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.: PV09-2024/25

28 August 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 April – June 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

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.

TABLE OF CONTENTS

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 (Pharmaceutical company) is anyone who has submitted an 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 the 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 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 the PI and PIL) which are communicated to the 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 a 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 like 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 the 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 provides information to healthcare professionals 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 Beta-lactam antibiotics – Kounis syndrome and linear IgA disease

a) Background

SAHPRA reviewed new evidence on the risks of Kounis syndrome and linear IgA disease associated with beta-lactam antibiotics. The review was based on the European Medicines Agency (EMA)'s regulatory decision to expand the recommendation to add Kounis syndrome to other beta lactam antibiotics, following an initial recommendation to include the risk in the product information for cefazolin. The EMA and the United States (US) Food and Drug Administration (FDA) also recommended the inclusion of linear IgA disease to the product information as an adverse drug reaction (ADR).

Decision

SAHPRA, based on the new evidence and actions of other regulatory authorities, recommended that applicants of beta-lactam antibiotics update the professional information (PI)/patient information leaflets (PILs) of their respective products to include the risks of Kounis syndrome and linear IgA disease.

1.2 Transmucosal fentanyl – Opioid use disorder, storage and overdose

a) Background

SAHPRA reviewed the safety concerns regarding opioid use disorder, storage and overdose of transmucosal fentanyl. The review was based on the EMA's decision to update the product information to include additional safety information on opioid use disorder, the safe and secure storage of transmucosal fentanyl to avoid accidental exposure and the risk of toxic leukoencephalopathy in the context of overdose. Available literature evidence suggests that toxic leukoencephalopathy can occur in the context of opioid overdose and is unlikely at therapeutic doses.

b) Decision

SAHPRA recommended that applicants for transmucosal fentanyl formulations should align with the EMA and update their PI/PILs to include the safety information on opioid use disorder, storage and overdose of transmucosal fentanyl.

1.3 Fentanyl – Dysphagia

a) Background

SAHPRA considered a notification regarding the risk of dysphagia associated with fentanyl use. The source of the signal was the EMA, following a recommendation to add dysphagia as an uncommon ADR in the European Union (EU) Summary of Product Characteristics (SmPC).

b) Decision

SAHPRA recommended that applicants for fentanyl-containing products update their PI/PILs to include the risk of dysphagia, in alignment with the EMA.

1.4 Minocycline – Hyperpigmentation, fixed drug eruptions, decreased hearing and headache not related to benign intracranial hypertension

a) Background

SAHPRA reviewed the risks of hyperpigmentation, fixed drug eruptions, decreased hearing and headache not related to benign intracranial hypertension associated with minocycline. The source of the signals was Medsafe, New Zealand, following a recommendation that applicants should update their PI/PILs to include hyperpigmentation as a warning and add fixed drug eruptions, decreased hearing and headache not related to benign intracranial hypertension as ADRs. The risks are already listed in the United Kingdom (UK) and Australian product information.

Decision

SAHPRA recommended that applicants for minocycline-containing products should update their PI/PILs to include hyperpigmentation, fixed drug eruptions, decreased hearing, headaches not related to benign intracranial hypertension, in the appropriate sections, in alignment with the UK SmPC.

1.5 Quetiapine – Serotonin syndrome

a) Background

SAHPRA considered a notification regarding the risk of serotonin syndrome associated with quetiapine use. The source of the signal was from the EMA based on their conclusion that, given the available data, there is a reasonable possibility of a drug-drug interaction (DDI) between quetiapine and serotonergic medicines leading to serotonin syndrome. The EMA recommended that the SmPC sections 4.4 and 4.5 should be amended accordingly.

b) Decision

SAHPRA recommended that the PI/PILs for quetiapine should be updated to include the safety information on serotonin syndrome in Sections 4.4 and 4.5, in alignment with the EMA.

1.6 Abatacept – Progressive multifocal leukoencephalopathy

a) Background

SAHPRA considered a notification regarding the risk of progressive multifocal leukoencephalopathy (PML) associated with abatacept use. The source of the signal is the EMA, following a request for applicants to conduct a cumulative review on the signal. The EMA concluded that although a causal relationship could not be established, a contributory role of abatacept in the development of PML cannot be excluded. The EMA recommended an amendment to section 4.4 of the SmPC, to include a warning on PML.

Decision

SAHPRA recommended that the PI/PILs for abatacept should be updated to include the risk of PML, in alignment with the EU SmPC.

1.7 Leuprorelin – Severe Cutaneous Adverse Reactions (SCARs)

a) Background

SAHPRA reviewed the risk of SCARs associated with leuprorelin use. The signal source was a regulatory decision by the EMA to add a warning on SCARs and to list Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN), erythema multiforme, and toxic skin eruptions as adverse reactions to the SmPC. The EMA concluded that there was no supportive evidence for a causal association for acute generalised exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic

symptoms (DRESS), dermatitis bullous, dermatitis exfoliative, cutaneous vasculitis. Applicants were requested to continue monitoring these SCARs in future periodic safety update reports (PSURs).

b) Decision

SAHPRA recommended that:

- The PI/PILs for leuprorelin should be updated to include the risks of SJS/TEN, erythema multiforme, and toxic skin eruptions, in alignment with the EMA's recommendation.
- Applicants should continue monitoring AGEP, DRESS, dermatitis bullous, dermatitis exfoliative and cutaneous vasculitis in future PSURs as recommended by the EMA.

