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COMMUNICATION TO STAKEHOLDERS

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Summary of Medicine Safety Regulatory Decisions

INTRODUCTION

This document provides an overview of the safety regulatory decisions taken by the South African Health Products Regulatory Authority (SAHPRA) during July – December 2022. This includes a summary of regulatory decisions, where safety concerns were reviewed and concluded, and those safety concerns that are not concluded but are severe and serious in nature. SAHPRA's decisions are actionable by the concerned stakeholders including applicants or holders of certificate of registration (HCRs). Safety decisions concerning the amendment of professional information and patient information leaflets (PI/PIL) are submitted to the Clinical Evaluations unit to review and ensure appropriate implementation and amendments thereof.

Applicants/HCRs, in line with Regulation 11 and 12 of the Medicines and Related Substance Act (Act 101 of 1965, as amended, (https://www.sahpra.org.za/document/guideline-for-professional-information-for-human-medicines/ and https://www.sahpra.org.za/document/guideline-for-patient-information-leaflet-for-human-medicines/), must ensure that their product information (also referred to as professional information) is kept up to date with the current scientific knowledge. Variations are handled according to the variation of human and veterinary medicines - https://www.sahpra.org.za/document/variations-addendum-for-human-and-veterinary-medicines/.

The timeline recommended by SAHPRA for submission of variations following signal assessment is applicable to both innovator and generic products, unless otherwise specified.

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1. Definitions

Applicant is anyone who has applied for the medicine registration.

Dear Healthcare Professional (DHCP) Letter is a communication in a form of a letter intended to convey important medicine safety information, distributed by holders of certificate of registration (HCR) directly to individual healthcare professionals, and also 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 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, dispensing, medicine preparation, administration, and monitoring errors.

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.

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.

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.

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.

2. Regulatory Safety Decisions

2.1 Update of Professional Information (PI) and Patient Information Leaflet (PIL)

2.1.1 Janus Kinase Inhibitors (e.g., Tofacitinib) – Risk of Hypoglycaemia and Retinal Venous Thrombosis

a) Background

SAHPRA conducted a review regarding the risk of hypoglycaemia and retinal venous thrombosis associated with the use of tofacitinib-containing medicines. Tofacitinib is a Janus kinase (JAK) inhibitor registered for various inflammatory disorders, including rheumatoid arthritis. The safety signals emanated from a review of a tofacitinib periodic safety update report (PSUR), by the EMA's PRAC. In view of the assessed data, PRAC considered a plausible causal relationship between the use of tofacitinib-containing medicines and the risk of hypoglycaemia and retinal venous thrombosis. A possible mechanism of action described in the literature suggests a JAK/signal transducer and activator of transcription (STAT) pathway on insulin resistance and/or sensitivity. Clinical trial data as well as available post-marketing case reports of hypoglycaemia, identified in the EudraVigilance, suggests that hypoglycaemia can occur in patients with diabetes after initiation of tofacitinib, requiring adjustment of antidiabetic drugs to prevent further events of hypoglycaemia.

PRAC, based on the available data on retinal venous thrombosis from fifteen spontaneous reports identified in the Eudravigilance (with a possible causality according to WHO-UMC criteria) and the established venous thromboembolism (VTE) risk for JAK inhibitors, considered a causal relationship between tofacitinib and retinal venous thrombosis to be at least a reasonable possibility.

b) Decision

In consideration of the available data and the significance of the safety signal, **SAHPRA recommended that all applicants/HCRs of JAK inhibitor medicines update the PI/PIL of their products to include the risk of hypoglycaemia and renal vein thrombosis (RVT)**. Moreover, hypoglycaemia should be included in the risk management plan as an important potential risk. SAHPRA considers the benefit-risk profile favourable, provided the recommended changes are implemented by applicants/HCRs.

2.1.2 Gabapentinoids - Serious Breathing Difficulty

a) Background

SAHPRA conducted a review regarding the risk of serious breathing difficulty associated with the use of gabapentinoids. Gabapentinoids are medicines that are registered for the management of convulsions and neuropathic pain. The safety signal emanated from a safety warning issued by the U.S. Food and Drug Administration (FDA) regarding serious breathing difficulties which may occur in patients using gabapentin or pregabalin with respiratory risk factors. These included the use of opioid pain medicines and other drugs that depress the central nervous system, and conditions that reduce lung function such as chronic obstructive pulmonary disease. Gabapentinoids are frequently prescribed as adjuncts to opioids for neuropathic pain syndromes. Due to their mechanism of action in the central nervous system, gabapentinoids are prone to misuse, abuse, and dependence.

