

## COMMUNICATION TO STAKEHOLDERS

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# 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 October – December 2023. 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 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 Sitagliptin - Risk of Bullous Pemphigoid

##### a) Background

SAHPRA became aware of the European Medicines Agency (EMA)'s decision for the applicant/holder of the certificate of registration (HCR) for sitagliptin to update their Professional Information (PI) and Patient Information Leaflet (PIL) with the risk of bullous pemphigoid. Sitagliptin is one of the medicines that belongs to a class of oral diabetic medications (dipeptidyl peptidase 4 (DPP-4) inhibitors) used to lower blood sugar levels in adults with type 2 diabetes. Bullous pemphigoid is a known adverse reaction with the use of DPP-4 inhibitors, and it is included as an adverse reaction and as a 'Special Warning and Precaution' in the PI of DPP-4 inhibitors.

The safety signal is based on the identified reports of adverse reactions of bullous pemphigoid, including fatal cases, suspected to be caused by the use of sitagliptin.

##### b) Decision

- SAHPRA took a regulatory decision to request the applicant/HCR of sitagliptin-containing medicine to align with EMA's SmPC by amending the PI/PIL of their products.
- The benefit-risk profile of sitagliptin-containing medicines remains positive, provided the applicant effect the recommended changes.

#### 1.2 Nirmatrelvir/Ritonavir (Paxlovid®) – Interactions with Other Medicines

##### a) Background

SAHPRA became aware of EMA's regulatory decision to include the risk of drug-drug interaction between nirmatrelvir/ritonavir (Paxlovid®) and other medicines. The risk of drug-drug interactions identified by EMA was found significant and SAHPRA adopted the regulatory decision.

##### b) Decision

- SAHPRA recommended that the applicant/HCR of nirmatrelvir/ritonavir-containing medicine align their PI/PIL with changes made in the European (EU) summary of product characterisation (SmPC) regarding the risk of drug-drug interactions with other medicines.
- The benefit-risk profile of nirmatrelvir/ritonavir-containing medicines remains positive, provided the applicants effect the recommended changes.

### 1.3 Abacavir - Risk of Cardiovascular Events

#### a) Background

SAHPRA became aware of EMA's regulatory decision to update the product information of abacavir-containing medicines so that it adequately reflects the risk of cardiovascular events and discourages the use of abacavir-containing products in patients with high cardiovascular risks.

The safety signal emanated from the EMA's Pharmacovigilance Risk Assessment Committee (PRAC's) assessment of the periodic safety update report(s) (PSUR(s)) for abacavir. Based on the reviewed available data on cardiovascular events from the literature regarding abacavir, including a plausible mechanism of action, PRAC considered the need for the 'warnings and precautions for use' section of abacavir product information to be revised so that it adequately reflects the current level of information on cardiovascular events. In line with the European therapeutic guidelines, PRAC further recommended that the product information should be amended to include that the use of abacavir-containing products in patients with high cardiovascular risk is discouraged.

#### b) Decision

- SAHPRA recommended that the applicants/HCRs of abacavir-containing medicines should amend the PI/PILs of their products to adequately reflect the risk of cardiovascular events and discourage the use of abacavir-containing products in patients with high cardiovascular risk, in line with the EMA's decision.
- The benefit-risk profile of abacavir-containing medicine remains positive provided the applicants effect the recommended changes.

### 1.4 Cariprazine - Risk of Severe Cutaneous Adverse Reactions (SCARs)

#### a) Background

SAHPRA conducted a review of a safety signal regarding the risk of severe cutaneous adverse reactions (SCARs) following the use of cariprazine. The safety signal originates from the PRAC's assessment of cariprazine PSURs. The reviewed available data including data from literature resulted in the update of the EU SmPC and characterisation of the risk of SCARs as an important potential risk. Moreover, the US-FDA also included the safety signal in the product monograph. It was further noted that other atypical antipsychotics are associated with the risk of SCARs.

