SAHPRA
South African Health Products Regulatory Authority

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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 SAHPRA on the safety concerns discussed during April – July 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 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 TOPICAL CORTICOSTEROIDS: RISK OF WITHDRAWAL REACTIONS

a) Background

The Authority conducted a review on the risk of withdrawal reactions associated with inappropriate and long-term use of topical corticosteroids. The safety issue was based on the available data from the Medicines & Healthcare products Regulatory Agency (MHRA) in United Kingdom. The data indicated that rare and severe adverse effects can occur on stopping treatment with topical corticosteroids, often after long-term continuous or inappropriate use of moderate to high potency products. Red burning skin and papulopustular rashes (including steroid rosacea and perioral/periorificial dermatitis) are the two distinct clinical presentations of topical steroid withdrawal reactions.

While the withdrawal reactions are rare, they are not usually recognised as a rebound effect. Moreover, irrespective of their class, topical corticosteroids are likely to be used without medical advice or prescription (i.e., via self-medication). This predisposes the users to misuse and long-term use. Therefore, the Authority regard this as an important signal that healthcare professionals (HCPs) and the public should be made aware of. Furthermore, the current information in the SAHPRA approved Professional Information (PI)s does not adequately articulate the possibility of a withdrawal syndrome.

b) Decision

In consideration of the significance of the risk of withdrawal reactions associated with the use of topical corticosteroids, the Authority recommended that applicants/holders of certificate of registration (HCRs) update the Professional Information (PI) and Patient Information Leaflet (PIL) of their products to appropriately convey the risks and distribute a Dear Healthcare Professional letter (DHCPL). To ensure that the benefit-risk profile of these medicines remain positive, continuous monitoring by applicants/HCRs is recommended.

2.1.2 ANAGRELIDE - RISK OF THROMBOSIS UPON ABRUPT DISCONTINUATION

a) Background

The Authority conducted a review of the risk of thrombosis (clotting of blood), including cerebral infarction, upon abrupt treatment discontinuation of anagrelide. The safety issue was based on the recommendations made by the European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC). PRAC's recommendations emanated from a cumulative analysis of Takeda's safety database (up to 6 August 2021). The analysis yielded 15 events of thrombotic complications, including cerebral infarction, after a recent discontinuation of anagrelide. Based on the available data, PRAC concluded that cerebral infarction, along with other thrombotic complications, while being part of the pre-existing condition/indication, may also occur upon abrupt anagrelide discontinuation, inadequate dosing, or lack of effect. The mechanism of cerebral infarction following abrupt treatment discontinuation is related to the rebound in platelet count. Platelet count typically start to rise within four days after discontinuation and return to baseline levels in one to two weeks, possibly rebounding above baseline values.

b) Decision

The Authority recommended that applicants/HCRs update the Professional Information (PI) and Patient Information Leaflet (PIL) of their anagrelide containing medicines and distribute a DHCPL to appropriately convey the risk of thrombosis, including cerebral infarction. The Authority consider the the benefit-risk profile favourable, provided the recommended changes are effected by the applicants/HCRs.

2.1.3 SPRYCEL (DASATINIB) - RISK OF CHYLOTHORAX

a) Background

The Authority conducted a review of a safety signal regarding the risk of chylothorax associated with the use of Sprycel® (dasatinib). The safety signal emanated from the assessment of a Periodic Safety Update Report (PSUR) (reporting interval 28 June 2020 to 27 June 2021) for Sprycel® by the European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC). PRAC recommended that the marketing authorisation holder (MAH) of Sprycel® update 'Special warnings and precautions for use' and 'Undesirable effects' sections of the European Union (EU) Summary of Product Characteristics (SmPC) to add chylothorax as an adverse reaction, based on the outcome of the PSUR assessment.

