28 November 2019
EMA/PRAC/107813/2020
Inspections, Human Medicines Pharmacovigilance and Committees Division

Pharmacovigilance Risk Assessment Committee (PRAC)

Minutes of PRAC meeting on 28 – 31 October 2019

Chair: Sabine Straus – Vice-Chair: Martin Huber

Health and safety information

In accordance with the Agency's health and safety policy, delegates were briefed on health, safety and emergency information and procedures prior to the start of the meeting.

Disclaimers

Some of the information contained in the minutes is considered commercially confidential or sensitive and therefore not disclosed. With regard to intended therapeutic indications or procedure scope listed against products, it must be noted that these may not reflect the full wording proposed by applicants and may also change during the course of the review. Additional details on some of these procedures will be published in the PRAC meeting highlights once the procedures are finalised.

Of note, the minutes are a working document primarily designed for PRAC members and the work the Committee undertakes.

Note on access to documents

Some documents mentioned in the minutes cannot be released at present following a request for access to documents within the framework of Regulation (EC) No 1049/2001 as they are subject to on-going procedures for which a final decision has not yet been adopted. They will become public when adopted or considered public according to the principles stated in the Agency policy on access to documents (EMA/127362/2006, Rev. 1).

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Table of contents

1. Introduction

1.1. Welcome and declarations of interest of members, alternates and experts

The Chairperson opened the 28-31 October 2019 meeting by welcoming all participants.

Based on the declarations of interest submitted by the Committee members, alternates and experts and based on the topics in the agenda of the current meeting, the Committee Secretariat announced the restricted involvement of some Committee members in upcoming discussions; in accordance with the Agency's policy on the handling of conflicts of interests, participants in this meeting were asked to declare any changes, omissions or errors to their declared interests concerning the matters for discussion (see Annex II – List of participants). No new or additional conflicts were declared.

Discussions, deliberations and voting took place in full respect of the restricted involvement of Committee members and experts in line with the relevant provisions of the Rules of Procedure. All decisions taken at this meeting were made in the presence of a quorum of members (i.e. 24 or more members were present in the room). All decisions, recommendations and advice were agreed unanimously, unless otherwise specified.

1.2. Agenda of the meeting on 28 – 31 October 2019

The agenda was adopted with some modifications upon request from the members of the Committee and the EMA secretariat.

1.3. Minutes of the previous meeting on 30 September - 03 October 2019

The minutes were adopted with some amendments received during the consultation phase and will be published on the EMA website.

Post-meeting note: the PRAC minutes of the meeting held on 30 September - 03 October 2019 were published on the EMA website on 19 February 2020 (EMA/PRAC/89165/2020).

2. EU referral procedures for safety reasons: urgent EU procedures

2.1. Newly triggered procedures

None

2.2. Ongoing procedures

None

2.3. Procedures for finalisation

None

3. EU referral procedures for safety reasons: other EU referral procedures

3.1. Newly triggered procedures

None

3.2. Ongoing procedures

3.2.1. Cyproterone acetate (NAP) - EMEA/H/A-31/1488

Applicant(s): various

PRAC Rapporteur: Menno van der Elst; PRAC Co-rapporteur: Adam Przybylkowski

Scope: Review of the benefit-risk balance following notification by France of a referral under Article 31 of Directive 2001/83/EC, based on pharmacovigilance data

Background

A referral procedure under Article 31 of Directive 2001/83/EC is ongoing for the review of cyproterone acetate-containing medicine(s) and the risk of meningioma. This follows the result of a pharmacoepidemiology study conducted by the French Health Insurance[1] (CNAM) showing that the longer women are treated with high dose of cyproterone, the higher is the risk of meningioma. A strong cumulative dose-effect relationship was observed. In addition, the results of a French pharmacovigilance survey finalised in 2019 completed these results and also showed identified cases of meningioma with low dose of cyproterone. For further background, see PRAC minutes July 2019.

Summary of recommendation(s)/conclusions

- The PRAC discussed the assessment reports produced by the Rapporteurs.
- The PRAC adopted a list of outstanding issues (LoOI), to be addressed by the MAHs in accordance with a revised timetable (EMA/PRAC/371761/2019 Rev 1).
- The PRAC agreed on a list of questions (LoQ) to the study authors *Weill et al.*[2].

3.2.2. Leuprorelin[3] (NAP) - EMEA/H/A-31/1486

Applicant(s): various

PRAC Rapporteur: Željana Margan Koletić; PRAC Co-rapporteur: Eva Segovia

Scope: Review of the benefit-risk balance following notification by Germany of a referral under Article 31 of Directive 2001/83/EC, based on pharmacovigilance data

Background

[1] Caisse nationale de l'Assurance Maladie
[2] Weill A et al. (2019 Jun). Exposition prolongée à de fortes doses d'acétate de cyprotérone et risque de méningiome chez la femme. Paris: ANSM. (https://www.ansm.sante.fr/var/ansm_site/storage/original/application/b632fbd0387cd9e80a8312469ed52d2a.pdf)
[3] Depot formulation(s)

A referral procedure under Article 31 of Directive 2001/83/EC is ongoing for the review of leuprorelin-containing products after reports indicated that handling errors with the products during preparation and administration can cause some patients to receive insufficient amounts of their medicine, potentially leading to a lack of efficacy. As the significant number of medication errors, observed for leuprorelin-containing depot products remain a serious risk to public health, it was considered that further action is warranted to further characterise and mitigate the risk of handling errors and associated risk of lack of efficacy of leuprorelin-containing depot-injections. For further background, see PRAC minutes June 2019.

Summary of recommendation(s)/conclusions

- The PRAC discussed the assessment reports by the Rapporteurs.
- The PRAC adopted a list of outstanding issues (LoOI), to be addressed by the MAHs in accordance with a revised timetable (EMA/PRAC/317693/2019 Rev 1).

3.3. Procedures for finalisation

3.3.1. Alemtuzumab - LEMTRADA (CAP) - EMEA/H/A-20/1483

Applicant: Sanofi Belgium

PRAC Rapporteur: Brigitte Keller-Stanislawski; PRAC Co-rapporteur: Ulla Wändel Liminga

Scope: Review of the benefit-risk balance following notification by European Commission of a referral under Article 20 of Regulation (EC) No 726/2004, based on pharmacovigilance data

Background

A referral procedure under Article 20 of Regulation (EC) No 726/2004 for the review of Lemtrada (alemtuzumab) is to be concluded. This referral procedure was initiated following new emerging and serious safety concerns referring to fatal cases, cardiovascular adverse events in close temporal association with infusion of the medicinal product as well as immune-mediated diseases such as auto-immune hepatitis, hepatic injury, auto-immune-mediated central nervous system disease and Guillain-Barre syndrome. In April 2019 the PRAC recommended provisional measures to amend the product information until a thorough review is finalised. A final assessment of the data submitted was produced by the Rapporteurs according to the agreed timetable. For further background, see PRAC minutes April 2019, PRAC minutes July 2019 and PRAC minutes October 2019[4].

Discussion

The PRAC discussed the conclusions reached by the Rapporteurs.

The PRAC reviewed data currently available from post-marketing setting and from clinical trials on fatal cases, cardiovascular adverse events in close temporal association with Lemtrada (alemtuzumab) infusions and immune-mediated diseases, including data provided in writing and at an oral explanation. The PRAC also considered the views expressed by the Scientific Advisory Group on Neurology (SAG-N) meeting.

The PRAC concluded that myocardial ischaemia, myocardial infarction, haemorrhagic stroke, dissection of the cervicocephalic arteries, pulmonary alveolar haemorrhage and

[4] Held 30 September – 03 October 2019

thrombocytopenia may occur in close temporal association with the infusion of Lemtrada (alemtuzumab). The PRAC also concluded that alemtuzumab is associated with immune-mediated diseases such as autoimmune hepatitis, haemophilia A and haemophagocytic lymphohistiocytosis (HLH), which can happen with a delay of months to years after the latest treatment. In addition, the PRAC noted that these risks, which are serious and which can in some cases have a fatal outcome, are largely unpredictable. Therefore, the PRAC recommended that treatment with Lemtrada (alemtuzumab) should be restricted to patients with highly active relapsing remitting multiple sclerosis (RRMS) for the following patient groups: patients with highly active disease despite a full and adequate course of treatment with at least one disease modifying therapy, and for patients with rapidly evolving severe RRMS defined by 2 or more disabling relapses in one year, and with 1 or more gadolinium enhancing lesions on brain magnetic resonance imaging (MRI) or a significant increase in T2 lesion load as compared to a previous recent MRI. Furthermore, Lemtrada (alemtuzumab) should be contraindicated in patients with severe active infections until complete resolution, uncontrolled hypertension, history of arterial dissection of the cervicocephalic arteries, history of stroke, history of angina pectoris or myocardial infarction, coagulopathy on antiplatelet or anti-coagulant therapy as well as in patients with concomitant autoimmune diseases other than multiple sclerosis (MS).