#### b) Decision

- SAHPRA recommended that applicants/HCRs of cariprazine should align with the US-FDA and update the PI/PIL for cariprazine, using similar wording as in the US monograph for their products.
- The benefit-risk profile of cariprazine-containing medicine remains positive, provided the applicants effect the recommended changes.

## 1.5 Somatropin - Risk of gynecomastia, pancreatitis and acute adrenal insufficiency

### a) Background

SAHPRA conducted a review of a safety signal regarding the risks of gynecomastia, pancreatitis and acute adrenal insufficiency associated with the use of somatropin (a medicine used to treat growth hormone deficiency (inability to produce enough growth hormone), chronic kidney disease and idiopathic short stature (unexplained shortness)). The safety signal was identified during routine pharmacovigilance activities for Norditropin®. These safety signals are already included in the Norditropin® current EU SmPC, and the risk of gynecomastia and pancreatitis is characterised as an identified risk. Acute adrenal insufficiency is characterised as a potential risk for Norditropin®.

Taking into consideration all available data, including inputs from HCRs of somatropin-containing medicines, SAHPRA found the consequences associated with unrecognised pancreatitis and acute adrenal insufficiency to be potentially serious, with the available data showing a higher risk of pancreatitis in children. Therefore, harmonisation of safety information and wording in the PI/PILs is important.

### Decision

- SAHPRA recommended that all applicants of somatropin-containing medicines should update their PI/PILs to include the risk of pancreatitis, gynecomastia and acute adrenal insufficiency in line with EMA regulations (in recommended sections of the PI/PIL).
- The benefit-risk profile of somatropin-containing medicine remains positive provided the applicants effect the recommended changes.

## 1.6 CDK4/6 Inhibitors - Risk of Venous Thromboembolism

### a) Background

SAHPRA conducted a review of safety signals regarding the risk of venous thromboembolism (VTE) associated with the use of palbociclib-containing medicines. The safety signal emanated from the Ministry of Food and Drug Safety's (MFDS's) decision to amend the label for palbociclib, based on the results of the European Commission (EC)'s review of safety information on palbociclib. A review of SAHPRA-approved PIs of palbociclib and other medicines in the same class revealed that venous thrombosis, pulmonary embolism and deep vein thrombosis are not mentioned in the PIs of palbociclib and ribociclib. However, the PIs of abemaciclib-containing medicines list venous thromboembolism under 'special warnings and precautions for use' and 'undesirable effects' sections.

The available data suggests that the events are a class effect. Appropriate recognition of VTE is very important due to its substantial contribution to long-term morbidity in people living with or surviving cancer. Therefore, proper adverse event identification and management will allow effective continuous treatment without any significant detrimental outcomes.

**b) Decision**

- SAHPRA adopted EMA's regulatory decision and recommended that applicants of CDK4/6 inhibitors be requested to update their PI/PIL to include the risk of venous thrombosis.
- The benefit-risk profile of CDK4/6-containing medicine remains positive, provided the applicants effect the recommended changes.

**1.7 Fluorouracil IV – Risks of Cutaneous Lupus Erythematosus, Stress Cardiomyopathy (Takotsubo Syndrome), Pneumatosis Intestinalis, Posterior Reversible Encephalopathy Syndrome, Lactic Acidosis and Tumour Lysis Syndrome****a) Background**

SAHPRA became aware of the newly identified risks associated with the use of fluorouracil-containing medicines. The risks include cutaneous lupus erythematosus, stress cardiomyopathy (Takotsubo syndrome), pneumatosis intestinalis, posterior reversible encephalopathy syndrome (PRES), lactic acidosis and tumour lysis syndrome (TLS).

The safety signal emanates from the EMA's PRAC's assessment of PSURs for the active substance 5-fluorouracil intravenous (i.v.) covering the reporting period from 17 December 2017 to 16 December 2020. Based on the available data from the literature and spontaneous reports, including a close temporal relationship and a positive dechallenge. Based on the available data and scientific evidence, PRAC considered a possible causal relationship between the newly identified risks and 5-fluorouracil-containing medicines. EMA took a regulatory decision to request that applicants of 5-fluorouracil-containing medicines to include the above risks in the product information.