Although company core datasheet (CCDS) and PI for Sprycel® state the risk and management of pleural effusion, it was noted that the risk of chylothorax associated with dasatinib is not addressed. Chylothorax is a type of pleural effusion; however, the pleural fluid of chylothorax is classified as a milky fluid due to its content of triglycerides, whereas the pleural fluid of the 'usual' pleural effusion may contain pus or blood depending on the aetiology. It is therefore essential to provide more information to healthcare professionals about dasatinib-related chylothorax since dasatinib is increasingly being used due to its effectiveness in the treatment of Chronic myeloid leukemia (CML) and Philadelphia-positive acute lymphoblastic leukemia (Ph+ ALL).

b) Decision

The Authority recommended that applicants/HCRs update the Professional Information (PI) and Patient Information Leaflet (PIL) of their dasatinib containing medicines to convey the risk of chlorothyrax. The overall risk/benefit balance of dasatinib containing medicines is considered favourable, provided the applicants/HCRs effect the recommended changes.

2.1.4 DONEPEZIL – RISK OF CARDIAC (HEART) CONDUCTION DISORDERS (QTC INTERVAL PROLONGATION AND TORSADES DE POINTES)

a) Background

The Authority conducted a review of a signal regarding the potential risk of heart problems associated with the use of donepezil. The safety signal emanates from the Therapeutic Goods Administration's (TGA's) assessement of evidence published in the literature and from post-marketing adverse events data in Australia and internationally. Up to 5 January 2022, there were 18 cases of cardiac conduction disorder (atrioventricular block, atrioventricular block complete, atrioventricular block second degree, bundle branch block, bifascicular block or Torsades de Pointes (TdP)) associated with donepezil reported to the TGA and included in the Database of Adverse Event Notifications (DAEN).

QTc prolongation and Torsade de Pointes are life-threatening adverse reactions, therefore PI/PIL should caution against use in the patients with known QTc prolongation or a family history of this condition, patients receiving other medicines that affect the QTc interval, or who have certain types of cardiac diseases or electrolyte disturbances. Clinical monitoring of cardiac function is recommended in high-risk individuals or where this adverse event is suspected by healthcare professionals.

b) Decision

The Authority recommended that applicants/HCRs update the Professional Information (PI) and Patient Information Leaflet (PIL) of their donepezil containing medicines to convey the risk of QTc prolongation and Torsade de Pointes. The overall risk/benefit balance of donepezil containing medicines remains favourable, provided the applicants/HCRs effect the recommended changes.

2.1.5 IMATINIB – PANNICULITIS (INCLUDING ERYTHEMA NODOSUM)

a) Background

The Authority conducted a review of a signal regarding the risk of panniculitis (erytherma nodosum (EN)) associated with the use of imatinib. The signal was identified during the review of Gleevec® (imatinib) PSUR (11 May 2018 – 10 May 2021) by the EMA's PRAC. In view of available data on panniculitis and based on a possible class effect, the PRAC considered a plausible causal relationship between imatinib and panniculitis (including erythema nodosum).

The use of tyrosine kinase inhibitor (TKIs) containing medicines is associated with dermatological side effects. Although many skin reactions attributed to the use of TKIs are documented, panniculitis /EN caused by imatinib use is rare and is undocumented in the imatinib PI/PIL. There is sufficient evidence

(from literature, spontaneous reports, PRAC imatinib PSUR review, etc) to suggest the causal relationship between the use of imatinib and the risk of panniculitis/EN.

b) Decision

The Authority recommended that applicants/HCRs update the Professional Information (PI) and Patient Information Leaflet (PIL) of their imatinib containing medicines to convey the risk of panniculitis/erytherma nodosum. The benefit-risk profile of imatinib is considered favourable subject to the implementation of the Authority's recommendation by the applicants/HCRs.

2.1.6 TICAGRELOR AND ROSUVASTATIN – DRUG-DRUG INTERACTIONS LEADING TO RHABDOMYOLYSIS

a) Background

The Authority conducted a review of a signal regarding the risk of rhabdomyolysis associated with the interaction between ticagrelor and rosuvastatin. The signal emanates from the Periodic Safety Update Single Assessment (PSUSA) procedure of ezetimibe / rosuvastatin, conducted by the EMA's PRAC. PRAC established the interaction between rosuvastatin and ticagrelor causing rhabdomyolysis and recommended that Marketing Authorisation Holders (MAHs) update the Summary of Product Characteristics (SmPC) of products containing rosuvastatin (as mono-component or in fixed dose combination) to include the interaction with ticagrelor. Additionally, the PRAC considered that the ticagrelor and rosuvastatin interaction would also be relevant to be included in products containing ticagrelor as all the reported cases presented positive dechallenge for ticagrelor and provided a plausible mechanism of action.