There are cases of respiratory depression and dyspnoea associated with the use of gabapentinoids reported globally. Furthermore, data from literature showed that when gabapentinoids are given concomitantly with opioids, they potentiate the respiratory depressant effect of opioids especially in patients with risk factors such as, advanced age, renal dysfunction, respiratory conditions as well as co-use with other central nervous system depressants.

b) Decision

SAHPRA recommended that applicants/HCRs update the PI/PIL of their gabapentinoid containing medicines to convey the risk of respiratory depression. The overall risk/benefit balance of gabapentinoid-containing medicines is considered favourable, provided applicants/HCRs effect the recommended changes.

2.1.3 Piroxicam – Risk of Fixed Drug Eruption

a) Background

SAHPRA conducted a review of a safety signal regarding the risk of fixed drug eruptions (FDE) associated with the use of piroxicam-containing medicines. These medicines are used to treat a variety of conditions requiring anti-inflammatory and /or analgesic activity, such as rheumatoid arthritis: osteo-arthritis (arthrosis, degenerative joint disease); ankylosing spondylitis: acute musculoskeletal disorders and acute gout. The safety signal emanated from a drug safety alert issued by the Indian Pharmacopoeia Commission based on the preliminary analysis of FDE case reports from the Pharmacovigilance Programme of India (PvPI) database. SAHPRA noted that although Steven-Johnson Syndrome (SJS)/Toxic Epidermal Necrosis (TEN) are listed under 'Side effects' and 'Warnings and Special Precautions' section of the SAHPRA approved PIs of piroxicam-containing medicines, information on FDE is not included. Data from literature showed that there are differences in clinical presentation, time to onset and severity between FDE and SJS/TEN.

b) Decision

SAHPRA recommended that applicants/HCRs update the PI/PIL of their piroxicam-containing medicines to communicate the risk of FDE and stipulate that piroxicam should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity. The overall risk/benefit balance of piroxicam-containing medicines remains favourable, provided the applicants/HCRs effect the recommended changes.

2.1.4 Metformin - Change in the Frequency of Vitamin B12 Deficiency Side Effect

a) Background

SAHPRA conducted a review of a safety signal regarding a change in frequency of vitamin B12 deficiency, a known metformin adverse drug reaction (ADR). Metformin is registered for the management of diabetes mellitus. A change in the vitamin B12 deficiency frequency was identified by the United Kingdom's Medicines and Healthcare products Regulatory Agency (MHRA) during its routine variation procedure for the brand leader Glucophage®. The MHRA noted from published literature that the frequency of vitamin B12 deficiency is higher than previously thought. Other

regulatory authorities like EMA and the US FDA also noted the change in vitamin B12 deficiency frequency and updated the product information – that is, changed from '*rare'* to '*common'* side effect.

Vitamin B12 deficiency is an important risk whose symptoms are likely to be masked by other diseases like diabetes or its symptoms such as peripheral neuropathy. It is very important for healthcare professionals to conduct annual assessment for vitamin B12 levels in patients taking metformin and to consider vitamin B12 deficiency as a differential diagnosis for other disorders such as anaemia.

b) Decision

SAHPRA recommended that applicants/HCRs of metformin-containing medicines update the PI/PIL of their products by changing the frequency of the ADR, vitamin B12 deficiency, from '*rare/ less common*' to '*common*'. The overall risk/benefit balance of metformin remains favourable provided the applicants/HCRs effect the recommended changes.

2.1.5 Janus Kinase Inhibitors (e.g., Tofacitinib) - Risk of Malignancy, Mortality, Major Cardiovascular Events and Venous Thromboembolism

a) Background

SAHPRA conducted a review regarding the risk of venous thromboembolism (VTE), major adverse cardiovascular events (MACE), and malignancies associated with the use of tofacitinib. The safety signal was based on the results of Oral Rheumatoid Arthritis Trial (ORAL) Surveillance study recommended by the US FDA and conducted by the applicant. The study was conducted to evaluate the risk of cardiovascular events (defined as cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke), malignancy excluding non-melanoma skin cancer, and infections based on the increased serum lipid levels and the incidence of cancers, including lymphoma observed during drug development.