**b) Decision**

- SAHPRA recommended that all applicants of fluorouracil-containing medicines update the PI/PIL of their products in line with EMA PRAC's recommendations.
- The benefit risk profile of fluorouracil-containing medicine remains positive, provided the applicants effect the recommended changes.

**1.8 Gemcitabine – Risk of Severe Cutaneous Adverse Reactions (SCARs)****a) Background**

SAHPRA became aware of the risk of acute generalised exanthematous pustulosis (AGEP) associated with the use of gemcitabine-containing medicines. The safety signal emanated from EMA's PRAC assessment of gemcitabine PSUR. The causal relationship between gemcitabine products and AGEP was found to be reasonably possible based on the available data on AGEP, including two post-marketing case reports with confirmed diagnosis and the causality was considered likely related to gemcitabine in view of the close temporal relationship, positive dechallenge, and no alternative causes. Furthermore, other types of severe cutaneous adverse reactions (SCARs), namely Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis

(TEN), are already listed as undesirable effects of gemcitabine in product information. Given the seriousness of AGEF, SJS/TEN, a more general warning regarding SCARs was recommended.

#### b) Decision

- SAHPRA recommended that the applicants/HCRs of gemcitabine-containing medicines amend the PI/PIL of their products to include a general warning regarding SCARs, and the adverse reaction acute generalised exanthematous pustulosis (AGEF) with a frequency 'not known' in line with the PRAC recommendations.
- The benefit risk profile of gemcitabine-containing medicine remains unchanged provided the applicants effect the recommended changes.

### 1.9 Genotoxic Anticancer Medicines - New Contraception Duration Calculation

#### a) Background

SAHPRA reviewed the new calculation for the duration of contraception use after completion of therapy with genotoxic anticancer medicines. This means that women of childbearing potential should use effective contraceptive measures while on treatment and for a specified number of months following completion of treatment on these medicines. Similarly, men should be recommended to use effective contraceptive measures and to not father a child while receiving treatment with these medicines and for a specified number of months, following completion of treatment.

The safety signal was based on actions taken by recognised regulatory authorities such as the US-FDA, EMA and Australia's Therapeutic and Goods Administration (TGA) who requested an update to the product information with regards to contraception calculations.

The potential embryotoxicity and teratogenicity of genotoxic pharmaceutical products is a serious adverse effect and therefore it is important that any safety updates that may potentially prevent/ reduce the occurrence of this effect are implemented. It was noted from the review of genotoxic medicines PIs that most applicants have not made changes to their PIs, and the contraception periods vary for the same product. A new calculation of contraception duration was recommended for all genotoxic anticancer treatments.

#### b) Decision

- SAHPRA recommended that applicants of genotoxic anticancer medicines amend the PI/PILs of their products by aligning to the EMA, where appropriate, if they have not done so.
- The benefit risk profile of genotoxic anticancer medicines remains positive provided the applicants effect the recommended changes.

### 1.10 Paracetamol - Risk of SCARs (DRESS and FDE)

#### a) Background

SAHPRA conducted a review of a safety signal regarding the risk of fixed drug eruptions (FDE) and drug induced hypersensitivity syndrome (DIHS) (also known as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)) associated with the use of paracetamol-containing medicines. The safety signal was identified by the Pharmaceuticals and Medical Devices Agency (PMDA), a Japanese regulatory agency, working together with Ministry of Health, Labour and Welfare (MHLW), based on a total of three (3) cases reported in the Japan safety database. No patient mortalities were reported. PMDA recommended that drug-induced hypersensitivity syndrome be added in the 'Precautions' section of the product information for preparations containing acetaminophen/paracetamol.

DRESS is a rare but significant risk that affects multiple organs and is potentially life-threatening. Therefore, as a risk minimisation measure, patients and healthcare professionals should be made aware of this risk to allow prompt recognition and withdrawal of the causative medicine. The risk of DRESS, despite being rare, can occur during paracetamol use and the inclusion in the PI/PIL is a risk minimisation measure for patients and healthcare professionals.