Moreover, the PRAC recommended that Lemtrada (alemtuzumab) should only be administered in a hospital setting with ready access to intensive care. Additional recommendations for the monitoring of patients before, during and after infusion were made to ensure timely diagnosis and management of adverse reactions. Given the serious and unpredictable nature of the risks, and that adherence to risk minimisation is key to support a positive benefit-risk balance, the PRAC considered that a drug utilisation study (DUS) is necessary to assess the effectiveness of risk minimisation measures (RMMs). The PRAC also noted that the data currently available on mortality incidence is limited and therefore, the MAH is additionally required to investigate the incidence of mortality in patients treated with Lemtrada (alemtuzumab) compared with a relevant patient population.

The PRAC concluded that the benefit-risk balance of Lemtrada (alemtuzumab) remains favourable subject to changes to the product information, the educational materials and additional pharmacovigilance activities as described above.

Summary of recommendation(s)/conclusions

- The PRAC adopted a recommendation by majority[5] to vary[6] the terms of the marketing authorisation(s) for Lemtrada (alemtuzumab) to be considered by CHMP for an opinion – see EMA Press Release (EMA/583516/2019) entitled 'Lemtrada for multiple sclerosis: measures to minimise risk of serious side effects' published on 31 October 2019.
- The PRAC agreed on the content of a direct healthcare professional communication (DHPC) along with a communication plan for its distribution.

Post-meeting note 1: the press release entitled 'Measures to minimise risk of serious side effects of multiple sclerosis medicine Lemtrada' (EMA/609015/2019) representing the opinion adopted by the CHMP was published on the EMA website on 04 February 2020.

[5] Twenty-eight members voted in favour of the outcome whilst three members had divergent views (Ghania Chamouni, Jean-Michel Dogné, Eva Segovia). The Icelandic PRAC member agreed with the outcome while the Norwegian PRAC member did not agree with it

[6] Update of SmPC sections 4.1, 4.2, 4.3, 4.4, 4.8, 5.1 and Annex II. The package leaflet is updated accordingly

Post-meeting note 2: the PRAC assessment report (EMA/682560/2019) was published on 28 January 2020.

3.3.2. Tofacitinib - XELJANZ (CAP) - EMEA/H/A-20/1485

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan; PRAC Co-rapporteur: Amelia Cupelli

Scope: Review of the benefit-risk balance following notification by the European Commission (EC) of a referral under Article 20 of Regulation (EC) No 726/2004, based on pharmacovigilance data

Background

A referral procedure under Article 20 of Regulation (EC) No 726/2004 for the review of Xeljanz (tofacitinib) is to be concluded. This referral procedure was initiated following an increased risk of pulmonary embolism (PE) and overall mortality arising from study A3921133[7] in patients with cardiovascular risk factors treated for rheumatoid arthritis with tofacitinib 10 mg twice daily (BID). The review assesses the impact of the risk of thromboembolic events, in particular PE and deep venous thrombosis (DVT) in the context of the benefit-risk balance of the medicinal product in the authorised indications and doses. In May 2019, the PRAC recommended provisional measures to amend the product information until a thorough review is finalised. For further background, see PRAC minutes May 2019 and PRAC minutes September 2019 and PRAC minutes October 2019[8].

Discussion

The PRAC discussed the conclusions reached by the Rapporteurs.

The PRAC considered the totality of the data submitted during the referral in relation to the risk of venous thromboembolism (VTE) and overall mortality, including the responses submitted by the MAH in writing as well as the outcome of the ad-hoc expert group meeting.

The PRAC concluded that tofacitinib is associated with an increased risk of VTE, both for DVT as well as PE, especially in patients with risk factors for VTE. The PRAC further concluded that the risk of VTE events is dose-dependent.

The PRAC also concluded that although the data for patients with ulcerative colitis and psoriatic arthritis are limited, the results from study A3921133 in rheumatoid arthritis (RA) patients are relevant for the other indications.

Based on the interim analyses of study A3921133, the PRAC concurred that there is a potential risk regarding increased mortality. This was partly driven by a higher mortality rate due to serious infections for tofacitinib. This was particularly apparent for patients aged 65 years and above and as such tofacitinib should be considered in these patients only if no suitable alternative treatment is available. To minimise these risks, the PRAC recommended warnings to be introduced in the product information regarding the increased risk of VTE observed in patients taking tofacitinib especially for patients with known risk factors for VTE. The PRAC also recommended that treatment with tofacitinib is discontinued in patients with suspected VTE.

[7] A phase 3B/4 randomised safety endpoint study of 2 doses of tofacitinib (tofacitinib 5 mg twice daily (BID) and tofacitinib 10 mg BID) in comparison to a tumour necrosis factor (TNF) inhibitor in subjects with rheumatoid arthritis
[8] Held 30 September – 03 October 2019

Furthermore, the PRAC introduced a warning that tofacitinib 10 mg BID for maintenance treatment is not recommended in patients with ulcerative colitis (UC) who have known VTE risk factors, unless there is no suitable alternative treatment available. Clarifications on the posology have also been added particularly for UC patients in maintenance. The PRAC recommended an update of the educational materials accordingly.

The Committee considered that the benefit-risk balance of Xeljanz (tofacitinib) remains favourable subject to the agreed amendments to the product information and the additional risk minimisation measures (RMMs).

Summary of recommendation(s)/conclusions

- The PRAC adopted a recommendation to vary[9] the terms of the marketing authorisation(s) for Xeljanz (tofacitinib) to be considered by CHMP for an opinion – see EMA Press Release (EMA/584781/2019) entitled 'Xeljanz to be used with caution for all patients at high risk of blood clots' published on 31 October 2019.
- The PRAC agreed on the content of a direct healthcare professional communication (DHPC) along with a communication plan for its distribution.

Post-meeting note: the press release entitled 'EMA confirms Xeljanz to be used with caution in patients at high risk of blood clots' (EMA/608520/2019) representing the opinion adopted by the CHMP was published on the EMA website on 15 November 2019.

3.4. Re-examination procedures[10]

3.4.1. Estradiol[11] (NAP) - EMEA/H/A-31/1482

Applicant(s): various

PRAC Rapporteur: Jan Neuhauser; PRAC Co-rapporteur: Nikica Mirošević Skvrce

Scope: Request for re-examination under Article 32 of Directive 2001/83/EC for the review of the benefit-risk balance of medicinal products containing estradiol 0.01% for topical use following notification by the European Commission of a referral under Article 31 of Directive 2001/83/EC, based on pharmacovigilance data

Background

Following the PRAC recommendation adopted at the October 2019 PRAC meeting[12], to vary the marketing authorisations of medicinal products containing estradiol 0.01% for topical use, a MAH concerned by this referral procedure requested a re-examination. For further background, see PRAC minutes April 2019, PRAC minutes July 2019 and PRAC minutes October 2019.

Upon receipt of the grounds for re-examination from the MAH concerned by this referral procedure, the PRAC will initiate a re-examination procedure[13], expected to finalise in January 2020.

Discussion

[9] Update of SmPC sections 4.2, 4.3, 4.4, 4.8, 5.1 and Annex II. The package leaflet is updated accordingly
[10] Re-examination of PRAC recommendation under Article 32 of Directive 2001/83/EC
[11] 0.01%, topical use only
[12] Held 30 September – 03 October 2019
[13] Under Article 32 of Directive 2001/83/EC

The PRAC noted the notification letter from the MAH concerned by this referral procedure requesting a re-examination of the recommendation adopted by the PRAC at its October 2019 PRAC meeting.

The PRAC appointed Jan Neuhauser as Rapporteur and Nikica Mirošević Skvrce as Co-Rapporteur for the re-examination procedure.

Summary of recommendation(s)/conclusions

- The Committee discussed a preliminary timetable for the re-examination procedure. The timetable will be finalised further to the receipt of the MAH's grounds for re-examination of the PRAC recommendation.

Post-meeting note: On 09 December 2019, the MAH submitted its grounds for re-examination of the PRAC recommendation. On 12 December 2019, the PRAC adopted a revised timetable (EMA/PRAC/214200/2019 rev2) by written procedure for the re-examination of the recommendation.

3.5. Others

None

4. Signals assessment and prioritisation[14]

4.1. New signals detected from EU spontaneous reporting systems

See also Annex I 14.1.