The possible interaction between ticagrelor and rosuvastatin is one of the important risk factors for rhabdomyolysis, taking into consideration other factors such as old age, higher than recommended rosuvastatin dose, and/or concurrent use of medicines that may affect rosuvastatin concentration. Although the mechanism of action for the drug-drug interactions is not well defined, the available data from post-marketing spontaneous reports and literature support the possible interactions.

b) Decision

The Authority recommended that applicants/HCRs of both rosuvastatin and ticagrelor containing medicines update the Professional Information (PI) and Patient Information Leaflet (PIL) of their products to convey the risk of drug-drug interactions. The overall risk/benefit balance of rosuvatatin and ticagrelor remains favourable provided the applicans/HCRs effect the recommended changes.

2.1.7 DENOSUMAB - RISK OF SERIOUS HYPERCALCAEMIA IN PATIENTS UNDER 18 YEARS

a) Background

The Authority conducted a review of an article published in the MHRA's Drug Safety Update, titled "*Denosumab 60mg (Prolia): should not be used in patients under 18 years due to the risk of serious hypercalcaemia*". The article indicated that serious and life-threatening hypercalcaemia (higher levels of calcium) were reported with denosumab in children and adolescents in clinical trials for

osteogenesis imperfecta and during off-label use. These clinical trials were investigating treatment with denosumab in patients younger than 18 years with osteogenesis imperfecta. Hypercalcaemia cases were reported during treatment and weeks to months after the last dose.

Furthermore, the MHRA, identified 20 cases of hypercalcaemia reported worldwide. The adverse events occurred during off-label treatment with denosumab in children and adolescents younger than 18 years. Reports included cases in paediatric patients with osteogenesis imperfecta, as well as in those with various other conditions. A small number of cases of hypercalcaemia were reported after stopping treatment (rebound hypercalcaemia).

Although the risk of hypercalcaemia in children <18 years is well-known and documented under 'Warnings and Special precautions' of the SAHPRA approved PI of denosumab, it was noted that off-label use in children <18 years occurs in some circumstances.

b) Decision

The Authority recommended that applicants/HCRs of denosumab containing medicines update the Professional Information (PI) and Patient Information Leaflet (PIL) of their products to include the risk of hypercalcaemia in children <18 years, under 'Side effects' section. The Authority considers the benefit-risk profile of denosumab containing medicines favourable provided the applicants effect the recommended changes.

2.1.8 BRINZOLAMIDE - RISK OF STEVENS-JOHNSON SYNDROME (SJS) AND TOXIC EPIDERMAL NECROLYSIS (TEN)

a) Background

The Authority conducted a review regarding the risk of Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) associated with topical ocular administration of brinzolamide. The safety issue emanates from the EMA's PRAC assessment and conclusion of the review of Azoptic PSUR (01-Sep-2016 to 31-Aug-2021). Based on the outcome of a comprehensive assessment of the individual case reports and reviewed scientific literature, a possible causal association between ophthalmic use of brinzolamide and development of SJS/TEN was considered plausible.

b) Decision

The Authority recommended that applicants/HCRs of brinzolamide containing medicines to update the Professional Information (PI) and Patient Information Leaflet (PIL) of their products to include the risk of Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN). The Authority considers the benefit-risk profile of brinzolamide containing medicines favourable, provided the applicants effect the recommended changes.

