of all cases of scleritis associated with brolucizumab.

It was noted that the current SAHPRA-approved Vsiqq® PI/PIL already adequately informs about scleritis symptoms and advises patients to seek medical attention should these symptoms appear. However, the applicant considers that an update of the PI/PIL to include the term "scleritis" as an adverse drug reaction is warranted, given the established causal relationship, and is committed to submitting a PI/PIL update.

b) Decision

- SAHPRA supports and endorses the applicant's proposed action of adding "scleritis" as a side effect.

- And that applicants of all anti-VEGF medicines administered intravitreally (Vsiqq®, Lucentis®, Aylea®) must update their PI/PIL to include scleritis as an ADR.

1.14 Ipilimumab – Risk of Coeliac Disease (CD)

a) Background

SAHPRA's PV Unit was notified about the risk of coeliac disease (CD) associated with the use of ipilimumab and other immune checkpoint inhibitor (ICI)-containing medicines. The risk was based on the EMA PRAC's preliminary signal assessment outcome regarding the risk of CD with immune checkpoint inhibitors as a class effect. Based on the available evidence, the impact of CD on quality of life, and the importance of prompt diagnosis to appropriately treat/manage patients, PRAC recommended that CD should be added to SmPC 4.8 of all ICIs. It was noted that none of the SAHPRA's approved PIs for ICI-containing medicines contain the risk of CD.

b) Decision

- SAHPRA recommended that the applicants of ipilimumab-containing medicines update to include the risk of coeliac disease as a rare adverse event in the PIs/PILs of their immune checkpoint inhibitor-containing medicines in line with EMA.
- The benefit-risk balance of ipilimumab remains favourable for its registered indication(s) provided the applicants/HCRs effect the recommended changes.

1.15 Linezolid – Risk of Rhabdomyolysis

a) Background

SAHPRA was notified about the risk of rhabdomyolysis associated with the use of linezolid. The notification was based on a regulatory decision made by the Australian TGA, regarding the inclusion of the risk of rhabdomyolysis as an ADR in the product information for linezolid-containing medicines. It was also noted that New Zealand, the US-FDA and EMA have also included the risk of rhabdomyolysis as a warning and an ADR in their linezolid product information. It was noted that the risk of rhabdomyolysis is not included in the SAHPRA-approved PI/PILs of linezolid-containing medicines.

b) Decision

- SAHPRA recommended that all applicants of linezolid-containing medicines update the PI/PIL of their products to include the risk of rhabdomyolysis as a "warning" and an "ADR", in line with other regulatory authorities such as EMA.
- The benefit-risk balance of linezolid remains favourable for its registered indication(s) provided the applicants/HCRs effect the recommended changes.

1.16 Nirmatrelvir/Ritonavir (Paxlovid®) – Risk of Haemorrhagic Diarrhoea and Dysgeusia

a) Background

SAHPRA was notified about the risks of haemorrhagic diarrhoea and dysgeusia associated with the use of Paxlovid®. The safety signals emanated from EMA's PSUR assessment outcome for Paxlovid®. Based on the review of the available data on safety and efficacy, PRAC recommended that the product information of Paxlovid® should be amended to include additional information regarding dysgeusia and haemorrhagic diarrhoea.

It was noted that the risk of dysgeusia is already documented in the PI and PIL as 'an altered sense of taste'. This is sufficient, and no regulatory action is required on this risk.

b) Decision

- SAHPRA recommended that applicant of Paxlovid® update the PI/PIL of their medicine to include the risk of haemorrhagic diarrhoea in line with EMA, in their following PI/PIL amendment.
- The benefit-risk balance of linezolid remains favourable for its registered indication(s) provided the applicants/HCRs effect the recommended changes in the following PI/PIL amendment.

2. Periodic Safety Update Reports /Periodic Benefit-Risk Evaluations Reports

2.1 Fremanezumab (Ajovy®) – PSUR

a) Background

SAHPRA's PV Unit considered a review of the 7th EURD PSUR (2nd for South Africa) for fremanezumab (Ajovy®) for the period from 14 September 2022 to 13 September 2023. There were no specific safety concerns or significant safety concerns in the South African context to consider in the PSUR of Ajovy® for the reporting period.

No new information regarding the efficacy within the approved indication was identified from studies performed during the PSUR monitoring period. The Literature review of efficacy/effectiveness publications did not reveal any new relevant information regarding the efficacy of Ajovy®.

b) Decisions

- The applicant should continue to monitor the safety profile for Ajovy® with appropriate action(s) taken when warranted. For harmonisation with the EU SmPC and USPI, the South

African PI and PIL should be updated to include the additional information on the risk of hypersensitivity reactions from the post-marketing setting in the Undesirable Effects section.
- SAHPRA found the benefit-risk balance of Ajovy® favourable for its registered indication(s).

2.2 Saxagliptin (Onglyza™) – PBRER

a) Background

SAHPRA conducted a review of a PBRER for Onglyza™ (saxagliptin) and Komboglyze™ and Kombiglyze™ XR (saxagliptin + metformin HCl fixed dose combination), for the period from 31 July 2022 to 30 July 2023. No new risks or signals were identified during the reporting period. No significant safety-related actions were taken or proposed during the reporting period.

No new data or information was received during the reporting period that impacts the previously established efficacy and effectiveness of saxagliptin in the approved indication of type 2 diabetes mellitus in adults. The benefit profile remains unchanged and favourable. The applicant has requested that after 11 years of reporting, the annual submission of a PBRER should be reviewed.

b) Decisions

- SAHPRA found the benefit risk profile for Onglyza® favourable for its registered indications.
- SCARs and their potential complications are serious, and therefore, the risk should be further investigated and characterised as it has an impact on the benefit-risk profile of saxagliptin.
- Therefore, the PBRER reporting frequency should remain unchanged (annual) until the risk of SCARs is further characterised.
- SAHPRA recommended continuous routine pharmacovigilance monitoring.