[14] Each signal refers to a substance or therapeutic class. The route of marketing authorisation is indicated in brackets (CAP for Centrally Authorised Products; NAP for Nationally Authorised Products including products authorised via Mutual Recognition Procedures and Decentralised Procedure). Product names are listed for reference Centrally Authorised Products (CAP) only. PRAC recommendations will specify the products concerned in case of any regulatory action required

4.1.1. Buprenorphine – BUVIDAL (CAP), SIXMO (CAP), NAP; buprenorphine, naloxone – SUBOXONE (CAP), ZUBSOLV (CAP), NAP; naloxone – NYXOID (CAP), NAP; Selective serotonin reuptake inhibitors (SSRIs): citalopram (NAP), escitalopram (NAP), fluvoxamine (NAP), fluoxetine (NAP), paroxetine (NAP), sertraline (NAP); Serotonin norepinephrine reuptake inhibitors (SNRIs): desvenlafaxine (NAP), duloxetine – CYMBALTA (CAP), DULOXETINE LILLY (CAP), DULOXETINE MYLAN (CAP), DULOXETINE ZENTIVA (CAP), XERISTAR (CAP), YENTREVE (CAP), NAP; milnacipran (NAP); venlafaxine (NAP); Tricyclic antidepressants (TCAs): amitriptyline (NAP), clomipramine (NAP), doxepin (NAP), imipramine (NAP), nortriptyline (NAP), trimipramine (NAP); Monoamine oxidase inhibitors (MAOIs): isocarboxazid (NAP), phenelzine (NAP), selegiline (NAP), tranylcypromine (NAP); Other psychiatric medicines: amoxapine (NAP), buspirone (NAP), lithium (NAP), maprotiline (NAP), mirtazapine (NAP), trazodone (NAP); Serotonin receptor agonists: almotriptan (NAP), frovatriptan (NAP), naratriptan (NAP), rizatriptan (NAP), sumatriptan (NAP), zolmitriptan (NAP); Antiemetics: granisetron - SANCUSO (CAP), NAP; ondansetron (NAP), palonosetron – ALOXI (CAP), PALONOSETRON ACCORD (CAP), NAP; netupitant, palonosetron – AKYNZEO (CAP), tropisetron (NAP); Other serotonergic drugs: cyclobenzaprine (NAP), dextromethorphan (NAP), Hypericum perforatum (NAP), linezolid (NAP), methylene blue (NAP), tryptophan (NAP)

Applicant(s): Indivior Europe Limited (Suboxone), Orexo AB (Zubsolv), various

PRAC Rapporteur: Martin Huber

Scope: Signal of drug-drug interaction with serotonergic drugs leading to serotonin syndrome

EPITT 19475 – New signal

Lead Member State(s): BE, CZ, DE, DK, EE, ES, FR, GR, HU, IE, LT, NL, PT, SE, SK, SL

Background

Buprenorphine is a partial agonist/antagonist of opioid μ-receptors and naloxone is an antagonist of opioid receptors. They are authorised as Buvidal (buprenorphine) for the treatment of opioid dependence within a framework of medical, social and psychological treatment and as Sixmo (buprenorphine) for substitution treatment for opioid dependence in clinically stable adult patients who require no more than 8 mg/day of sublingual buprenorphine, within a framework of medical, social and psychological treatment. They are also indicated as Suboxone and Zubsolv (buprenorphine/naloxone) for the treatment of opioid drug dependence within a framework of medical, social and psychological treatment and as Nyxoid (naloxone) for the emergency treatment of known or suspected opioid overdose as manifested by respiratory and/or central nervous system depression.

The exposure for buprenorphine is estimated to have been more than 15.34 million patient-years worldwide, in the period from first authorisation in 1982 to 2017. The exposure for buprenorphine/naloxone is estimated to have been more than 5.29 million patient-years worldwide, in the period from first authorisation in 2006 to 2016. The exposure for Nyxoid (naloxone) is estimated to have been more than 476,903 patients worldwide, in the period from first authorisation in 2016 to 2019.

During routine signal detection activities, a signal of drug-drug interaction with serotonergic drugs leading to serotonin syndrome was identified by the EMA, based on 22 cases

retrieved from EudraVigilance (EV). Germany confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

Having considered the available evidence in EudraVigilance and in the literature, the PRAC agreed that the signal needs to be further investigated and recommended to perform further EV analysis of serotonin syndrome due to the interaction between buprenorphine and serotonergic drugs.

The PRAC appointed Martin Huber as Rapporteur for the signal.

Summary of recommendation(s)

- The Rapporteur should assess EudraVigilance data on the interaction within 60 days.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.1.2. Infliximab - FLIXABI (CAP), INFLECTRA (CAP), REMICADE (CAP), REMSIMA (CAP), ZESSLY (CAP)

Applicant(s): Celltrion Healthcare Hungary Kft. (Remsima), Janssen Biologics B.V. (Remicade), Pfizer Europe MA EEIG (Inflectra), Samsung Bioepis NL B.V. (Flixabi), Sandoz GmbH (Zessly)

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of Kaposi's sarcoma

EPITT 19480 – New signal

Lead Member State(s): FI, SE

Background

Infliximab is a chimeric human-murine monoclonal antibody that binds with high affinity to both soluble and transmembrane forms of tumour necrosis factor alfa (TNFα) but not to lymphotoxin α (TNFβ). It is indicated, as Flixabi, Inflectra, Remicade, Remsima and Zessly for the treatment of rheumatoid arthritis, adult and paediatric Crohn's disease, ulcerative colitis, paediatric ulcerative colitis, ankylosing spondylitis, psoriatic arthritis and psoriasis, subject to certain conditions.

The exposure for the originator product Remicade (infliximab) is estimated to have been more than 2,629,802 patients worldwide, in the period from first authorisation in 1998 to 2016.

During routine signal detection activities, a signal of Kaposi's sarcoma was identified by Sweden, based on 5 cases identified in the Spanish national database (FEDRA). The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

Having considered the available evidence from the case reports and the literature, the PRAC agreed that the signal deserves further analysis and the evaluation should be extended to all TNFα inhibitors (infliximab, adalimumab, etanercept, certolizumab pegol and golimumab). The PRAC recommended an analysis of EudraVigilance data on all TNFα inhibitors.

The PRAC appointed Ulla Wändel Liminga as Rapporteur for the signal.

Summary of recommendation(s)

- The Rapporteur should assess the overview of EudraVigilance data which is to be provided by the EMA within 60 days.
- A 90-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.2. New signals detected from other sources

4.2.1. Ceftriaxone (NAP)

Applicant(s): various

PRAC Rapporteur: Zane Neikena

Scope: Signal of encephalopathy

EPITT 19492 – New signal

Lead Member State(s): LV

Background

Ceftriaxone is a third-generation cephalosporin antibiotic indicated for the treatment of bacterial infections in adults and children including term neonates.

The exposure for cephalosporin-containing products is estimated to have been more than 183 million patients worldwide, in the period from first authorisation in 1982 to 2018.

During routine signal detection activities, a signal of encephalopathy was identified by France, based on an analysis of the French pharmacovigilance database published by *Lacroix et al*[15]. Latvia as the lead Member State for ceftriaxone confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

Having considered the available evidence from the literature, EudraVigilance data and the French national review, the PRAC agreed that the signal should be further investigated and requested further data from the MAH.

The PRAC appointed Zane Neikena as Rapporteur for the signal.

Summary of recommendation(s)

- Roche, as the originator MAH for ceftriaxone-containing product, should submit to the EMA, within 60 days, a cumulative review of cases of central nervous system (CNS) adverse drug reactions reported with ceftriaxone, together with a proposal to amend the product information and/or the RMP as appropriate.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

Post-meeting note: Following a requests from the originator MAH to extend the timelines

[15] Lacroix C et al. Serious central nervous system side effects of cephalosporins: a national analysis of serious reports registered in the French pharmacovigilance database. J Neurol Sci. 2019;398:196-201

for submission of the responses to the list of questions (LoQ), an additional 30 days were granted.

4.3. Signals follow-up and prioritisation

4.3.1. 5 alfa-reductase inhibitors (5ARIs): finasteride (NAP); dutasteride (NAP)

Applicant(s): various

PRAC Rapporteur: Annika Folin

Scope: Signal of type 2 diabetes mellitus (T2DM)

EPITT 19424 – Follow-up to May 2019

Background

For background information, see PRAC minutes May 2019.

The authors of the article by *Wei et al*[16] replied to the request for information on the signal of type 2 diabetes mellitus (T2DM) and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence from literature as well as the responses from the authors regarding the potential association of new onset T2DM in men with benign prostatic hyperplasia (BPH) exposed to 5α-reductase inhibitors (dutasteride; finasteride), the PRAC agreed that the signal should be further investigated and requested further information from the MAHs.

Summary of recommendation(s)

- The MAHs Merck Sharp & Dohme Ltd and GlaxoSmithKline for the originator products containing finasteride and dutasteride respectively should submit to EMA, within 60 days, a cumulative review of cases of new onset T2DM reported for finasteride and for dutasteride respectively from clinical studies. The MAHs should also provide a review of data from the literature.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.3.2. Azacitidine – AZACITIDINE CELGENE (CAP), VIDAZA (CAP)

Applicant(s): Celgene Europe BV

PRAC Rapporteur: Menno van der Elst

Scope: Signal of progressive multifocal leukoencephalopathy (PML)

EPITT 19422 – Follow-up to June 2019

Background

For background information, see PRAC minutes June 2019.

[16] Wei L et al. Incidence of type 2 diabetes mellitus in men receiving steroid 5α-reductase inhibitors: population-based cohort study. BMJ. 2019;365:l1204

The MAH replied to the request for information on the signal of progressive multifocal leukoencephalopathy (PML) and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence from clinical trials, post-marketing cases and literature, the PRAC agreed that the number of possible PML cases with a temporal relationship to azacitidine is low and that a mechanism of action for development of PML with azacitidine has not been established. The PRAC agreed that no further regulatory actions are warranted at present.

Summary of recommendation(s)

- The MAHs for azacitidine-containing products should continue to monitor PML as part of routine safety surveillance.

4.3.3. Ferric carboxymaltose (NAP); iron (NAP); iron dextran (NAP); iron (III) isomaltoside (NAP); iron sucrose (NAP); sodium ferric gluconate (NAP)

Applicant(s): various

PRAC Rapporteur: Zane Neikena

Scope: Signal of arteriospasm coronary

EPITT 19408 – Follow-up to May 2019

Background

For background information, see PRAC minutes May 2019.