2.1.9 CEFTRIAXONE - RISK OF HEPATOTOXICITY

a) Background

The Authority conducted a review regarding the risk of hepatotoxicity associated with the use of ceftriaxone – containing medicines. This safety signal emanated from assessment conducted by the EMA's PRAC based on the available evidence (e.g., EudraVigilance, literature), as well as a plausible biological mechanism of action, that corroborates the causal relationship of hepatotoxicity with the use of ceftriaxone. Applicants/HCRs of registered ceftriaxone – containing medicines were requested to conduct a detailed analysis of clinical, non-clinical data and literature data on the risk of hepatotoxicity associated with ceftriaxone and provide comments. Based on the review of the data submitted by the Applicants/HCRs, the Authority concluded that on a plausible causal relationship between hepatotoxity and the use of ceftriaxone.

b) Decision

The Authority recommended that applicants/HCRs of ceftriaxone containing medicines update the PI/PIL of their products to include the risk of hepatotoxicity. The Authority considers the benefit-risk profile of ceftriaxone containing medicines favourable, provided the applicants effect the recommended changes.

2.1.10 SEROTONIN RECEPTOR ANTAGONISTS (ONDANSETRON, GRANISETRON AND PALONOSETRON) - RISK OF MYOCARDIAL ISCHAEMIA

a) Background

The Authority discussed a review regarding the risk of myocardial ischaemia (MI) associated with the use of serotonin receptor antagonist containing medicines. The safety issue emanated from recommendations made by the EMA's PRAC based on the available data on myocardial ischaemia from the literature, and spontaneous case reports. The available data showed a close temporal relationship, a positive dechallenge (observed after withdrawal and/or dose reduction) and a plausible mechanism of action, that led to consideration of a reasonable possible causal relationship between ondansetron and MI. Based on the post-marketing data and the mechanism of action, the risk of MI was considered as a class effect.

The risk of MI associated with the use of serotonin receptor antagonists is a serious life-threatening side effect which may occur immediately after administration of the medicine. It is important to include MI as an add-on to documented cardiac side effects associated with the use of these medicines.

b) Decision

The Authority recommended that the applicants/HCRs of serotonin receptor antagonists containing medicines update the PI/PIL of their products to include the risk of myocardial ischaemia. The benefit-risk profile of serotonin receptor antagonists remains favourable, provided the applicants/HCRs effect the recommended changes.

2.1.11 SEVOFLURANE – RISK OF BRADYCARDIA IN DOWN SYNDROME (DS)

a) Background

The Authority conducted a review regarding the risk of bradycardia in Down Syndrome (DS) associated with the use of sevoflurane. The safety issue emanates from the United States Food and Drug Administration's (US FDA's) review of case reports of bradycardia and cardiac arrest associated with sevoflurane use, independent of underlying congenital heart disease. The US FDA found that there is a reasonable causal association for this serious and life-threatening adverse event with sevoflurane use, and bradycardia is not adequately labelled in terms of the event or steps to decrease its likelihood or minimise its severity. Although SAHPRA approved PI for sevoflurane mentions bradycardia as a side effect, it does not adequately address the risk of bradycardia in Down Syndrome.

b) Decision

The Authority recommended that the applicants/HCRs of sevoflurane containing medicines update the PI/PIL of their products to include the risk of bradycardia in Down Syndrome. The Authority considers the benefit-risk profile of sevoflurane containing medicines favourable, provided the applicants effect the recommended changes.

2.1.12 CANNABIDIOL, CALCINEURIN INHIBITORS (CNI) AND MECHANISTIC TARGET OF RAPAMYCIN (MTOR) INHIBITORS - RISK OF DRUG-DRUG INTERACTIONS

a) Background

The Authority conducted a review of a potential risk drug-drug interactions of cannabidiol (CBD) with calcineurin inhibitors (CNIs) and mechanistic target of rapamycin (mTOR) inhibitors leading to serum levels increase and toxicity, including serum creatinine increased, encephalopathy (disease that affects brain structure or function), and mental status change. The safety issue emanated from EMA PRAC assessment of PSUR of cannabidiol covering the period June to December 2019 . The evidence considered included one (1) literature case with serum creatinine increased and tacrolimus serum level increased, with recovery on tacrolimus dose reduction. Three (3) additional cases identified in EudraVigilance with compatible chronology, including 2/3 cases with recovery on dechallenge for cannabidiol or tacrolimus; events included tacrolimus serum level increased in all three (3) cases and in addition serum creatinine increased, encephalopathy, mental status change in 2/3 cases. Additionally, signal of drug-dug interaction between cannabidiol and tacrolimus was considered from the published literature.