#### b) Decision

- SAHPRA, in view of the extensive use of paracetamol and the risk of DRESS being potentially life threatening, recommended that all applicants of paracetamol-containing medicines update the PI/PIL of their product to include a general warning regarding the risk of SCARs, instead of mentioning individual SCARs and/or the risk of Fixed Drug Eruptions (FDE) and Drug-induced hypersensitivity syndrome (DIHS) under 'Side effects' and 'Post-Marketing Experience' sections.
- The benefit risk profile of paracetamol-containing medicines remains positive provided the applicants effect the recommended changes.

### 1.11 Etanercept – Risk of Glomerulonephritis

#### a) Background

SAHPRA became aware of EMA's regulatory decision to update etanercept product information to include the risk of glomerulonephritis. EMA's decision was based on PRAC's recommendation that the product information of products containing etanercept be amended to include the risk of glomerulonephritis following a PSUR assessment EMEA/H/C/PSUSA/00010795/202302.

#### b) Decision

- SAHPRA recommended that applicants of etanercept-containing medicines update their PI/PIL to include the risk of glomerulonephritis.
- The benefit risk profile of etanercept-containing medicines remains positive provided the applicants effect the recommended changes.

### 1.12 Etoposide – Opportunistic Infections and Infusion related Hypersensitivity

#### a) Background

SAHPRA became aware of EMA’s regulatory decision to request applicants of etoposide-containing medicines to update their PI/PIL to include the risk of opportunistic infections and infusion related hypersensitivity following the use of etoposide. The recommendation was based on EMA’s PRAC decision following a PSUR assessment.

#### b) Decision

- SAHPRA recommended that applicants of etoposide-containing medicines to update their PI/PIL to include the risk of opportunistic infections and infusion-related hypersensitivity following the use of etoposide.
- The benefit risk profile of etoposide-containing medicines remains positive provided the applicants effect the recommended changes.

### 1.13 Mycophenolate mofetil & Mycophenolic acid – Acute Inflammatory Syndrome

#### a) Background

SAHPRA became aware of the regulatory decision taken by EMA to update the EU SmPC for mycophenolate mofetil (MMF) and mycophenolic acid (MPA) with the risk of acute inflammatory syndrome (AIS). EMA identified the safety signal from the assessment of PSUR for MMF and MPA-containing products. Based on reports from literature and post-marketing reports with close temporal relationship between medicine use and the onset of acute inflammatory syndrome, positive dechallenge and rechallenge and plausible mechanism of action, PRAC considered a causal relationship between MMF/ MPA and AIS. Inconsistencies were observed between SAHPRA-approved PI of MMF and EMA SmPC and USPI in relation to the risk of AIS.

#### b) Decision

- SAHPRA recommended that applicants of mycophenolate mofetil and mycophenolic acid align the PI/PIL of their products with EMA’s SmPC (of mycophenolic acid) by including the risk of AIS as a “rare” side effect and under “warnings and precautions for use”.
- The benefit risk profile of mycophenolate mofetil and mycophenolic acid-containing medicines remains positive provided the applicants effect the recommended changes.

### 1.14 Opioid Use in Patients with a History of Mental Health Disorders

#### a) Background

SAHPRA conducted a review of a safety signal regarding the use of opioid-containing medicines in patients with a history of mental health disorders. The review follows a review by the Health Canada, published in a World Health Organization (WHO) newsletter in May 2023, which indicated a potential risk of progressive

multifocal leukoencephalopathy (PML) (a disease of the white matter of the brain, caused by a virus infection (Human polyomavirus 2) that targets cells that make myelin—the material that insulates nerve cells) in section 4.4.

It was noted that the analysis from Health Canada and other literature sources provide sufficient evidence to warrant a more cautious approach to the use of opioids in patients with a history of mental health disorders. Due to the increased use of opioids for pain relief in patients with mood disorders, it is important that PI/PILs contain the necessary safety information as these products are susceptible to misuse and abuse. Healthcare professionals and the public need to be aware of the increased risk for addiction and abuse in patients with a history of mood disorders, so that the benefits and risks of opioid medications are carefully assessed based on the needs of each patient before prescribing.