The results of the ORAL study showed a higher rate of serious heart-related events such as heart attack and stroke, cancer, blood clots, and death in patients treated with tofacitinib compared to those treated with tumour necrosis factor (TNF) blockers. Importantly, a higher rate of blood clots and death was seen with tofacitinib compared to TNF blockers. For cancers, a higher rate of lymphomas was observed in patients treated with tofacitinib compared to those treated with TNF blockers. A higher rate of lung cancers was observed in current or past smokers treated with tofacitinib compared to those treated with TNF blockers. Current or past smokers had an additional increased risk of overall cancers.

b) Decision

SAHPRA, in view of the available data, considered the increased risk of serious heart-related events such as heart attack or stroke, cancer, blood clots, and death significant for all JAK inhibitors and recommended that all applicants/HCRs of JAK inhibitor-containing medicines update PIs/PILs and the risk management plans (RMPs) of their products to include the newly identified risks. SAHPRA considers the benefit-risk profile of JAK inhibitor containing medicines favourable provided the applicants effect the recommended changes.

2.1.6 Leuprorelin Acetate – Risk of Idiopathic Intracranial Hypertension

a) Background

SAHPRA conducted a review regarding the risk of idiopathic intracranial hypertension (IIH)/ Pseudotumor cerebri (PTC) associated with the use of leuprorelin acetate in paediatric and adult populations. Leuprolide is registered for the management and treatment of symptoms associated with advanced prostate cancer and central precocious puberty (CPP; a condition causing girls [usually younger than 8 years of age] and boys [usually younger than 9 years of age] to enter puberty too soon, resulting in faster than normal bone growth and development of sexual characteristics). Leuprolide is also registered to treat uterine fibroids (noncancerous growths in the uterus) and endometriosis (a condition in which the type of tissue that lines the uterus [womb] grows in other areas of the body and causes pain, heavy or irregular menstruation [periods], and other symptoms).

The safety signal was based on the data from surveillance of scientific literature relevant to leuprolide treatment for central precocious puberty (CPP) in paediatrics, post-marketing adverse events reports, the cumulative analysis of cases from the Medical Safety Assessment (MSA) (with a review period of 01 January 1900 to 30 September 2016) and the EMA PRAC's assessment of leuprorelin acetate PSUR (for the period of 01 August 2017 to 31 July 2021). A causal relationship was established between the use of leuprorelin and the risk of idiopathic intracranial hypertension in children and in adults.

b) Decision

SAHPRA recommended that applicants/HCRs of leuprorelin-containing medicines update the PI/PIL of their products to include the risk of idiopathic intracranial hypertension in children and in adults. SAHPRA considers the benefit-risk profile of leuprorelin containing medicines favourable, provided the applicants effect the recommended changes.

2.1.7 Dexmedetomidine – Risk of Diabetes Insipidus

a) Background

SAHPRA conducted a review regarding the risk of diabetes insipidus associated with the use of dexmedetomidine-containing medicines. These medicines are registered for use post-surgery to sedate intubated and mechanically ventilated adult patients during treatment in an intensive care setting. The safety signal was based on the data from literature and spontaneous reports in which several cases demonstrated a close temporal relationship, a positive de-challenge and a plausible mechanism of action, reviewed by the Korea's Ministry of Food and Drug Safety (MFDS). Based on the available data, the MFDS considered a possible causal relationship between diabetes insipidus and the use of dexmedetomidine. Diabetes insipidus is a rare but serious life-threatening adverse effect that may occur abruptly post administration of dexmedetomidine.

b) Decision

SAHPRA recommended that applicants/HCRs of dexmedetomidine containing medicines update the PI/PIL of their products to include 'diabetes insipidus' and 'polyuria' under 'special warnings and precautions for use' section. SAHPRA considers the benefit-risk profile of dexmedetomidine containing medicines favourable, provided the applicants effect the recommended changes.

2.1.8 Crizotinib – Risk of Ocular Toxicity

a) Background

SAHPRA conducted a review regarding the risk of ocular toxicity associated with the use of crizotinib (Xalkori®). Xalkori® is registered for the treatment of advanced non-small cell lung cancer. The safety signal was based on a non-interventional, descriptive study of potential sight threatening events and severe visual loss following exposure to crizotinib. The study was reviewed by the EMA's PRAC as part of the application for the extension of indication to include treatment of paediatric patients aged ≥ 6 to < 18 years with relapsed or refractory systemic anaplastic large cell lymphoma (ALCL) that is anaplastic lymphoma kinase (ALK)-positive or patients with unresectable, recurrent, or refractory ALK-positive inflammatory myofibroblastic tumour (IMT).