The MAHs Vifor (iron sucrose and ferric carboxymaltose), Pharmacosmos (iron isomaltoside and iron dextran) and Sanofi (sodium ferric gluconate complex) replied to the request for information on the signal of coronary arteriospasm and the responses were assessed by the Rapporteur.

Discussion

Having considered the data from clinical trials and post–marketing use provided by the MAHs, together with the available evidence from the literature, the PRAC agreed that the there is sufficient evidence to establish a causal relationship between coronary arteriospasm/ Kounis syndrome and the use of iron-containing medicinal products for intravenous administration. Therefore, the PRAC recommended to add a warning to the product information of iron sucrose-, ferric carboxymaltose-, iron isomaltoside-, iron dextran- and sodium ferric gluconate-containing medicinal products.

Summary of recommendation(s)

- The MAHs for iron sucrose-, ferric carboxymaltose-, iron isomaltoside-, iron dextran- and sodium ferric gluconate-containing products should submit to relevant National Competent Authorities (NCAs) of the Member States, within 60 days, a variation to amend the product information[17].

For the full PRAC recommendation, see EMA/PRAC/580132/2019 published on 25 November 2019 on the EMA website.

[17] Update of SmPC sections 4.4 and 4.8. The package leaflet is to be updated accordingly

4.3.4. Ibuprofen – PEDEA (CAP), NAP; ketoprofen (NAP) and fixed-dose combinations: chlorphenamine, ibuprofen, phenylephrine (NAP); dimenhydrinate, ibuprofen, caffeine (NAP); ibuprofen, ascorbic acid (NAP); ibuprofen, caffeine (NAP); ibuprofen, codeine (NAP); ibuprofen, hydrocodone (NAP); ibuprofen, paracetamol (NAP); ibuprofen, phenylephrine (NAP); ibuprofen, pseudoephedrine (NAP); ketoprofen, omeprazole (NAP), ketoprofen, sucralfate (NAP)

Applicant(s): Recordati Rare Diseases (Pedea), various

PRAC Rapporteur: Anette Kirstine Stark

Scope: Signal of serious exacerbation of infections

EPITT 19415 – Follow-up to May 2019

Background

For background information, see PRAC minutes May 2019.

The MAHs Reckitt Benckiser (brandleader for ibuprofen-containing products), Recordati Rare Diseases Group (MAH for Pedea (ibuprofen)) and Sanofi-Aventis (brandleader for ketoprofen-containing products) replied to the request for information on the signal of serious exacerbation of infections and the responses were assessed by the Rapporteur.

Discussion

Having considered the existing evidence regarding ibuprofen, ketoprofen and the serious exacerbation of infections, the PRAC recommended that the signal is further assessed via the collection of further data, including an analysis of existing warnings in the product information across the Member States, with a review of literature on the association between ibuprofen, ketoprofen and serious exacerbation of infections. The PRAC also recommended that expert advice is sought from the Paediatric Committee (PDCO) and from the CHMP Infectious Disease Working Party (IDWP).

Summary of recommendation(s)

- The PRAC adopted a list of questions (LoQ) to the PDCO and a LoQ to the IDWP.
- The PRAC agreed on the content and distribution of a non-urgent information (NUI) in order to collect additional information from EU Member States on the existing wording in the product information of ibuprofen- and ketoprofen-containing products.
- The EMA will perform a full literature review on the issue.
- The Rapporteur should assess the literature review, alongside the responses provided by the PDCO and the IDWP and the responses to the NUI.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.3.5. Imiquimod – ALDARA (CAP); ZYCLARA (CAP); NAP

Applicant(s): Meda AB, various

PRAC Rapporteur: Adam Przybylkowski

Scope: Signal of pemphigus

EPITT 19441 – Follow-up to July 2019

Background

For background information, see PRAC minutes July 2019.

The MAH Meda AB replied to the request for information on the signal of pemphigus and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence from EudraVigilance and the literature, and the responses from the MAH, the PRAC agreed that a causal relationship between imiquimod and pemphigus or pemphigoid cannot be established at this stage and that no further regulatory actions are warranted at present.

Summary of recommendation(s)

- The MAHs for imiquimod-containing products should continue to monitor pemphigus as part of routine safety surveillance.

4.3.6. Tigecycline – TYGACIL (CAP); NAP

Applicant(s): Pfizer Europe MA EEIG, various

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Signal of bradycardia

EPITT 19394 – Follow-up to May 2019

Background

For background information, see PRAC minutes May 2019.

The MAH Pfizer replied to the request for information on the signal of bradycardia and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence including the data from clinical trials and post-marketing use together with a literature review provided by the MAH, the PRAC agreed that a causal relationship between tigecycline and bradycardia cannot be established at present and that no further regulatory actions are warranted at this stage.

Summary of recommendation(s)

- The MAHs for tigecycline-containing products should continue to monitor bradycardia as part of routine safety surveillance.

4.3.7. Vascular endothelial growth factor (VEGF) inhibitors[18]: aflibercept – EYLEA (CAP), ranibizumab – LUCENTIS (CAP)

Applicant(s): Bayer AG (Eylea), Novartis Europharm Limited (Lucentis)

PRAC Rapporteur: Annika Folin

Scope: Signal of artery dissections and aneurysms

[18] For intravitreal use

EPITT 19330 – Follow-up to May 2019

Background

For background information, see PRAC minutes May 2019.

The MAHs for Eylea (aflibercept) and Lucentis (ranibizumab) replied to the request for information on the signal of artery dissections and aneurysms and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence including the cumulative reviews provided by the MAHs, the PRAC agreed that the causal association between the development or aggravation of aneurysms and artery dissections following intravitreal administration of ranibizumab and aflibercept cannot be established at this stage and that no further regulatory actions are warranted at present.

Summary of recommendation(s)

- The MAHs for Eylea (aflibercept) and Lucentis (ranibizumab) should continue to monitor artery dissections and aneurysms as part of routine safety surveillance.

5. Risk management plans (RMPs)

5.1. Medicines in the pre-authorisation phase

The PRAC provided the CHMP with advice on the proposed RMPs for a number of products (identified by active substance below) that are under evaluation for initial marketing authorisation. Information on the PRAC advice will be available in the European Public Assessment Reports (EPARs) to be published at the end of the evaluation procedure.

Please refer to the CHMP pages for upcoming information (http://www.ema.europa.eu/Committees>CHMP>Agendas, minutes and highlights).

See also Annex I 15.1.

5.1.1. Bempedoic acid - EMEA/H/C/004958

Scope: Treatment of primary hypercholesterolaemia or mixed dyslipidaemia

5.1.2. Bempedoic acid, ezetimibe - EMEA/H/C/004959

Scope: Treatment of primary hypercholesterolaemia or mixed dyslipidaemia

5.1.3. Darolutamide - EMEA/H/C/004790

Scope: Treatment of non-metastatic castration resistant prostate cancer (nmCRPC)

5.2. Medicines in the post-authorisation phase – PRAC-led procedures

See also Annex I 15.2.

5.2.1. Bortezomib - VELCADE (CAP) - EMEA/H/C/000539/II/0093

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Amelia Cupelli

Scope: Submission of an updated RMP (version 30.1) in order to revise the list of safety concerns as requested in the conclusions of periodic single assessment procedure PSUSA/00000424/201804 adopted in December 2018. As a consequence, Annex II is updated to reflect the removal of the additional risk minimisation activities. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet. Furthermore, the product information is being brought in line with the latest quality review of documents (QRD) template (version 10.1)

Background

Bortezomib is a proteasome inhibitor indicated, as Velcade, as monotherapy or in combination with pegylated liposomal doxorubicin or dexamethasone for the treatment of adult patients with progressive multiple myeloma (MM) who have received at least 1 prior therapy and who have already undergone or are unsuitable for haematopoietic stem cell transplantation. It is also indicated in combination with melphalan and prednisone for the treatment of adult patients with previously untreated MM who are not eligible for high-dose chemotherapy with haematopoietic stem cell transplantation. Additionally, it is indicated in combination with dexamethasone, or with dexamethasone and thalidomide, for the induction treatment of adult patients with previously untreated MM who are eligible for high-dose chemotherapy with haematopoietic stem cell transplantation. Finally, it is indicated in combination with rituximab, cyclophosphamide, doxorubicin and prednisone for the treatment of adult patients with previously untreated mantle cell lymphoma who are unsuitable for haematopoietic stem cell transplantation.

The PRAC is evaluating a type II variation procedure for Velcade, a centrally authorised medicine containing bortezomib, to update the RMP in order to revise the list of safety concerns as requested in the outcome of the PSUSA procedure (PSUSA/00000424/201804) finalised in December 2018 and to remove the existing educational materials as additional risk minimisation measures (aRMM). The PRAC is responsible for producing an assessment report to be further considered at the level of the CHMP, responsible for adopting an opinion on this variation.