#### b) Decision

- SAHPRA recommended that all applicants with registered opioid-containing products, except those used for anaesthesia and those that have already been updated, to update their respective PI/PILs with information on the increased risk of addiction in patients with a personal or family history of substance abuse or mental health disorders.
- The benefit risk profile of opioid-containing medicines remains positive provided the applicants effect the recommended changes.

### 1.15 Levodopa/Carbidopa Intestinal Gel – Risk of Polyneuropathy

#### a) Background

SAHPRA became aware of Swissmedic’s decision to update the product information for DUODOPA®/LCIG (levodopa/carbidopa intestinal gel) as well as an update to the preclinical data section for hydrazine PI under warning and precautions sections to include the risk of polyneuropathy.

It was noted that DUODOPA® has not been marketed in South Africa since its registration. Furthermore, the applicant has already updated the PI/PIL of their product in line with other RRAs regarding the risk.

#### b) Decision

- SAHPRA recommended that the applicants for levodopa/carbidopa gel and for hydrazine update the PI/PIL of their product to include the risk of polyneuropathy.
- The benefit risk profile of levodopa/carbidopa gel and hydrazine-containing medicines remains positive, provided the applicants effect the recommended changes.

## 1.16 Tofacitinib – Risk of Progressive Multifocal Leukoencephalopathy

### a) Background

SAHPRA conducted a review of the risk of progressive multifocal leukoencephalopathy (PML) associated with the use of tofacitinib. The safety signal was based on a case report for a patient treated with tofacitinib for rheumatoid arthritis (RA), who developed PML. There have been reports of PML with other Janus kinase (JAK) inhibitors such as ruxolitinib, therefore, this could be a class effect.

### b) Decision

- SAHPRA recommended that the applicant(s) update the PI/PIL to include:
  - the concomitant use with immunomodulatory drugs and any other drugs that increase the risk of infection;
  - the risk factors associated with PML; and
  - if PML develops in patients, the drug should be stopped, and plasma exchange should be done to remove the residual circulating drug.
- The benefit risk profile of tofacitinib and other JAK inhibitors remains positive provided the applicants effect the recommended changes.

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

### 2.1 Ivermectin (Soolantra®) – Periodic Benefit-Risk Evaluations Reports (PBRER)

#### a) Background

SAHPRA conducted a review of Soolantra® (ivermectin) periodic benefit risk evaluation report (PBRER), submitted as a condition of registration for the period 23 April 2022 to 22 April 2023. The review of Soolantra® PBRER did not reveal any safety concerns or newly identified risks for the reporting period. No safety signals were ongoing or identified during the reporting period. No studies with new information of efficacy and effectiveness were published in the literature during the reporting interval. The estimated exposure in the interval period was noted as 751 545 patients; however, there was no South African data included in the PBRER.

During the reporting period, there was no withdrawal or suspension of marketing authorisation or safety concern reported globally that had a significant influence on the benefit-risk balance of Soolantra®; and/or an impact on the conduct of a specific clinical trial(s) or on the overall clinical development program. The benefit/risk ratio of Soolantra® QD remains favourable in the treatment of papulopustular rosacea under the recommended conditions of use.

#### b) Decision

- SAHPRA found the benefit-risk balance of Soolantra® favourable for its registered indication(s).

- SAHPRA recommended continuous pharmacovigilance monitoring of the benefit-risk profile of Soolantra®.

## 2.2 Cipla Warfarin® - Periodic Safety Update Report (PSUR)

### a) Background

SAHPRA conducted a review of Cipla warfarin® PSUR. The review was triggered by adverse event reports (ten cases) relating to haemorrhage and increased international normalised ratio (INR) levels linked with Cipla warfarin® (in low to normal doses) noted by SAHPRA in the safety monitoring database, VigiBase®.

The review of the Cipla warfarin® PSUR revealed no new safety concerns for warfarin identified during the reporting period. However, there were two signals of ‘anticoagulant-related nephropathy’ and ‘menorrhagia’ that were closed and characterised as identified risks. Three ongoing signals and 11 closed signals for warfarin during the reporting period were noted.