The study involved 121 patients who were ≤21 years of age treated with Xalkori®. The outcome of the study showed 65% of vision disorders occurred in 26 patients with anaplastic large cell lymphoma (ALCL) who were included in the study. The overall, most common visual symptoms for the 121 patients treated with Xalkori® were blurred vision and visual impairment, with median onset of approximately 1 week of treatment. Other visual symptoms included photopsia, vitreous floaters, and photophobia. Vision disorders and ocular toxicity are more challenging to detect in children. Children are unlikely to report or notice changes in their vision unless specific questioning of symptoms and examinations are conducted.

Based on the reviewed data, it was noted that the risk of visual impairment associated with the use of crizotinib is serious, difficult to detect in children, and may occur a week after administration of the medicine. Visual disorders are documented in the SAHPRA approved PI of Xalkori®, however, monitoring of paediatric patients is not documented.

b) Decision

SAHPRA recommended that the applicants/HCRs of crizotinib-containing medicines update the PI/PIL of their products to include the monitoring of paediatric patients for the risk of visual disorders under *Warning and Precautions* and distribute a DHCPL to alert healthcare professionals about monitoring of the risk of ocular toxicity in children and young adults. The benefit-risk profile of crizotinib-containing medicines remains favourable, provided the applicants/HCRs effect the recommended changes.

2.1.9 Systemic Corticosteroids – Risk of Pheochromocytoma Crisis when administered to patients with Identified, Suspected or Unsuspected Pheochromocytoma

a) Background

SAHPRA conducted a review regarding the risk of pheochromocytoma crisis associated with systemic use of corticosteroids. Corticosteroids are a group of medicines used for reducing inflammation in the body. They are useful in any condition in which inflammation occurs, including rheumatoid arthritis and other connective tissue disorders, multiple sclerosis, and in asthma attacks, and severe allergic reactions. Pheochromocytoma is a rare and often undiagnosed catecholamine-secreting tumour that

grows in adrenal glands, specifically from the cells known as chromaffin cells. The clinical presentation may vary, but characteristic signs and symptoms include hypertension, sweating, palpitations, and headache. On rare occasions, patients may experience sudden surges (high levels) of catecholamines released from a pheochromocytoma and develop acute, severe haemodynamic instability, which may lead to multi-organ dysfunction. This life-threatening emergency situation is known as pheochromocytoma crisis.

The safety signal was based on the EMA's PRAC Assessment Report of the PSUR(s) for betamethasone. PRAC considered evidence from literature reports of pheochromocytoma crisis indicating a close temporal relationship, including two cases describing a positive rechallenge, which suggests that administration of betamethasone may precipitate pheochromocytoma crisis. Literature reports of pheochromocytoma crisis in association with other corticosteroids suggested a class effect, and the serious and potentially life-threatening nature of the condition.

b) Decision

In consideration of the plausible mechanism of action, the serious and potentially life-threatening nature of pheochromocytoma crisis, **SAHPRA recommended that all applicants/HCRs of corticosteroid containing medicines intended for systemic use update the PI/PIL of their products to include the risk of pheochromocytoma crisis.** SAHPRA considers the benefit-risk profile of corticosteroid containing medicines favourable, provided the applicants effect the recommended changes.

2.1.10 Glucagon-Like Peptide-1 Receptor Agonists (Glp-1 Ras) - Risk of Cholecystitis/ Cholelithiasis

a) Background

SAHPRA conducted a review regarding the risk of cholecystitis/cholelithiasis associated with the use of dulaglutide. Dulaglutide is a glucagon-like peptide-1 receptor agonists (GLP-1 RAs) registered for the treatment of type 2 diabetes. The safety signal was based on published data from a systematic review and meta-analysis of randomised clinical trials (RCTs) which found that the use of glucagon-like peptide-1 receptor agonist is associated with increased risk of gallbladder or biliary diseases, especially when used at higher doses, for longer durations and for weight loss.

The systemic review and meta-analysis conducted by He et al., (2022), aimed to evaluate the association of GLP-1 RA treatment with gallbladder and biliary diseases and to explore risk factors for these associations. The results showed that in all included trials, randomisation to GLP-1 RA treatment was associated with increased risks of gallbladder or biliary diseases, specifically, cholelithiasis, cholecystitis and biliary disease. The use of GLP-1 RAs was also associated with increased risk of gallbladder or biliary diseases in trials for weight loss and for type 2 diabetes or other diseases. GLP-1 RA use was associated with higher risks of gallbladder or biliary diseases at higher doses compared with lower doses and with longer duration of use compared with shorter duration.

b) Decision

SAHPRA recommended that the applicants/HCRs of glucagon-like peptide-1 receptor agonists containing medicines update the PI/PIL of their products to include the risk of cholecystitis/cholelithiasis. SAHPRA considers the benefit-risk profile of GLP-1 RAs containing medicines favourable, provided the applicants effect the recommended changes.