Summary of advice

- The RMP for Velcade (bortezomib) in the context of the variation procedure under evaluation could be considered acceptable provided that an update to RMP version 30.1 and satisfactory responses to the request for supplementary information (RSI) are submitted.
- The PRAC supported the removal of the existing educational materials on 'medication/dispensing errors' in order to mitigate and prevent dispensing and dosing errors between subcutaneous (SC) and intravenous (IV) administration as well confusion between two different regimens in the transplant induction regimen. It is considered that these risks are well integrated into clinical practice and adequately controlled by routine risk minimisation measures (RMMs). Also, no safety concern emerged from the results of the survey assessing the effectiveness of the aRMMs.

5.3. Medicines in the post-authorisation phase – CHMP-led procedures

See also Annex I 15.3.

5.3.1. Mecasermin - INCRELEX (CAP) - EMEA/H/C/000704/II/0060

Applicant: Ipsen Pharma

PRAC Rapporteur: Kirsti Villikka

Scope: Update of sections 4.1, 4.2, 4.3, 4.4, 4.8 and 4.9 of the SmPC in order to update the safety information on benign or malignant neoplasia based on a EU registry study: the Ipsen global safety database and literature review. The package leaflet and the RMP (version 11) are updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet

Background

Mecasermin is a human insulin-like growth factor-1 (rhIGF-1) produced by recombinant deoxyribonucleic acid (DNA) technology. It is indicated, as Increlex, for the long-term treatment of growth failure in children and adolescents from 2 to 18 years with severe primary insulin-like growth factor-1 deficiency (primary IGFD).

The CHMP is evaluating a type II variation for Increlex, a centrally authorised product containing mecasermin, consisting of an update of the safety information on benign or malignant neoplasia based on the results of an EU registry study. The MAH is proposing to update the existing key elements of the educational materials (physician and patient information) on the risk of benign or malignant neoplasia as well as to communicate the update via a direct healthcare professional communication (DHPC). The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this variation. For background information, see PRAC minutes September 2019.

Summary of advice

- The RMP version 11.3 for Increlex (mecasermin) in the context of the variation procedure under evaluation by the CHMP is considered acceptable.
- The PRAC confirmed the inclusion of benign and malignant neoplasia as an important identified risk in the safety specification of the RMP. The PRAC also agreed on the update of pharmacovigilance plan to include the proposed planned study to further characterise the important identified risk of benign and malignant neoplasia with a first milestone being the submission of a study feasibility report in December 2019. Finally, the committee endorsed the proposed revisions to the existing key elements of the educational materials (physician information pack and patient information pack) in Annex II-D on 'Conditions or restrictions with regard to the safe and effective use of the medicinal product' to include information on the risk of neoplasia.
- The PRAC agreed on the content of a DHPC along with a communication plan for its distribution in order to inform EU healthcare professionals (HCPs) on the risk of benign and malignant neoplasia.

6. Periodic safety update reports (PSURs)

6.1. PSUR single assessment (PSUSA) procedures including centrally authorised products (CAPs) only

See also Annex I 16.1.

6.1.1. Axicabtagene ciloleucel - YESCARTA (CAP) - PSUSA/00010703/201904

Applicant: Kite Pharma EU B.V., ATMP[19]

PRAC Rapporteur: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

Background

Axicabtagene ciloleucel is a an anti-CD[20]19 chimeric antigen receptor (CAR) T-cell advanced therapy, indicated as Yescarta, for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma (PMBCL), after two or more lines of systemic therapy.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Yescarta, a centrally authorised medicine containing axicabtagene ciloleucel and issued a recommendation on its marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Yescarta (axicabtagene ciloleucel) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include as undesirable effects spinal cord oedema with a frequency 'uncommon', myelitis with a frequency 'uncommon', quadriplegia with a frequency 'uncommon' and dysphagia with a frequency 'common'. Therefore, the current terms of the marketing authorisation(s) should be varied[21].
- In the next PSUR, the MAH should provide detailed reviews of loss of target antigen in relapsed patients taking Yescarta (axicabtagene ciloleucel) and on the persistence of active CAR-T cells in relapsed patients taking Yescarta (axicabtagene ciloleucel).

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC.

6.1.2. Canagliflozin – INVOKANA (CAP); canagliflozin, metformin - VOKANAMET (CAP) - PSUSA/00010077/201903

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Martin Huber

[19] Advanced therapy medicinal product
[20] Cluster of differentiation
[21] Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

Scope: Evaluation of a PSUSA procedure

Background

Canagliflozin is an inhibitor of sodium-glucose transport protein 2 (SGLT2) indicated, as Invokana, and in combination with metformin as Vokanamet, for the treatment of adults with insufficiently controlled type 2 diabetes mellitus (T2DM) as an adjunct to diet and exercise as monotherapy when metformin is considered inappropriate due to intolerance or contraindications and in addition to other medicinal products for the treatment of diabetes.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Invokana and Vokanamet, centrally authorised medicines containing canagliflozin and canagliflozin/metformin respectively and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Invokana (canagliflozin) and Vokanamet (canagliflozin/metformin) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include photosensitivity as an undesirable effect with a frequency 'uncommon'. In addition, the undesirable effects of urinary tract infection (UTI) is reclassified under the system organ class (SOC) 'infections and infestations', and 'vulvovaginal candidiasis' and 'balanitis or balanoposthitis' under the SOC 'reproductive system and breast disorders'. Moreover, the package leaflet is updated to include the signs and symptoms of serious UTIs. Therefore, the current terms of the marketing authorisation(s) should be varied[22].
- In the next PSUR, the MAH should provide a cumulative review of cases of pancreatitis. The MAH should also review cases of renal injury in patients with severe hepatic impairment and cases of serious UTIs and discuss for the latter whether any product information update is deemed necessary in relation to the management of treatment with canagliflozin in case of serious UTI.

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC.

6.1.3. Dimethyl fumarate[23] - TECFIDERA (CAP) - PSUSA/00010143/201903

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

Dimethyl fumarate is methyl ester of fumaric acid indicated, as Tecfidera, for the treatment of adult patients with relapsing remitting multiple sclerosis (RRMS).

[22] Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion
[23] Indicated for the treatment of adult patients with relapsing remitting multiple sclerosis (RRMS)

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Tecfidera, a centrally authorised medicine containing dimethyl fumarate and issued a recommendation on its marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Tecfidera (dimethyl fumarate) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add Fanconi syndrome as a new warning. Therefore, the current terms of the marketing authorisation(s) should be varied[24].
- In the next PSUR, the MAH should provide a detailed discussion on cases of interest reporting arthritis or arthralgia. The MAH should also provide a cumulative review of cases of rhinorrhoea together with a discussion of the potential mechanism behind dimethyl fumarate-induced rhinorrhoea. In addition, a cumulative review of cases of tendinitis should be provided.

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC.

6.1.4. Insulin glargine - ABASAGLAR (CAP); LANTUS (CAP); SEMGLEE (CAP); TOUJEO (CAP) - PSUSA/00001751/201904

Applicant(s): Eli Lilly Nederland B.V. (Abasaglar), Mylan S.A.S (Semglee), Sanofi-Aventis Deutschland GmbH (Lantus, Toujeo)

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

Background

Insulin glargine is an insulin, indicated, as Abasaglar, Lantus, Semglee and Toujeo for the treatment of type 1 and type 2 diabetes mellitus (T1DM and T2DM).

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Abasaglar, Lantus, Semglee and Toujeo, centrally authorised medicines containing insulin glargine and issued a recommendation on their marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Abasaglar, Lantus, Semglee and Toujeo (insulin glargine) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include cutaneous amyloidosis as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[25].

[24] Update of SmPC section 4.4. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion
[25] Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC.

6.2. PSUR single assessment (PSUSA) procedures including centrally authorised products (CAPs) and nationally authorised products (NAPs)

See also Annex I 16.2.

6.2.1. Dexmedetomidine - DEXDOR (CAP); NAP - PSUSA/00000998/201903

Applicant(s): Orion Corporation, various

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

Background

Dexmedetomidine is a indicated, as Dexdor, for the sedation of adult intensive care unit (ICU) patients requiring a sedation level not deeper than arousal in response to verbal stimulation (corresponding to Richmond agitation-sedation scale (RASS) 0 to -3) and for the sedation of non-intubated adult patients prior to and/or during diagnostic or surgical procedures requiring sedation, i.e. procedural/awake sedation.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Dexdor, a centrally authorised medicine containing dexmedetomidine, and nationally authorised medicines containing dexmedetomidine and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of dexmedetomidine-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to amend the existing warning on cardiovascular effects and to add higher degree atrioventricular block and cardiac arrest as undesirable effects with a frequency 'uncommon'. Therefore, the current terms of the marketing authorisations should be varied[26].
- The MAH should submit to EMA, within 60 days, an analysis of all available mortality data from controlled clinical trials in the dexmedetomidine development program and conduct age-stratified analyses.
- In the next PSUR, the MAH should provide a targeted summary of the literature data identified for the PSUR period together with a discussion of the relevance for the characterisation of the safety profile of dexmedetomidine.

[26] Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC.