b) Decision

The Authority recommended that the applicants/HCRs of calcineurin inhibitor (CNI) and mechanistic target of rapamycin (mTOR) inhibitor containing medicines update the PI/PIL of their products to include the risk of drug-drug interactions. The Authority considers the benefit-risk profile of calcineurin inhibitor (CNI) and mechanistic target of rapamycin (mTOR) inhibitor containing medicines favourable, provided the applicants effect the recommended changes.

2.2 PERIODIC SAFETY UPDATE REPORTS (PSURs)

2.2.1 PROTON PUMP INHIBITORS (PPIs) - INCREASED RISK OF SUBCLINICAL ACUTE INTERSTITIAL NEPHRITIS LEADING TO ACUTE KIDNEY INJURY AND/OR CHRONIC RENAL FAILURE

a) Background

The Authority conducted a review of PSURs/PBRERs of proton pump inhibitors (PPIs). The applicants/HCRs of PPI containing medicines were requested to submit PSURs/PBRERs annually in order to monitor the risk of interstitial nephritis which may progress to acute kidney injury (AKI) and/or chronic renal failure (CRF) even after PPI treatment discontinuation. The safety signal was based on an article by Wu et al. (2021) titled "*Proton pump inhibitors associated acute kidney injury and chronic kidney disease (CKD): data mining of US FDA adverse event reporting*". Based on the available data, significant association between PPI and event of AKI and CKD was identified.

The PSUR/PBRER review did not reveal any significant risks for the reporting period, therefore, the overall benefit risk profile for PPIs remains positive for their registered indications.

b) Decision

The Authority recommended continuous monitoring of the benefit-risk profile for PPI containing medicines and submission of annual PSURs/PBRER by affected applicants.

2.2.2 BOTOX: PSUR (01 JANUARY 2019 TO 31 DECEMBER 2021)

a) Background

The Authority conducted a review of the 30th botulinum toxin A (Botox®) PSUR (reporting period 01 January 2019 to 31 December 2021). It was noted that during the reporting period no significant actions related to Botox® were taken by the Holder of Certificate of Registration, for safety reasons and no new risk management activities were required, including significant restrictions on distribution, risk minimisation measures, safety related labelling changes, healthcare professional communications, or post marketing commitments. It was further noted that data included in the Botox® PSUR focused on mostly on EU and United States rather than South Africa. The Botox® PI is approved by SAHPRA and addresses the routine risk minimisation activities and is aligned with the SAHPRA guidelines for PI.

The PSUR review did not reveal any significant risks for the reporting period, therefore, the overall benefit risk profile for botulinum toxin remains positive for their registered indications.

b) Decision

The Authority recommended continuous monitoring of the benefit-risk profile for botulinum toxin containing medicines by applicants/HCRs.

2.2.3 COMIRNATY® – MONTHLY SUMMARY SAFETY REPORT (MSSR) (16 FEBRUARY 2022 - 15 APRIL 2022) AND PSUR (19 JUNE 2021 THROUGH 18 DECEMBER 2021)

a) Background

The Authority conducted a review of Comirnaty® MSSR (16 February 2022 through 15 April 2022) report. In SA, Comirnaty® is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 virus, in individuals 12 years of age and older. The submission of MSSR is condition of registration for Comirnaty®, which was registered in SA since 25 January 2022. Comirnaty® is widely used in South Africa for vaccination of the public following the requirements of the National Department of Health. There were no market withdrawals and regulatory actions taken for safety reasons during the reporting interval. There were no new safety concerns that emerged during the reporting interval.

b) Decision

The MSSR/PSUR supports a positive safety profile of Comirnaty®. The overall benefit-risk profile of Comirnaty® remains favourable. The Authority recommended continuous monitoring of the benefit–risk profile of this vaccine.