2.1.11 Glucagon-Like Peptide-1 Receptor Agonists (Glp-1 Ras)– Risk of Medullary Thyroid Carcinoma (MTC)

a) Background

SAHPRA conducted a review regarding the risk of medullary thyroid carcinoma (MTC) associated with the use of glucagon peptide-like 1 receptor agonists (GLP-1 RAs). The review was based on the US FDA's requirement for a post-marketing Medullary Cancer Thyroid Registry to be kept as part of ongoing pharmacovigilance for this class of medicines. Medullary thyroid carcinoma (MTC) is a rare form of human cancer associated with the use of GLP1 receptor agonists. It accounts for a small percentage of the overall thyroid cancer incidence. The post marketing Medullary Cancer Thyroid Registry is conducted to monitor for any signal indicating a possible association between treatment with long-acting GLP-1 RAs and the development of MTC in the United States population. This is based on the very low incidence of MTC in the general population, limited data on underlying risk factors for development of MTC and the uncertainty of the association of MTC in humans treated with GL-1 RAs.

b) Decision

SAHPRA recommended that the applicants/HCRs of glucagon-like peptide-1 receptor agonists containing medicines update the PI/PIL and RMPs of their products to include the risk of MTC if not already included. SAHPRA considers the benefit-risk profile of GLP-1 Ras-containing medicines favourable, provided the applicants effect the recommended changes.

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

2.2.1 Proton Pump Inhibitors – Risk of Interstitial Nephritis – PSUR

a) Background

SAHPRA conducted a review of PSURs for various proton pump inhibitors (PPIs)-containing medicines for the risk of interstitial nephritis. PPI containing medicines ae registered for the management of various medical disorders of the gastrointestinal (GI) tract related to excess of gastric acid secretion, including ulcers and heartburns. The PSURs submission was a response to SAHPRA's Pharmacovigilance recommendation of 21 April 2021 that requested HCRs to monitor the safety of their PPI-containing products in relation to the risk of interstitial nephritis by submitting annual PSURs. HCRs were further requested to update the PI/PIL of their products under 'Side effects', 'Post-Marketing exposure' and '*Warnings and Precautions'* sections to point out that interstitial nephritis may progress to acute kidney injury and/or chronic renal failure even after PPI treatment discontinuation. Additionally, distribution of a dear healthcare professional letter (DHCL) was recommended.

The review of safety information regarding PPIs during the reporting period (i.e., cumulative data from different sources), did not reveal any significant risks or change or re-characterisation in the safety concerns. Moreover, the risk of interstitial nephritis resulting in kidney failure had been closely monitored by other regulatory authorities since 2016. Most regulatory authorities such as Health Canada have ceased close monitoring and reverted to routine pharmacovigilance activities.

b) Decision

In consideration of the available data, **SAHPRA recommended discontinuation of close monitoring and continuation with routine pharmacovigilance activities for this safety signal since there has not been any new development regarding the risk of interstitial nephritis**. The overall benefit-risk profile of PPI medicines remains favourable provided applicants/HCRs complied with all the recommendations.

2.3 Safety Signals Recommended for Continuous Routine Pharmacovigilance Monitoring

2.3.1 COVID-19 Vaccine Janssen – Risk of Encephalitis

a) Background

SAHPRA conducted a review of a safety signal regarding the risk of encephalitis associated with COVID-19 Vaccine Janssen administration. COVID-19 Vaccine Janssen® is registered for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older. The safety signal emanated from the Japanese Ministry of Health, Labour and Welfare (MHLW)'s regulatory action to include a precautionary statement in the Japan Package Insert (PI) as a risk minimisation measure under "*Immune mediated and neuroinflammatory events*" and update the important potential risk section in the Japan Risk Management Plan (J-RMP). The Pharmaceuticals and Medical Devices Agency (PMDA) of MHLW noted from the then latest available Development Safety Update Report (DSUR) and post marketing safety data in the Safety Summary Report (SSR), serious immune-mediated and neuroinflammatory events (Encephalitis including acute disseminated encephalomyelitis and meningoencephalitis, and transverse myelitis), reported in clinical studies and international post-marketing experience following administration of the Janssen COVID-19 Vaccine.