6.2.2. Tenofovir disoproxil - TENOFOVIR DISOPROXIL MYLAN (CAP); TENOFOVIR DISOPROXIL ZENTIVA (CAP); VIREAD (CAP); NAP - PSUSA/00002892/201903

Applicant(s): Mylan S.A.S (Tenofovir disoproxil Mylan), Zentiva k.s. (Tenofovir disoproxil Zentiva), Gilead Sciences Ireland UC (Viread), various

PRAC Rapporteur: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

Background

Tenofovir disoproxil is a nucleoside monophosphate (nucleotide) analogue indicated for the treatment of human immunodeficiency virus-1 (HIV-1) infection in combination with other antiretroviral medicinal products and for the treatment of chronic hepatitis B (CHB), subject to certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Tenofovir Disoproxil Mylan, Tenofovir Disoproxil Zentiva and Viread, centrally authorised medicines containing tenofovir disoproxil, and nationally authorised medicines containing tenofovir disoproxil and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of tenofovir disoproxil-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to remove and amend the existing information and warnings regarding the co-administration of tenofovir disoproxil and didanosine, and to add safety results from three studies with tenofovir disoproxil including data on the prevention of mother-to-child transmission of hepatitis B virus (HBV) infection. In addition, information on the undesirable effect lactic acidosis reported with tenofovir disoproxil is further included and the warnings regarding the co-administration of tenofovir disoproxil and didanosine are amended. Therefore, the current terms of the marketing authorisations should be varied[27].
- In the next PSUR, the MAH Gilead should provide a review of the literature on tenofovir transfer to breast milk and safety in breastfed infants of mothers with a hepatitis B infection. The MAH should provide the proportion of each type of birth defect, taking into account prospective and retrospective cases and major and minor malformations. The MAH Gilead should also provide a cumulative safety review on cutaneous leukocytoclastic vasculitis and provide a review of the signal on chronic progressive external ophthalmoplegia and provide a cumulative review of osteoporosis and osteopenia. The MAH Cipla should provide more information on the signal on hypospadias.

[27] Update of SmPC sections 4.4, 4.5, 4.6 and 4.8. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC.

6.3. PSUR single assessment (PSUSA) procedures including nationally authorised products (NAPs) only

See also Annex I 16.3.

6.3.1. Erythromycin (NAP) - PSUSA/00001257/201903

Applicant(s): various

PRAC Lead: Ronan Grimes

Scope: Evaluation of a PSUSA procedure

Background

Erythromycin is a macrolide antibiotic that is active against gram-positive cocci and gram-positive bacilli and some gram-negative cocci and bacilli. It is indicated for respiratory tract infections, genital chlamydia and skin infections. It is also indicated for the treatment of acne and as an eye ointment for the treatment of superficial ocular infections and for prophylaxis of neonatal ophthalmia.

Based on the assessment of the periodic safety update report(s) (PSUR(s)), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing erythromycin and issued a recommendation on their marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of erythromycin-containing product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add a contraindication to reflect that erythromycin should not be given to patients with a history of QT prolongation or ventricular cardiac arrhythmia and that it should not be given to patients with electrolyte disturbances due to the risk of QT prolongation. In addition, a warning is added to reflect the increased short-term risk of adverse cardiovascular (CV) outcomes reported in observational studies. Furthermore a warning is added to reflect the association between exposure to erythromycin in infants and the risk of infantile hypertrophic pyloric stenosis (IHPS). The product information is also updated to include the interaction between erythromycin and rivaroxaban. Finally, ventricular fibrillation and cardiac arrest are added as undesirable effects with a frequency 'not known'. Therefore, the current terms of the marketing authorisations should be varied[28].
- In the next PSUR, all MAHs should comment on patterns of use in the exposure data, in particular if there has been an increase/decrease in the marketing exposure of their respective medicinal product(s).

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive

[28] Update of SmPC sections 4.3, 4.4, 4.5 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

2001/83/EC. The frequency of submission of the subsequent PSURs should be changed from thirteen-yearly to three-yearly and the list of Union reference dates (EURD list) will be updated accordingly.

In addition, the PRAC considered that a separate entry in the EURD list should be added for erythromycin for topical use only with a frequency of submission of the subsequent PSURs changed from thirteen-yearly to five-yearly. The EURD list will be updated accordingly.

6.3.2. Ezetimibe, simvastatin (NAP) - PSUSA/00001347/201903

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

Ezetimibe is a non-statin lipid-lowering substance and simvastatin is an inhibitor (statin) of HMG-CoA[29] reductase. In combination, ezetimibe/simvastatin is indicated for the reduction of the risk of cardiovascular events in patients with coronary heart disease (CHD) and a history of acute coronary syndrome (ACS) either previously treated with a statin or not. It is also indicated as adjunctive therapy to diet for use in patients with primary (heterozygous familial and non-familial) hypercholesterolaemia or mixed hyperlipidaemia where use of a combination product is appropriate. Finally, it is indicated as adjunctive therapy to diet for use in patients with homozygous familial hypercholesterolaemia (HoFH).

Based on the assessment of the periodic safety update report(s) (PSUR(s)), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing ezetimibe/simvastatin and issued a recommendation on their marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of ezetimibe/simvastatin-containing product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add vision blurred - visual impairment as an undesirable effect with a frequency 'rare', lichenoid drug eruptions with a frequency 'very rare', muscle rupture with a frequency 'very rare' and gynecomastia with a frequency 'very rare'. Therefore, the current terms of the marketing authorisations should be varied[30].
- In the next PSUR, the MAH(s) should closely monitor cases of haemorrhagic stroke, tinnitus, drug interaction with ticagrelor, serious ocular events (including cataract and blindness), diplopia and drug-induced liver injury.

Given that the undesirable effects of vision blurred, visual impairment, lichenoid drug eruptions, muscle rupture and gynecomastia are considered to be at least causally associated with simvastatin, the PRAC also agreed that the recommendation to update the product information is also applicable to simvastatin-containing product(s) as well as all fixed dose

[29] 3-hydroxy-3-methylglutaryl-CoA
[30] Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

combination (FDC) containing simvastatin. Further consideration is to be given at the level of the CMDh.

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC.

6.3.3. Rocuronium (NAP) - PSUSA/00002656/201902

Applicant(s): various

PRAC Lead: Eva Jirsová

Scope: Evaluation of a PSUSA procedure

Background

Rocuronium is a fast onset, intermediate acting non-depolarizing neuromuscular blocking agent indicated in adults and paediatric patients from term neonates to adolescents (0 to 18 years) as an adjunct to general anaesthesia to facilitate tracheal intubation during routine and rapid sequence induction and to provide skeletal muscle relaxation during surgery. Rocuronium is also indicated as an adjunct in the intensive care unit (ICU) to facilitate intubation and mechanical ventilation.

Based on the assessment of the periodic safety update report(s) (PSUR(s)), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing rocuronium and issued a recommendation on their marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of rocuronium-containing product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add Kounis syndrome as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisations should be varied[31].

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC.

6.4. Follow-up to PSUR/PSUSA procedures

See also Annex I 16.4.

6.4.1. Dibotermin alfa - INDUCTOS (CAP) - EMEA/H/C/000408/LEG 074.1

Applicant: Medtronic BioPharma B.V.

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to LEG 074 [detailed evaluation of the effectiveness of the current educational materials as requested in the conclusions of PSUSA/00001034/201709 adopted

[31] Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

in April 2018] as per the request for supplementary information (RSI) adopted in January 2019

Background

Dibotermin alfa is a recombinant human bone morphogenetic protein-2 indicated, as Inductos, for the treatment of single-level lumbar interbody spine fusion as a substitute for autogenous bone graft in adults with degenerative disc disease and for the treatment of acute tibia fractures in adults, as an adjunct to standard care using open fracture reduction and intramedullary unreamed nail fixation.

Following the evaluation of the most recently submitted PSUR for the above mentioned medicine, the PRAC requested the MAH to submit further data on the evaluation of the effectiveness of the educational materials that are put in place as an additional risk minimisation measure in the current RMP (for background, see PRAC minutes April 2018). The responses were assessed by the Rapporteur for further PRAC advice.

Summary of advice/conclusion(s)

- The PRAC agreed with the Rapporteur's assessment that an observational study is considered not feasible. The Committee advised that the MAH should perform an online survey to assess the knowledge and understanding of physicians in relation to the key elements of the educational materials.
- The MAH should submit to EMA, within 60 days, a full protocol including the actual online survey, taking into account the issues highlighted in the assessment report.

7. Post-authorisation safety studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)[32]

See Annex I 17.1.

7.2. Protocols of PASS non-imposed in the marketing authorisation(s)[33]

See Annex I 17.2.

7.3. Results of PASS imposed in the marketing authorisation(s)[34]

None

7.4. Results of PASS non-imposed in the marketing authorisation(s)[35]

See Annex I 17.4.

[32] In accordance with Article 107n of Directive 2001/83/EC
[33] In accordance with Article 107m of Directive 2001/83/EC, supervised by PRAC in accordance with Article 61a (6) of Regulation (EC) No 726/2004
[34] In accordance with Article 107p-q of Directive 2001/83/EC
[35] In accordance with Article 61a (6) of Regulation (EC) No 726/2004, in line with the revised variations regulation for any submission as of 4 August 2013

7.5. Interim results of imposed and non-imposed PASS submitted before the entry into force of the revised variation regulation

See Annex I 17.5.

7.6. Others

See Annex I 17.6.

7.7. New Scientific Advice

None

7.8. Ongoing Scientific Advice

Information related to this section cannot be released at the present time as it is deemed to contain commercially confidential information.