The PSUR provided a global assessment of the safety profile of warfarin during the reporting period. Data contained in the Cipla warfarin® PSUR was not supportive in deciding on whether there is/was an altered occurrence of increased INR and/or haemorrhage specifically related to Cipla warfarin® use. The signal required a comparison of adverse events reported with the use of Cipla-warfarin® versus those reported with the use of other brands of warfarin.

Although the PSUR review could not answer the question of whether Cipla-warfarin® is causally associated with an increased risk of adverse events compared to other warfarin brands, the benefit–risk profile of warfarin when used for the registered indications within the recommended dosages remains acceptable.

### b) Decision

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

## 2.3 Kyprolis® (Carfilzomib) – Periodic Safety Update Report (PSUR)

### a) Background

SAHPRA conducted a review of Kyprolis® (carfilzomib) PSUR (period 20 July 2022 to 19 July 2023), submitted as a condition of registration. Carfilzomib, as a single agent, is registered for use in the treatment of patients with relapsed and refractory multiple myeloma (RRMM) who have received two (2) prior therapies that include a bortezomib and an immunomodulatory agent. In combination with other medicines, carfilzomib is used in the treatment of patients with multiple myeloma (MM) who have received at least one 1) therapy.

During the reporting period of this PSUR, no significant actions were taken for safety reasons, and no significant change was made to the product information. Evaluation of safety data received in the reporting

period from clinical trials and post marketing sources did not result in the detection of any new risks, significant new insight or highlight new concerns for carfilzomib. The overall benefit-risk balance of carfilzomib for its approved indications remains favourable.

#### b) Decision

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

### 2.4 Comirnaty® - Periodic Safety Update Report

#### a) Background

SAHPRA reviewed Comirnaty® PSUR for the period 19 December 2022 to 18 June 2023, submitted as a condition of registration. Cumulative exposure from post-marketing experience was estimated at 4,615,732,025 doses (original and bivalent), while cumulative exposure and interval exposure from post-marketing experience in South Africa were 390 300 standard units and 221 972 standard units respectively.

Newly identified information on the efficacy and effectiveness of Comirnaty® presented in the PSUR was specific to bivalent (Omicron-modified) presentations of the vaccine. The data reinforced the importance of a bivalent booster dose in different age groups. However, there are no registered bivalent vaccines in SA, therefore, the benefits realised from the Omicron-modified vaccines were not applicable to SA. There were no significant changes in the risk-benefit profile of the product, which remains favourable. No additional risk minimisation measures are required. The PSUR reporting frequency remained unchanged.

#### b) Decision

SAHPRA recommended that:

- The applicant presents a more detailed and accurate national appendix, taking into consideration all reported ADRs in South Africa.
- the PI for the Comirnaty vaccine should be updated to reflect the frequency of diarrhoea as an adverse reaction (if not already in the process).
- The applicant should continue to monitor the safety profile for Comirnaty® with appropriate action taken, when warranted.
- PSUR reporting frequency and submission will be changed to 12 months.

### 3. Risk Management Plans (RMPs)

#### 3.1 Dolutegravir/Lamivudine/Tenofovir - Risk Management Plan (RMP)

##### a) Background

SAHPRA conducted a review of dolutegravir/lamivudine/tenofovir RMP version 3 dated 23 March 2023 with a data lock point of 14 March 2023. The RMP was submitted as part of the renewal process. Patient exposure from post-marketing data in South Africa was 1,109,727 patient-treatment years until February 2023.

There are no additional pharmacovigilance plans and no plans for post-authorisation efficacy studies. However, there are additional risk minimisation measures (aRMMs) comprising of educational materials intended for physicians who are expected to prescribe/use dolutegravir/lamivudine/tenofovir disoproxil fumarate in paediatric patients. A physician educational pack containing the PI and HIV and HBV paediatric educational brochure will be made available on the applicant's website. The RMP outlines risk minimisation materials for children and adolescents aged 2 to <18 years on tenofovir in HIV-1 and those with chronic hepatitis to address the risk of bone events due to proximal renal tubulopathy/loss of bone mineral density (BMD). The risk minimisation measures, including the educational material concept to reinforce the PI and PIL, were found acceptable.