The risk of "Immune mediated and neuroinflammatory events" is sufficiently addressed in the available SAHPRA approved safety documents.

b) Decision

SAHPRA considers the benefit-risk balance of COVID-19 vaccine Janssen positive regarding the risk of encephalitis and transverse myelitis and no regulatory action is required.

2.3.2 Dexmedetomidine - Potential Risk of Mortality in ICU Patients ≤65 Years

a) Background

SAHPRA conducted a review regarding increased risk of mortality in intensive care unit (ICU) patients ≤65 years associated with the use of dexmedetomidine. The safety signal was based on the SPICE III study, a randomised clinical trial comparing the effect of sedation with dexmedetomidine on all-cause mortality (deaths from any cause) with the effect of usual standard of care in 3,904 critically ill adult ICU patients in need of mechanical ventilation. The study showed no difference in the overall 90-day mortality between dexmedetomidine and alternative sedatives (propofol, midazolam). However, dexmedetomidine was associated with an increased risk of mortality in patients aged 65 years and less, compared with alternative sedatives.

There is limited data including undefined mechanism of action for which the use of dexmedetomidine results in increased risk of mortality, particularly in patients younger than 65 years. There is a wide usage and high risk of mortality associated with dexmedetomidine in general, therefore, continuous monitoring is essential.

b) Decision

SAHPRA recommended continuous monitoring of the benefit-risk profile for dexmedetomidine containing medicines by applicants/HCRs.

2.3.3 Methotrexate – Risk of Genotoxicity

a) Background

SAHPRA conducted a review of a signal regarding the risk of genotoxicity associated with the use of methotrexate. Methotrexate is registered for the treatment of leukaemia, cancers, psoriasis, and rheumatoid arthritis. Genotoxicity refers to the ability of harmful substances to damage genetic information in cells. The safety signal emanated from PRAC's assessment of a report for methotrexate (procedure no. EMEA/H/C/PSUSA/00002014/202110). Based on the available data, there is no new significant information on the risk of genotoxicity. The SAHPRA approved PI sufficiently addresses the risk in its current version.

b) Decision

SAHPRA considers the benefit-risk profile of methotrexate-containing medicines favourable and recommended continuous monitoring by applicants/HCRs.

2.3.4 Vortioxetine – Risk of Sexual Dysfunction

a) Background

SAHPRA conducted a review regarding the risk of sexual dysfunction associated with the use of vortioxetine. Vortioxetine is registered for the treatment of major depressive disorder and to reduce the risk of relapse. The safety signal was based on the cases of sexual dysfunction (including loss of libido and erectile dysfunction) reported with the use of all strengths of vortioxetine received by the UK MHRA. The data from spontaneously reported cases of vortioxetine and sexual dysfunction, which

include the patients' medical history and previous or concomitant use of other selective serotonin reuptake inhibitors (SSRIs)/antidepressants, did not reveal any confounding factors that may have attributed to the reported events. The UK-MHRA indicated that information presented in the European Public Assessment Report (EPAR) suggests an increased risk of sexual dysfunction compared with placebo for the lower treatment doses.

Further analysis of non-clinical, clinical, literature, post-marketing surveillance and EudraVigilance Data Analysis System (EVDAS) data yielded insufficient evidence to support sexual dysfunction associated with vortioxetine.

b) Decision

In view of insufficient evidence to support the safety signal regarding increased risk of sexual dysfunction for the lower vortioxetine doses, **SAHPRA recommended continuous monitoring of the benefit-risk profile for vortioxetine containing medicines by applicants/HCRs**.

2.3.5 Venlafaxine – Increased Risk of Bleeding

a) Background

SAHPRA conducted a review regarding increased risk of bleeding associated with the use of venlafaxine-containing medicines. Venlafaxine-containing medicines are registered for the treatment of depression, including depression with associated anxiety. The safety signal was identified by the Saudi Food and Drug Authority (SFDA). The SFDA recommended amendment of the venlafaxine products under 'Special warnings and Precautions' to add that concomitant use of aspirin, Nonsteroidal Anti-Inflammatory Drugs (NSAIDs), warfarin, and other anti-coagulants or other drugs known to affect platelet function may aggravate the risk of bleeding. Case reports and epidemiological studies (case-control and cohort design) demonstrated an association between use of drugs that interfere with serotonin reuptake and the occurrence of gastrointestinal bleeding.

b) Decision

The safety concern is adequately addressed in the SAHPRA approved venlafaxine containing medicines PIs, therefore, **SAHPRA recommended continuous monitoring of the benefit-risk profile of venlafaxine-containing medicines by applicants/HCRs**.

