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Regulatory Authority

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COMMUNICATION TO STAKEHOLDERS

Issue No: 01/2022/23

13 June 2022

Summary of Medicines Safety Regulatory Decisions

INTRODUCTION

This document provides an overview of the safety regulatory decisions taken by SAHPRA on the safety concerns discussed during January – March 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 decisions are actionable by the concerned stakeholders including applicants or holders of certificate of registration (HCRs). Safety decisions concerning amendment of a professional information are submitted to the Clinical Evaluations unit to review and ensure appropriate implementation of Professional Information and Patient Information Leaflet (PI/PIL) amendments.

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 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 submitted any kind of application

Dear Healthcare Professional (DHCP) Letter is a communication in a form of a letter intended to convey important medicine safety information, distributed by holders of certificate of registration (HCR) directly to individual healthcare professionals and published on 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 errors;
- dispensing errors;
- medicine preparation errors;
- administration errors
- 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) 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 manufacturer's guideline (either printed or in a soft copy) for 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 and include:

- Educational programmes or tools for healthcare providers and/or patients
- Controlled access programmes
- Dear Healthcare Professional letter
- Professional Information
- Patient Information Leaflet
- Packaging and labelling
- Scheduling status

2. REGULATORY SAFETY DECISIONS

2.1 UPDATE OF PROFESSIONAL INFORMATION (PI) AND PATIENT INFORMATION LEAFLET (PIL)

2.1.1 REVELLEX® (INFLIXIMAB): RESTRICTION OF ADMINISTRATION OF LIVE VACCINES TO INFANTS EXPOSED TO INFLIXIMAB DURING THE LATTER PARTS OF PREGNANCY

a) Background

The Authority conducted a review on the warning against administration of live vaccines in infants exposed to Revellex® (infliximab) during latter part of pregnancy and during breastfeeding. The review was based on the European Medicines Agency (EMA) recommendations for Janssen Biologics B.V. to issue a Dear Healthcare Professional Letter (DHCPL) for Revellex® (infliximab) to warn healthcare professionals not to administer live vaccines to infants being breastfed by mothers treated with infliximab due to increased risk of undesirable effects. Revellex® is a "Disease-Controlling Anti-Rheumatic Therapy" (DCART) indicated for use in the treatment of ulcerative colitis, Crohn's disease, ankylosing spondylitis, rheumatoid arthritis, psoriatic arthritis and psoriasis.

b) Decision

The Authority recommended that aplicants/HCRs updatethe Professional Information (PI) and Patient Information Leaflet (PIL) documents to appropriately convey the risks and warnings/precautions. The overall risk/benefit balance of Revellex® remains favourable. The applicants/HCRs are advised to continuously monitor the benefit–risk profile of this medicine and inform the Authority accordingly.

2.2 RISK MINIMISATION MATERIALS APPROVAL

2.2.1 LEMTRADA® - EDUCATIONAL MATERIALS (LEMTRADA® PATIENT CARD, HEALTHCARE PROFESSIONALS (HCPS) GUIDE, AND CHECKLIST)

a) Background

The Authority conducted a review of Lemtrada®'s risk minimisation measures. The risk minimisation measures were based on the European Medicine Agency (EMA) recommendation to restrict the use of Lemtrada® due to rare but serious side effects including deaths. The side effects include

cardiovascular disorders (affecting the heart, circulation and bleeding as well as stroke) and immune-related disorders (caused by the body's defense system not working properly).

Lemtrada® contains alemtuzumab and is used as a single disease modifying therapy to treat adults with relapsing-remitting multiple sclerosis (MS), a disease in which inflammation damages the protective insulation around nerves as well as the nerves themselves. 'Relapsing-remitting' means that the patient has attacks (relapses) between periods with few or no symptoms (remissions).

b) Decision

Risk minimisation measures developed i.e. Professional Information (PI) and educational materials (Lemtrada® patient card, Lemtrada® Healthcare Professionals (HCPs) Guide, and Checklist) were found to be acceptable and were approved for implemetation. The overall benefit-risk of Lemtrada® remains favourable. The applicants/HCRs are advised to continuously monitor the benefit–risk profile of this medicine and inform the Authority accordingly.

2.2.2 AMGEVITA® (ADALIMUMAB BIOSIMILAR)- PATIENT ALERT CARDS

a) Background

The Authority conducted a review of Amgevita® (adalimumab) risk minimisation materials (RMMs). The risk minimisation materials comprised of two patient alert cards (one for adult patients and one for paediatric patients) prepared in accordance with the approved additional risk minimisation material included in the European Union (EU) and the local Amgevita® Risk Management Plan (RMP).

The patient alert cards are intended to inform patients/caregivers about the risks associated with the use of Amgevita®, the specific symptoms associated with those risks and informing healthcare professionals (HCP) if such symptoms arise. Patients are to carry the cards with them, during consultation with their HCPs, in order to indicate that they are using Amgevita®.

b) Decision

All applicants/HCRs of adalimumab containing medicines must include these patient alert cards as an additional risk minimisation measure in their Risk Management Plan. The patient alert cards are in line with the SAHPRA approved professional information (PI) and patient information leaflet (PIL) and were therefore accepted and approved for implementation. The overall benefit-risk of Amgevita® remains favourable. The applicants/HCRs are advised to continuously monitor the benefit–risk profile of this medicine and inform the Authority accordingly.

2.2.3 NPLATE® - DOSING CALCULATOR

a) Background

The Authority conducted a review of Nplate® (romiplostim)'s risk minimisation material. The Nplate® risk minimisation materials were prepared in accordance with the approved additional risk minimisation material included in the Amgen Core Risk Management Plan (RMP) and aligned with the SAHPRA approved Professional Informaiton (PI) which includes new indication for use in immune

thrombocytopenia purpura (ITP) patients 1 year of age and older who are refractory to other treatments.