1.8 Donepezil – Hypersexuality and pleurothotonus

a) Background

SAHPRA considered a notification regarding the risks of hypersexuality and pleurothotonus (Pisa syndrome) associated with the use of donepezil. The source of the signal is Health Canada after they became aware of a labelling update requested by the EMA to add hypersexuality and pleurothotonus as ADRs of unknown frequency in the EU SmPC.

Decision

SAHPRA recommended that the PI/PILs for donepezil should be updated to include the risks of hypersexuality and pleurothotonus, in alignment with the EU SmPC.

1.9 Parecoxib – Drug-Drug Interaction with enzyme inducers

a) Background

SAHPRA considered a notification regarding a DDI between parecoxib and medicines that induce its metabolism (enzyme inducers), e.g., apalutamide, enzalutamide, cenobamate and sotorasib. The signal emanated from the French National Agency for the Safety of Medicines and Health Products. SAHPRA noted that the parecoxib EU SmPC already lists examples of these medicine classes as enzyme inducers in section 4.5, and the addition of apalutamide, enzalutamide, cenobamate and sotorasib is not warranted.

b) Decision

SAHPRA recommended that the PI/PILs for parecoxib should be amended to include the DDI, in alignment with the EU SmPC.

1.10 Vincristine – Interaction with azole antifungals

a) Background

SAHPRA considered a notification regarding a DDI between vincristine and azole antifungals. The signal emanated from the EMA's recommendation to add the DDI in sections 4.4 and 4.5 of the vincristine EU SmPC.

b) Decision

SAHPRA recommended that the PI/PILs for vincristine should be updated to include the DDI with azole antifungals, in alignment with the EU SmPC.

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

2.1 Comirnaty® – South Africa national PSUR

a) Background

SAHPRA reviewed an updated South Africa national PSUR containing the most recent available information on Comirnaty® use in South Africa for the period from 19 June 2023 to 20 December 2023. Comirnaty® is currently not commercialised in South Africa; hence, the patient exposure was zero, and no safety concerns were identified during the reporting interval. SAHPRA concluded that the PSUR submission frequency stipulated in the current conditions of registration should be revised as Comirnaty® is no longer commercialised in South Africa.

b) Decision

SAHPRA concluded that the benefit-risk balance of Comirnaty® remains favourable and recommended that the applicant be requested to submit a formal application to reduce the frequency of PSUR submissions based on data from recognised regulatory authorities.

2.2 Janssen COVID-19 vaccine – PBRER

a) Background

SAHPRA reviewed a PBRER for the Janssen COVID-19 vaccine for the period from 25 February 2023 to 24 February 2024. No information was provided for the interval exposure from the post-marketing experience in South Africa. Updates were made to the EU SmPC and Risk Management Plan (RMP) to include the risks of myocarditis and pericarditis, particularly in males under the age of 40 years, in the first two weeks following vaccination with the Janssen COVID-19 vaccine. No new safety concerns were identified as use of this vaccine has been discontinued in South Africa and globally.

b) Decision

SAHPRA concluded that the overall benefit-risk balance of the Janssen COVID-19 vaccine remains favourable and recommended that the outstanding sections of the South Africa annex to the PBRER should be submitted.

2.3 Meningococcal A, C, Y, W Vaccine (MenACYW Conjugate Vaccine) – PSUR

a) Background

SAHPRA reviewed a PSUR for the MenACYW conjugate vaccine (Tetanus toxoid conjugate vaccine), for the period from 20 April 2023 to 19 October 2023. The vaccine was registered in South Africa in November 2023; therefore, no vaccine was marketed in South Africa during the reporting period.

There were no new safety concerns, and no actions were taken for safety reasons during the reporting period. It was noted that there is strong evidence towards the benefit of the MenACYW conjugate vaccine in the active primary and booster immunisation for the prevention of invasive meningococcal disease caused by Neisseria meningitis serogroups A, C, W, and Y for use in individuals 12 months of age and older.

b) Decision

SAHPRA concluded that the benefit-risk profile of the MenACYW conjugate vaccine is positive for its approved indications and recommended that future PSUR submissions must include a South Africa-specific annexure.

3 Risk Management Plans (RMPs)

3.1 Xalkori® (crizotinib) – RMP

a) Background

SAHPRA reviewed version 9.0 of the RMP for Xalkori® (crizotinib) submitted as a response to SAHPRA's recommendation to include the risk of bone toxicity and impaired bone growth in the paediatric population as an important potential risk. The RMP detailed the important risks, risk minimisation measures, and a pharmacovigilance plan for Xalkori®. There was no new safety concerns identified. Routine and additional risk minimisation activities for each of the important identified and potential risks were found acceptable and were approved by the EMA. However, the SAHPRA approved PI/PIL was not aligned with the EU SmPC and RMP on the important potential risk of bone toxicity and impaired bone growth in the paediatric population.

Decision

SAHPRA found the Xalkori® RMP acceptable and recommended that the applicant should update the PI/PIL to align with the RMP and EU SmPC on the information regarding bone toxicity and impaired bone growth in the paediatric population.

Boitumelo Semete-Makokotlela

Dr Boitumelo Semete-Makokotlela
SAHPRA Chief Executive Officer