2.3.6 Voriconazole - Phototoxicity and Severe Dermatological Reactions

a) Background

SAHPRA conducted a review regarding the risk of phototoxicity and severe dermatological reactions associated with the use of voriconazole. Voriconazole is registered for the treatment of fungal infections caused by a variety of organisms. The safety signal was identified by the Saudi Food and Drug Authority (SFDA) which requested applicants of voriconazole to update the *'Special Warnings and Precautions for Use'*, and *'Undesirable effects*' sections with additional information regarding phototoxicity and serious dermatological reactions. Phototoxicity and the dermatological adverse reactions following the use of voriconazole are documented as expected side effects in the SAHPRA approved PI.

b) Decision

SAHPRA recommended continuous monitoring of the benefit-risk profile for voriconazole containing medicines by applicants/HCRs.

2.3.7 Warfarin - Risk of Abnormal Uterine Bleeding

a) Background

SAHPRA conducted a review regarding the risk of abnormal uterine bleeding associated with the use of warfarin. Warfarin is registered for the prevention and management of deep vein thrombosis, pulmonary embolism, thromboembolism in atrial fibrillation, prosthetic heart valves and post myocardial infarction and transient ischaemic attacks. The safety signal was based on the ongoing review by MEDSAFE of abnormal uterine bleeding in individuals using oral anticoagulants aimed at obtaining more information about anticoagulants and the risk of abnormal uterine bleeding.

A haemorrhagic effect is an expected side effect of anticoagulants due to the pharmacological mode of action. Haemorrhaging and abnormal uterine bleeding are documented in the SAHPRA approved PIs of warfarin-containing medicines.

b) Decision

SAHPRA recommended continuous monitoring of the benefit-risk profile for warfarin-containing medicines by applicants/HCRs.

2.3.8 Sevoflurane – Risk of Malignant Hyperthermia and Delirium

a) Background

SAHPRA conducted a review regarding the risk of malignant hyperthermia associated with the use of sevoflurane-containing medicines. Sevoflurane containing medicines are registered for induction and maintenance of general anaesthesia in adults and children during surgery. The safety signal emanated from a regulatory action taken by United States Food and Drug Administration (US FDA) to update the risk of malignant hyperthermia documented in the United States Package Insert. The US FDA stated, "*Since Ultane® was approved on June 7, 1995, we have become aware of risk factors for identifying patients with malignant hyperthermia susceptibility (MHS) based on their genetic background. Malignant hyperthermia is a known adverse event for volatile anaesthetic agents and for succinylcholine. Patients with MHS that are exposed to these products are at a higher risk of developing malignant hyperthermia*."

The US FDA recommended pharmacogenetic testing to assess the variant pathogenicity and include detailed information on the management of MH under '*Warnings*' section. The risk of MH associated with sevoflurane use is well known and is documented in the SAHPRA approved PI. However, the feasibility of pharmacogenetic testing in South Africa may be a challenge due to limited resources. It is therefore concluded that the PI of sevoflurane adequately addresses the risk of MH and requires no further amendments.

b) Decision

SAHPRA concluded that the SAHPRA approved sevoflurane PI sufficiently addresses significant information about the risk of MH and recommended continuous monitoring of the benefit-risk profile for sevoflurane-containing medicines by applicants/HCRs.

2.3.9 Upadacitinib – Risk of Gastrointestinal Perforations

a) Background

SAHPRA conducted a review regarding the risk of gastrointestinal perforations associated with the use of upadacitinib-containing medicines. Upadacitinib is a Janus kinase (JAK) inhibitor, registered for the treatment of rheumatoid arthritis by SAHPRA. The safety signal was based on data from Crohn's Disease (CD) clinical studies. The study results showed that patients with moderate to severe inflammatory bowel diseases (Irritable bowel disease (IBD), CD or ulcerative colitis (UC)) have a higher risk of Gastrointestinal (GI) perforation compared to those with mild IBD and the general population. The risk of GI perforation increases when CD is severe or worsening, particularly in patients with stricture, stenosing, fistulising or penetrating disease. Hence, most of the GI perforations reported in the CD upadacitinib studies were attributed to progressing CD. Additionally, the observed events of GI perforation in subjects on upadacitinib may reflect the inherent higher risk of GI perforation in patients with underlying moderate to severe CD included in the clinical trials.