2.3 MEDICATION ERRORS

2.3.1 PRAXBIND® - DISPENSING/ADMINISTRATION ERROR

a) Background

The Authority conducted a review of the risk of wrong dose errors associated with the use of Praxbind® (idarucizumab). The safety concern was identified by the US FDA based on the six (6) case reports that the US FDA received from 2015-2021, where confusion regarding the number of vials required to deliver the recommended 5 g dose was identified. The Praxbind® US carton label was then updated.

The Authority considered the safety concern important; however, based on insufficient evidence to support the risk of product package-related medication errors occuring in South Africa, continuous monitoring of the benefit-risk profile remains adequate at this stage.

b) Decision

The Authority recommended continuous monitoring of the benefit-risk profile of Praxbind® products by applicants/HCRs.

2.4 SAFETY SIGNALS RECOMMENDED FOR CONTINUOUS ROUTINE PHARMACOVIGILANCE MONITORING

2.4.1 FINASTERIDE – POTENTIAL RISK OF SUICIDAL IDEATION, MAJOR DEPRESSION AND SEXUAL PROBLEMS

a) Background

The Authority conducted a review regarding the potential risk of suicidal ideation, major depression and sexual problems associated with the use of finasteride. Finasteride is a 5α-reductase inhibitor used to treat male pattern baldness (MPB) and it exerts its action by converting testosterone into active metabolite, dihydrotestosterone (DHT).

The safety signal emanates from the US FDA's public response after receiving a petition from the Post Finasteride Syndrome Foundation (PFSF) to withdraw the product from the market due to the risk of serious adverse effects.

The Authority noted that the US FDA indicated that the petition does not provide reasonable evidence of a causal link between finasteride and persistent sexual problems, depression or suicide. However, the US FDA agreed that MAH make labelling changes by adding suicidal ideation and behaviour to the list of nervous system/psychiatric reactions in the adverse reaction (Post marketing Experience) section of the finasteride label.

b) Decision

The Authority found the PI/PIL of finasteride containing medicines sufficient at its current state and recommended continous monitoring of the benefit-risk profile of this medicine.

2.4.2 STATINS - RISK OF BULLOUS PEMPHIGOID

a) Background

The Authority conducted a review of a signal regarding bullous pemphigoid associated with the use of statins. The safety concern was identified by France, during routine signal detection activities, based on cases retrieved from the French pharmacovigilance database as well as published cases.

Based on the cumulative reviews of the available data, the Authority concluded that there is insufficient evidence to confirm a causal association between bullous pemphigoid and statins administration and recommended continuous monitoring of cases of bullous pemphigoid, particularly cases with a positive dechallenge and positive re-challenge as part of routine safety surveillance.

b) Decision

The Authority recommended continuous monitoring of the benefit-risk profile for statin containing medicines by applicants/HCRs.

2.4.3 SELECTIVE SEROTONIN REUPTAKE INHIBITORS, SEROTONIN AND NORADRENALINE REUPTAKE INHIBITORS (SSRIs/SNRIs) - ANOSMIA AND HYPOSMIA

a) Background

The Authority conducted a review regarding the potential risk of anosmia and hyposmia associated with the use of selective serotonin reuptake inhibitors, serotonin and noradrenaline reuptake inhibitors (SSRIs/SNRIs). The safety signal was identified and validated by the US FDA from a cumulative review of available data from all sources (literature, clinical trials, post marketing setting) on cases with Preferred Terms (PTs) Anosmia (lack of smell), Hyposmia (reduced ability to smell) and Olfactory (organs related to smell) Dysfunction. Based on the review, there is very limited data to support a causal association between the risk of anosmia/hyposmia and the use of SSRI/SNRI. HCRs of SSRIs/SNRIs should continue monitoring the safety issue through routine pharmacovigilance activities and inform the Authority when new data becomes available.

b) Decision

The Authority recommended that applicants/HCRs of SSRI/SNRI containing medicines continue monitoring the risk of anosmia and hyposmia through routine pharmacovigilance activities. The Authority considers the benefit-risk profile of SSRI/SNRI containing medicines favourable.

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