7.9. Final Scientific Advice (Reports and Scientific Advice letters)

Information related to this section cannot be released at the present time as it is deemed to contain commercially confidential information.

8. Renewals of the marketing authorisation, conditional renewal and annual reassessments

8.1. Annual reassessments of the marketing authorisation

See Annex I 18.1.

8.2. Conditional renewals of the marketing authorisation

See Annex I 18.2.

8.3. Renewals of the marketing authorisation

See also Annex I 18.3.

8.3.1. Tolvaptan - JINARC (CAP) - EMEA/H/C/002788/R/0027 (without RMP)

Applicant: Otsuka Pharmaceutical Netherlands B.V.

PRAC Rapporteur: Amelia Cupelli

Scope: 5-year renewal of the marketing authorisation

Background

Tolvaptan is a vasopressin antagonist indicated, as Jinarc, to slow the progression of cyst development and renal insufficiency of autosomal dominant polycystic kidney disease (ADPKD) in adults with CKD stage 1 to 4 at initiation of treatment with evidence of rapidly progressing disease.

Jinarc, a centrally authorised medicine containing tolvaptan, was authorised in 2015.

The MAH submitted an application for renewal of the marketing authorisation for opinion by the CHMP. The PRAC is responsible for providing advice to the CHMP on this renewal with regard to safety and risk management aspects.

Summary of advice

- Based on the review of the available pharmacovigilance data for Jinarc (tolvaptan) and the CHMP Rapporteur's assessment report, the PRAC considered that the MAH should submit satisfactory responses to a request for supplementary information (RSI) on several aspects, in particular on idiosyncratic hepatic toxicity, before this procedure can be concluded.

9. Product related pharmacovigilance inspections

9.1. List of planned pharmacovigilance inspections

None

9.2. Ongoing or concluded pharmacovigilance inspections

Disclosure of information on results of pharmacovigilance inspections could undermine the protection of the purpose of these inspections, investigations and audits. Therefore such information is not reported in the minutes.

9.3. Others

None

10. Other safety issues for discussion requested by the CHMP or the EMA

10.1. Safety related variations of the marketing authorisation

None

10.2. Timing and message content in relation to Member States' safety announcements

None

10.3. Other requests

None

10.4. Scientific Advice

Information related to this section cannot be released at the present time as it is deemed to contain commercially confidential information.

11. Other safety issues for discussion requested by the Member States

11.1. Safety related variations of the marketing authorisation

None

11.2. Other requests

None

12. Organisational, regulatory and methodological matters

12.1. Mandate and organisation of the PRAC

None

12.2. Coordination with EMA Scientific Committees or CMDh-v

None

12.3. Coordination with EMA Working Parties/Working Groups/Drafting Groups

None

12.4. Cooperation within the EU regulatory network

12.4.1. Heads of Medicines Agencies (HMA)-EMA joint big data taskforce – draft recommendations

The PRAC was presented the draft recommendations from the Heads of Medicines Agencies (HMA)-EMA joint task force on big data. PRAC members were invited to send comments on the proposals by 8 November 2019. As next steps, the recommendations are to be presented to all EMA committees, other relevant bodies and to the EMA Management Board (MB) at its December 2019 meeting.

Post-meeting note: In January 2020, the HMA-EMA task force on big data published its final report (phase two) containing practical recommendations on how the European medicines regulatory network could make best use of big data by evolving its approach to data use and evidence generation in support of innovation and public health.

12.5. Cooperation with International Regulators

None

12.6. Contacts of the PRAC with external parties and interaction with the Interested Parties to the Committee

None

12.7. PRAC work plan

None

12.8. Planning and reporting

12.8.1. EU Pharmacovigilance system – quarterly workload measures and performance indicators – Q3 2019 and predictions

At the organisational matters teleconference held on 14 November 2019, the EMA Secretariat presented quarterly figures on the EMA pharmacovigilance system-related workload and performance indicators. For previous update, see PRAC minutes September 2019.

12.9. Pharmacovigilance audits and inspections

12.9.1. Pharmacovigilance systems and their quality systems

None

12.9.2. Pharmacovigilance inspections

None

12.9.3. Pharmacovigilance audits

None

12.10. Periodic safety update reports (PSURs) & Union reference date (EURD) list

12.10.1. Periodic safety update reports

None

12.10.2. Granularity and Periodicity Advisory Group (GPAG)

PRAC lead: Menno van der Elst, Maia Uusküla

The meeting of the GPAG was cancelled.

12.10.3. Periodic safety update reports single assessment (PSUSA) – updates to the assessment report template – call for volunteers

The EMA Secretariat presented to PRAC a proposal to introduce some simplification and clarification to the PSUSA assessment report (AR) template. PRAC members were invited to send interest in reviewing the proposal by 5 November 2019. Follow-up discussion is planned in December 2019.

Post-meeting note: The following members expressed interest and were involved in the review of the proposed revised PSUSA AR template: Jana Lukačišinová, Ana Sofia Martins, Menno van der Elst, Ulla Wändel Liminga.

12.10.4. Union reference date (EURD) list –maintenance process optimisation

PRAC lead: Menno van der Elst

At the organisational matters teleconference held on 14 November 2019, the EMA Secretariat presented a proposal for optimising the maintenance of the Union reference date (EURD) list. This includes the implementation of a universal 7 day-cut-off date for all PSUSAs (between the submission deadline and the procedure start date).

Post-meeting note: On 18 November 2019, the PRAC adopted the amended process via written procedure.

12.10.5. PSURs repository

None

12.10.6. Union reference date list – consultation on the draft list

The PRAC endorsed the draft revised EURD list, version November 2019, reflecting the PRAC's comments impacting on the data lock point (DLP) and PSUR submission frequencies of the substances/combinations. The PRAC endorsed the newly allocated Rapporteurs for upcoming PSUSAs in accordance with the principles previously endorsed by the PRAC (see PRAC minutes April 2013).

Post-meeting note: following the PRAC meeting of November 2019, the updated EURD list was adopted by the CHMP and CMDh at their November 2019 meetings and published on the EMA website on 20 November 2019, see:

Home> Human Regulatory>Pharmacovigilance>Periodic safety update reports>EURD list> List of Union reference dates and frequency of submission of periodic safety update reports (PSURs)

12.11. Signal management

12.11.1. Signal management – feedback from Signal Management Review Technical (SMART) Working Group

PRAC lead: Menno van der Elst

The PRAC was updated on the progress from the signal management review technical (SMART) working group meeting held on 28 October 2019. The SMART working group (WG) discussed the issues of information arising regarding the effectiveness or risk minimisation measures (RMMs) and whether these fall within the definition of a signal, and discussed further details on issues which do not fall within the definition of a signal (e.g. national variations submitted to Member States, invalid emerging safety information notifications).

12.11.2. Signal Management Review Technical (SMART) Working Group Methods activities - update

At the organisational matters teleconference held on 14 November 2019, the EMA Secretariat presented an update on the topics selected for investigation by the working group.

12.12. Adverse drug reactions reporting and additional monitoring

12.12.1. Management and reporting of adverse reactions to medicinal products

None

12.12.2. Additional monitoring

None

12.12.3. List of products under additional monitoring – consultation on the draft list

The PRAC was informed of the updates made to the list of products under additional monitoring.

Post-meeting note: The updated additional monitoring list was published on the EMA website on 27 November 2019, see:

Home>Human Regulatory>Post-authorisation>Pharmacovigilance>Medicines under additional monitoring>List of medicines under additional monitoring

12.13. EudraVigilance database

12.13.1. Activities related to the confirmation of full functionality

None

12.14. Risk management plans and effectiveness of risk minimisations

12.14.1. Risk management systems

None

12.14.2. Tools, educational materials and effectiveness measurement of risk minimisations

None

12.15. Post-authorisation safety studies (PASS)

12.15.1. Post-authorisation Safety Studies – imposed PASS

None

12.15.2. Post-authorisation Safety Studies – non-imposed PASS

None

12.16. Community procedures

12.16.1. Referral procedures for safety reasons

None

12.17. Renewals, conditional renewals, annual reassessments

None

12.18. Risk communication and transparency

12.18.1. Public participation in pharmacovigilance

None

12.18.2. Safety communication

None

12.19. Continuous pharmacovigilance

12.19.1. Incident management

None

12.20. Others

12.20.1. Type II variations – PRAC and CHMP involvement

PRAC lead: Ghania Chamouni, Laurence de Fays, Martin Huber, Eva Segovia, Ulla Wändel Liminga

In line with the PRAC work plan 2019, the EMA Secretariat presented to PRAC a follow-up to the discussion dated June 2018 where PRAC and CHMP agreed with the initiative to revisit PRAC involvement in specific type II variations and a call for creating a working group composed of PRAC and CHMP delegates. This group delivered a proposal to rationalise CHMP and PRAC involvement in type II variations in line with the expertise and legal mandates of the two committees. For further background, see PRAC minutes June 2018. The PRAC agreed with the proposed new rules. The PRAC will lead the assessment of: 1) type II variations resulting from PRAC requests (falling under its remit) made in earlier PSUSA or signal procedures, 2) non-interventional PASS results with product information changes. The Committee highlighted the need to ensure adequate trainings to both EMA and assessors of the National competent Authorities to conduct the assessment of such procedures.