SAHPRA concluded that the GI perforations associated with upadacitinib-containing medicines may be a case of confounding by indication where patients with GI pathology have an increased risk of GI perforation, which is not necessarily related to the medicine but to the disease for which the medicine is indicated.

b) Decision

SAHPRA considers the benefit-risk profile of upadacitinib-containing medicines favourable in relation to GI perforations and recommended continuous monitoring of upadacitinib-containing medicines by applicants/HCRs.

2.3.10 Upadacitinib – Risk of Fractures

a) Background

SAHPRA discussed a review regarding the risk of fractures associated with the use of upadacitinib-containing medicines. The risk of fractures was identified by EMA's PRAC during the assessment of the variation to include ulcerative colitis as a new indication for upadacitinib. PRAC based the inclusion of fractures on the preclinical studies for abrocitinib, another JAK inhibitor that revealed abnormal findings on bone development in rats. Thus, post-approval studies were required to investigate potential impact on bone growth and development in patients < 18 years of age, with an important potential risk included in the RMP for abrocitinib.

Due to the findings of effects on bone development in preclinical studies and the uncertainties of the relevance of these findings for growing adolescents, the therapeutic indication for abrocitinib has been restricted to adults > 18 years of age only.

b) Decision

SAHPRA found the association of fractures with the use of upadacitinib to be confounded, including confounding by indication. SAHPRA recommended that applicants/HCRs of upadacitinib-containing medicines update the RMP to include the risk of fractures as a potential risk and continuous monitoring of the risk of fractures via post-marketing surveillance. The benefit-risk profile of upadacitinib-containing medicines remains favourable, provided the applicants/HCRs effect the recommended changes.

2.3.11 Citalopram/Escitalopram: Risk of Agranulocytosis

a) Background

SAHPRA conducted a review of a safety signal regarding the risk of agranulocytosis associated with the use of citalopram and escitalopram-containing medicines. Citalopram and escitalopram-containing medicines are registered for the management of depression, panic attacks and obsessive-compulsive disorder. The safety signal was based on the PSUR (for the period of 1 Jan 2017 – 31 Dec 2021) review by PRAC. PRAC requested the MAH to provide a cumulative review on citalopram/escitalopram and agranulocytosis. Agranulocytosis occurs when the absolute neutrophil count is less than 100 neutrophils per microliter. The reported incidence ranges from six (6) to eight (8) cases per million population per year and is classified as a rare condition. Two main mechanisms include inadequate or ineffective granulopoeisis and accelerated removal or destruction of neutrophils. Acquired agranulocytosis may be due to various medications (e.g., cancer chemotherapies, carbimazole, captopril, phenytoin), infections (e.g., tuberculosis) an autoimmune condition (e.g., rheumatoid arthritis).

Based on the available reviewed data, there was insufficient data to support the association of agranulocytosis with the use of citalopram and escitalopram due to confounders identified in the post-marketing cases.

b) Decision

SAHPRA recommended continuous monitoring of the benefit-risk profile for citalopram and escitalopram-containing medicines by applicants/HCRs.

2.3.12 Oxaliplatin – Risk of Focal Nodular Hyperplasia

a) Background

SAHPRA conducted a review regarding the risk of focal nodular hyperplasia associated with the use of oxaliplatin-containing medicines. Oxaliplatin-containing medicines are registered for the treatment of colon cancer. The safety signal emanated from the PRAC assessment report on the PSUR for oxaliplatin (procedure no. PSUSA/00002229/202104; dated 2 December 2021). The SAHPRA approved PIs of

oxaliplatin-containing medicines documented nodular regenerative hyperplasia as a very rare adverse effect.

b) Decision

SAHPRA recommended continuous monitoring of the benefit-risk profile for oxaliplatin-containing medicines by applicants/HCRs.

2.3.13 Clotrimazole - Risk of Vaginal Haemorrhage

a) Background

SAHPRA conducted a review regarding the risk of vaginal haemorrhage associated with the use of clotrimazole-containing medicines. Clotrimazole-containing medicines are registered for the treatment of skin infections caused by a fungus (yeast). The safety signal was based on spontaneous adverse drug reaction reports. Vaginal bleeding may be indicative of additional vaginal or endometrial conditions. Vaginal haemorrhage is documented in the "*side effects*" section of the SAHPRA approved PI under '*reproductive system and breast disorders*'.

b) Decision

SAHPRA recommended continuous monitoring of the benefit-risk profile for clotrimazole containing medicines by applicants/HCRs.

Digitally Signed by:
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Dr Boitumelo Semete-Makokotlela
SAHPRA Chief Executive Officer (CEO)

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