There were no new safety concerns or risks added to the RMP. The PI adequately addresses the safety concerns. The RMP was recommended for acceptance because the applicant has developed sufficient risk management plans for all identified and potential risks as well as missing information.

##### b) Decision

- SAHPRA found the RMP acceptable and recommended that the applicant continue monitoring the benefit risk profile of dolutegravir/lamivudine/tenofovir.

SAHPRA found the benefit risk balance of dolutegravir/lamivudine/tenofovir favourable for its registered indications.

#### 3.2 Paxlovid® (Nirmatrelvir/Ritonavir) – Risk Management Plan (RMP)

##### a) Background

SAHPRA conducted a review of Paxlovid® (nirmatrelvir/ritonavir) risk management plan (RMP). There were no important identified and potential risks for Paxlovid that required more actions, other than routine risk minimisation activities. The safe use of Paxlovid® in patients with renal impairment and hepatic impairment and during pregnancy were characterised as missing information. There were ongoing post authorisation safety studies in pregnant and breastfeeding women, in patients with moderate and severe renal impairment and patients with moderate and severe hepatic impairment.

A QR code and website links were included on the PIL and the outer carton to support the risk minimisation of drug-drug interactions beyond the information contained in the PI. There were no additional risk minimisation measures.

The RMP was found acceptable. It clearly and sufficiently outlined risk minimisation measures and pharmacovigilance measures to assess and monitor the missing information.

#### b) Decision

- SAHPRA found the Paxlovid® RMP acceptable and recommended that the applicant:
  - submits the results of the ongoing studies once they become available.
  - submits a statement regarding the distribution of a patient card on dosage adjustment in renal impairment and interactions, as well as the implementation of a QR code on interactions on the patient information and folding box.
  - Continue monitoring the benefit-risk profile of Paxlovid®.
- SAHPRA found the benefit-risk balance of Paxlovid® favourable for its registered indications, provided the applicant effect the recommendation.

### 3.3 Tuvigin® (fingolimod) – Risk Management Plan

#### a) Background

SAHPRA reviewed a Tuvigin® (fingolimod) RMP version 19.1 dated 01 July 2021 with a data lock point of 28 February 2020. The RMP was submitted due to an update made following the completion of the additional pharmacovigilance activities (the PASSAGE studies (CFTY720D2403 and CFTY720D2406 (including CFTY720D2409 cardiac sub-study)). A comprehensive reassessment of all important risks and missing information was performed.

The RMP outlined activities and measures for addressing important identified risks, important potential risks and missing information. Routine pharmacovigilance activities included specific adverse reaction follow-up questionnaires for collecting more safety information for the risk of PML, CM and VZV. Two ongoing post-authorisation safety studies (FTY720D2404 and FTY720D2311) were planned to collect outcome data on the babies born to women treated with fingolimod and to assess the long-term use in pediatric patients, including impact on growth and development (including cognitive development), respectively.

Additional risk minimisation measures include educational materials for physicians and patients (physician's checklist for adult and paediatric population, patient/parent/caregiver guide); a pregnancy-specific patient reminder card and distribution of a DHPCL to inform healthcare professionals regarding the label update and pregnancy prevention.

Furthermore, the applicant requested to discontinue contracted nurse, case manager and courier pharmacy support due to the generics being easily accessible through retail pharmacies and they believe that healthcare professionals have developed expertise in the treatment and monitoring of patients on Tuvigin® for the past 10 years.

#### b) Decision

- SAHPRA found acceptable in its current format and acceded to the applicant's request to discontinue contracted nurse, case manager and courier pharmacy support due to the generics being easily accessible through retail pharmacies.
- SAHPRA recommended that the applicant submit the results of the ongoing studies (study FTY720D2404 and FTY720D2311) once they become available.

Boitumelo Semete-Makokotlela  
  
SIGNIFLOW

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