The educational materials were in the form of a dosing calculator which is intended to address the risk of romiplostim dosing/administration medication errors for relevant physicians involved in the prescribing of romiplostim to children. In some paediatric patients, accurate dosing relies on an additional dilution step after reconstitution which may increase the risk for medication errors.

b) Decision

All applicants/HCRs of romiplostim containing medicines to ensure that the dosing calculator is distributed to the appropriate target audience. The risk minimisation materials were accepted and approved for implementation. The overall benefit-risk of Nplate® remains favourable. The applicants/HCRs are advised to continuously monitor the benefit–risk profile of this medicine and inform the Authority accordingly.

2.3 PERIODIC SAFETY UPDATE REPORTS (PSURs)

2.3.1 JANSSEN COVID-19 VACCINE® (AD26.COV2.S VACCINE)

a) Background

The Authority conducted a review of Janssen COVID-19 Vaccine® periodic safety update report (25 February to 24 August 2021). Janssen COVID-19 Vaccine® suspension for injection is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2, in individuals 18 years of age and older. The review revealed that a total of 78,231 doses of Janssen COVID-19 Vaccine® were administered to healthy subjects in clinical trials and about 33,584,049 doses of Janssen COVID-19 Vaccine® were administered worldwide during the reporting period. Identified safety concerns were addressed and included in the professional information documents.

b) Decision

The Authority found the risk benefit profile of the Janssen COVID-19 Vaccine® acceptable and advised the applicant/HCR to continue monitoring safety profile of Janssen COVID-19 Vaccine® and to evaluate emerging safety data in real time.The overall benefit-risk of Janssen COVID-19 Vaccine® remains favourable. The applicants/HCRs are advised to continuously monitor the benefit–risk profile of this vaccine and i nform the Authority accordingly.

2.3.2 VEKLURY® (REMDESIVIR)

a) Background

The Authority conducted a review of Veklury® PSUR. It was noted that remdesivir has been approved in many countries for the treatment of COVID-19, however, it is not registered in SA but is available under a Section-21 permit since June 2021. Veklury® contains remdesevir, which is used for the treatment of COVID-19 disease in:

- adults and adolescents (aged 12 to less than 18 years and weighing at least 40 kg) with pneumonia requiring supplemental oxygen (low- or high-flow oxygen or other non-invasive ventilation at start of treatment).
- adults who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19.

b) Decision

The PSUR supports the positive safety profile of Veklury® and the aquisition through Section-21 approval process. The overall benefit-risk of Veklury® remains favourable. Continuous monitoring of the benefit–risk profile of this medicine was recommended .

2.4 RISK MANAGEMENT PLAN

2.4.1 LAGEVRIO® (MOLNUPIRAVIR)

a) Background

The Authority conducted a review Lagevrio® (molnupiravir) risk management plan. Molnupiravir is used for the treatment of confirmed COVID-19 disease in adults who do not require supplemental oxygen and who are at risk of progression to severe COVID-19.

The review of the RMP revealed no major safety concerns for use of molnupiravir 800 mg twice daily for 5 days. Furthermore, molnupiravir is not recommended for use during pregnancy or breastfeeding with a 4-day post-treatment window for use of contraception and avoidance of breastfeeding.

b) Decision

The overall risk/benefit balance of molnupiravir was found to be favourable, however the safety database of molnupiravir remains rather limited, including data for use of molnupiravir in the vaccinated and the pediatric populations. The Authority recommends continuous monitoring of the benefit–risk profile of this medicine by the applicant/HCR.

2.5 MEDICATION ERRORS

2.5.1 MEDICATION ERRORS ASSOCIATED WITH THE USE OF BLINCYTO® (BLINATUMOMAB)

a) Background

The Authority conducted a review of a proposed Blincyto® Dear Healthcare Professional (DHCP) letter. A DHCP letter was submitted as a risk minimisation measure to address the need for healthcare professionals to adhere to the preparation and administration instructions in the label, in order to minimise the potential for medication errors (such as pharmacy preparation errors) as identified in the clinical trials and the post-marketing setting. Blincyto® contains blinatumomab which is indicated for the treatment of leukaemia in adults and children.

b) Decision

The Authority recommended to the applicant/HCR of Blincyto® to implement training of healthcare professionals, instead of distribution of a DHCPL, as an appropriate risk minimisation measure to mitigate against medication errors observed with preparation and administration of Blincyto®. The overall benefit-risk of Blincyto® remains favourable. The Authority recommended continuous monitoring of the benefit–risk profile of Blincyto® by the applicant/HCR.

2.6 QUARTERLY MONITORING REPORT

2.6.1 ELTROXIN (LEVOTHYROXINE) NEW FORMULATION® – QUARTERLY MONITORING REPORT (01 OCTOBER 2021 TO 31 DECEMBER 2021)

a) Background

The Authority conducted a review of Eltroxin New formulation® quarterly monitoring report. The quarterly monitoring report follows a SAHPRA recommendation that requested the applicant/HCR to monitor the safety and afficacy of Eltroxin New Formulation® and submit quarterly reports. The recommendation was based on an increase in adverse reactions/events received by SAHPRA following the use of Eltroxin New Formulation® as compared with the Eltroxin® old formulation, which was discontinued due to product stability concerns. Eltroxin New Formulation® contains levothyroxine sodium used in the treatment of hypothyroidism.

b) Decision

The Authority found the risk benefit profile of the Eltroxin New formulation® acceptable and recommended that the applicant/HCR continue monitoring the safety pofile of the product.The overall benefit-risk of Eltroxin New formulation® remains favourable. The applicant/HCR was recommeded to continuously monitor the benefit–risk profile of this medicine.

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