2.3 Tremelimumab (Imjudo®) – PBRER

a) Background

SAHPRA has conducted a review of PBRER for Imjudo® (tremelimumab) for the period 21 April 2023 to 20 October 2023. Tremelimumab was registered in South Africa on 21 November 2023, therefore the PSUR reporting period does not include data from South Africa.

It was noted that no significant actions related to safety were taken or proposed during this period and the Imjudo Core Data Sheet (CDS) was updated to include safety related to changes on uveitis, immune-mediated arthritis and Guillain-Barré syndrome (GBS). These validated signals were classified as closed signals that are identified risks not categorised as important and were closed during the reporting period. These ADRs are not included in the current South African PI/PIL; no new or potential risks were identified; no missing information was presented in the RMP during the reporting period, and no new safety signals were identified.

b) Decision

- SAHPRA recommended acceptance of the PBRER.
- Furthermore, the applicant must update the South African PI/PIL with the new adverse drug reactions of immune-mediated arthritis, Guillain-Barre Syndrome and uveitis as well as other items from the updated CCDS.
- SAHPRA has concluded that the benefit-risk balance of IMJUDO® (tremelimumab) remains favourable for its registered indications.

3. Risk Management Plans (RMPs)

3.1 Nepexto® (Etanercept) - Risk Management Plan (RMP)

a) Background

SAHPRA conducted a review of Nepexto® (etanercept) RMP update version 2.1, dated 23 December 2020. It was noted that multiple identified and potential safety concerns were either removed from the etanercept RMP or consolidated into one single risk, based on EMA's decision and to align with the originator RMP for Enbrel®. The consolidation of Chronic Inflammatory Demyelinating Polyneuropathy (CIDP), Guillain-Barre Syndrome (GBS) and central demyelinating disorders into "Demyelinating disorders" was noted.
No significant safety information was identified. Results from clinical studies have demonstrated an acceptable efficacy and safety profile for etanercept.

The Patient Card (PC), proposed as an additional risk minimisation measure, was noted and accepted. The applicant's intention to implement and distribute the PC in South Africa, after receiving approval from SAHPRA, is acceptable. Apart from the ongoing post-authorisation study to further characterise specified safety concerns and address missing information in the EU, no additional pharmacovigilance activities are planned to be conducted in South Africa.

The SAHPRA approved PI and PIL for Nepexto® include guidance for screening and testing for tuberculosis (TB) before and during treatment. However, the PI/PIL only consists of the Tuberculin Skin Test (TST) as the method of testing for TB. The current European Centre for Disease Prevention and Control (ECDC) – World Health Organization (WHO) guidance recommends that both the TST and Interferon-Gamma Release Assay (IGRA) tests can be used for TB diagnosis. It was concluded that the amended RMP, as approved by EMA, is acceptable for the South African context.

b) Decision

- SAHPRA found the benefit-risk balance of NEPEXTO® (etanercept) favourable for its registered indications.

- SAHPRA recommended that the applicant continue with the proposed changes, as approved by EMA PRAC, which are noted to be acceptable in the SA context.
- The Proposed Patient information card is recommended for acceptance, and the amended RMP for NEPEXTO is recommended for approval, considering the EU-approved and the proposed SA-RMP.

3.2 Delamanid – RMP

a) Background

SAHPRA reviewed the updated RMP version 5.0 (v5.0) for delamanid (Deltyba®). The submission was in response to the recommendation on reviewed educational materials for Deltyba®. It was concluded that the educational materials for delamanid are no longer applicable, including the previous recommendations relating to the educational materials. There was no safety concerns reported in the RMP, and the benefit-risk balance of delamanid remains positive.

b) Decision

- SAHPRA noted and accepted EU RMP v 5.0 in its current form with its changes, and the risk-benefit balance remain the same.
- SAHPRA recommended that the applicant to continue pharmacovigilance monitoring of the benefit-risk balance of delamanid.

4. Additional Risk Minimisation Measures (aRMMs)

4.1 Propofol – Medication Errors that could Potentially Lead to Life-Threatening/Fatal Cases – Risk Minimisation MeasureS (RMMs)

a) Background

SAHPRA reviewed a safety signal regarding the risk of medication errors associated with the use of propofol. The signal that could potentially lead to life-threatening/fatal cases was identified in 2022 by the EMA. EMA requested that the applicants of propofol-containing products provide information on the signal.

Following the review of responses and data from EudraVigilance, the PRAC considered that there is sufficient evidence to establish a causal relationship between the risk of contamination of propofol and lack of compliance with recommendations for use in the product information, such as adequate aseptic procedures during preparation and administration of propofol, and the use of vials intended for single use in multiple patients. Available literature supports the signal relating to medication errors that result in microbial contamination of propofol in practice.

The PRAC agreed that the applicants for propofol-containing products should submit a variation to amend the product information and include warnings that the product is for single use in one patient and should be used immediately after opening, as a risk minimisation measure.

It was noted that SAHPRA approved PIs for propofol containing products contain warnings on the need to prevent contamination when using propofol.

b) Decisions

- SAHPRA recommend applicants align with EMA's recommendations, to update product information for all propofol containing products.
- The benefit-risk balance of propofol remains favourable for its registered indication.

Boitumelo Semete-Makokotlela

Dr Boitumelo Semete-Makokotlela
SAHPRA Chief Executive Officer (CEO)