Post-meeting note: On 20 December 2019, the PRAC was informed that the new rules will apply as of January 2020.

13. Any other business

None

14. Annex I – Signals assessment and prioritisation[36]

14.1. New signals detected from EU spontaneous reporting systems

As per agreed criteria for new signal(s), the PRAC adopted without further plenary discussion the recommendation of the Rapporteur to request MAH(s) to submit a cumulative review following standard timetables[37].

14.1.1. Adalimumab – AMGEVITA (CAP), HALIMATOZ (CAP), HEFIYA (CAP), HULIO (CAP), HUMIRA (CAP), HYRIMOZ (CAP), IDACIO (CAP), IMRALDI (CAP), KROMEYA (CAP)

Applicant(s): AbbVie Deutschland GmbH & Co. KG (Humira), Amgen Europe B.V. (Amgevita), Fresenius Kabi Deutschland GmbH (Idacio, Kromeya), Mylan S.A.S (Hulio), Samsung Bioepis NL B.V. (Imraldi), Sandoz GmbH (Halimatoz, Hefiya, Hyrimoz)

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of autoimmune encephalitis

14.1.2. Mycophenolic acid (NAP); mycophenolate mofetil - CELLCEPT (CAP), MYCLAUSEN (CAP), MYCOPHENOLATE MOFETIL TEVA (CAP), MYFENAX (CAP), NAP

Applicant(s): Passauer Pharma GmbH (Myclausen), Roche Registration GmbH (Cellcept), Teva B.V. (Mycophenolate Mofetil Teva, Myfenax)

PRAC Rapporteur: Hans Christian Siersted

Scope: Signal of posterior reversible encephalopathy syndrome (PRES)

EPITT 19473 – New signal

Lead Member State(s): DK

14.1.3. Paroxetine (NAP)

Applicant(s): various

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Signal of microscopic colitis

EPITT 19474 – New signal

Lead Member State(s): NL

[36] Each signal refers to a substance or therapeutic class. The route of marketing authorisation is indicated in brackets (CAP for Centrally Authorised Products; NAP for Nationally Authorised Products including products authorised via Mutual Recognition Procedures and Decentralised Procedure). Product names are listed for reference Centrally Authorised Products (CAP) only. PRAC recommendations will specify the products concerned in case of any regulatory action required

[37] Either MA(s)'s submission within 60 days followed by a 60 day-timetable assessment or MAH's submission cumulative review within an ongoing or upcoming PSUR/PSUSA procedure (if the DLP is within 90 days), and no disagreement has been raised before the meeting

14.1.4. Pazopanib – VOTRIENT (CAP)

Applicant(s): Novartis Europharm Limited

PRAC Rapporteur: Hans Christian Siersted

Scope: Signal of tumour lysis syndrome (TLS)

EPITT 19494 – New signal

Lead Member State(s): DK

14.2. New signals detected from other sources

None

14.3. Signals follow-up and prioritisation

None

15. Annex I – Risk management plans

15.1. Medicines in the pre-authorisation phase

As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of the RMP for the below mentioned medicines under evaluation for initial marketing authorisation application. Information on the medicines containing the below listed active substance(s) will be made available following the CHMP opinion on their marketing authorisation(s).

15.1.1. Cefiderocol - EMEA/H/C/004829

Scope (accelerated assessment): Treatment of infections due to aerobic Gram-negative bacteria

15.1.2. Insulin lispro - EMEA/H/C/005037

Scope: Treatment of diabetes mellitus in adults

15.2. Medicines in the post-authorisation phase – PRAC-led procedures

As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of the variation procedure for the below mentioned medicine(s).

15.2.1. Alirocumab - PRALUENT (CAP) - EMEA/H/C/003882/II/0050/G

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Submission of an updated RMP (version 5.0) in order to amend the list of safety concerns to remove 'cataract (in the context of very low 'low-density lipoprotein cholesterol'

(LDL-C))' as an important potential risk; 'long-term use (>5years)' and 'clinical impact of very low LDL-C for extended period of time' as missing information. As a consequence, the following additional pharmacovigilance activities (listed as category 3 studies in the RMP) are removed from the RMP: 1) study R727-CL-1609: a long term safety study of Praluent (alirocumab) in patients with heterozygous familial hypercholesterolemia or with non-familial hypercholesterolemia at high and very high cardiovascular risk and previously enrolled in the neurocognitive function trial (MEA 016); 2) study OBS14697: a drug utilisation study (DUS) of alirocumab in Europe to assess the effectiveness of the dosing recommendation to avoid very low low-density lipoprotein (LDL)-C levels (MEA 019); 3) study ALIROC07997: a PASS using healthcare databases, in order to monitor the safety of Praluent (alirocumab) in patients affected with the human immunodeficiency virus (HIV) (MEA 017) based on a review of data since the marketing authorisation (MA) was granted including the first interim report for study OBS14697 (in fulfilment of MEA 019.4)

15.2.2. Brinzolamide, brimonidine - SIMBRINZA (CAP) - EMEA/H/C/003698/II/0019

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Submission of an updated RMP (version 3.0) in order to remove 'metabolic acidosis/renal impairment' as an important potential risk from the list of safety concerns and to bring it in line with revision 2 of GVP module V on 'Risk management systems'

15.2.3. Daptomycin - CUBICIN (CAP) - EMEA/H/C/000637/II/0074

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Pernille Harg

Scope: Submission of an updated RMP (version 11.1) in order to delete all risks and additional risk minimisation measures in line with revision 2 of GVP module V on 'Risk management systems'. Annex II is updated accordingly. In addition, the MAH took the opportunity to align the product information with the quality review of documents (QRD) template (version 10.1) and update the list of local representatives

15.2.4. Infliximab - FLIXABI (CAP) - EMEA/H/C/004020/II/0039

Applicant: Samsung Bioepis NL B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of an updated RMP (version 9.0) to replace the current registries with one company-sponsored initiated registry, PERFUSE: one-year persistence to treatment of patients receiving Flixabi (infliximab): a French cohort study; together with three inflammatory bowel disease (IBD) registries, namely: long-term observation registry in German IBD patients (CEDUR), Czech registry of IBD patients on biological therapy (CREDIT) and Dutch network of hospitals IBD registry (DREAM)

15.2.5. Melatonin - SLENYTO (CAP) - EMEA/H/C/004425/II/0010

Applicant: RAD Neurim Pharmaceuticals EEC SARL

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Submission of an updated RMP (version 1.3) to remove 'delay of sexual maturation and development' as an important potential risk based on the results of study NEUCH7911 showing a lack of effect on sexual maturation and growth after 2 years of continuous treatment, and temporary recommendation for use (RTU) data demonstrating a lack of effect on growth after continuous use of up to 3 years

15.3. Medicines in the post-authorisation phase – CHMP-led procedures

As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of the updated versions of the RMP for the below mentioned medicine(s).

15.3.1. Adalimumab - HALIMATOZ (CAP) - EMEA/H/C/004866/X/0013

Applicant: Sandoz GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension application to add a new strength of 20 mg (20 mg/0.4 mL) for Halimatoz (adalimumab) solution for injection in pre-filled syringe. The RMP (version 2.0) is updated accordingly. The MAH took also the opportunity to consolidate the RMP with changes approved in two other procedures (WS1565 and IA/11 finalised in March 2019 and June 2019 respectively) and to align the product information with the latest quality review of documents (QRD) template (version 10.1)

15.3.2. Adalimumab - HEFIYA (CAP) - EMEA/H/C/004865/X/0013

Applicant: Sandoz GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension application to add a new strength of 20 mg (20 mg/0.4 mL) for Hefiya (adalimumab) solution for injection in pre-filled syringe. The RMP (version 2.0) is updated accordingly. The MAH took also the opportunity to consolidate the RMP with changes approved in two other procedures (WS1565 and IA/11 finalised in March 2019 and June 2019 respectively) and to align the product information with the latest quality review of documents (QRD) template (version 10.1)

15.3.3. Adalimumab - HYRIMOZ (CAP) - EMEA/H/C/004320/X/0013

Applicant: Sandoz GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension application to add a new strength of 20 mg (20 mg/0.4 mL) for Hyrimoz (adalimumab) solution for injection in pre-filled syringe. The RMP (version 2.0) is updated accordingly. The MAH took also the opportunity to consolidate the RMP with changes approved in two other procedures (WS1565 and IA/11 finalised in March 2019 and June 2019 respectively) and to align the product information with the latest quality review of documents (QRD) template (version 10.1)

15.3.4. Bevacizumab - AVASTIN (CAP) - EMEA/H/C/000582/II/0110

Applicant: Roche Registration GmbH

PRAC Rapporteur: Hans Christian Siersted

Scope: Submission of the final report from study NEJ026 (listed as a category 1/obligation in Annex II): an open-label, randomised, phase 3 study conducted in Japan to compare erlotinib + bevacizumab combination therapy versus erlotinib monotherapy as first-line therapies for patients with non-small-cell lung carcinoma (NSCLC) with epidermal growth factor receptor (EGFR) gene mutations (exon 19 deletion or exon 21 L858R substitution). The RMP (version 30.0) is updated accordingly. In addition, the package leaflet is updated to reflect information on sodium content in line with the Annex to the European Commission (EC) guideline on 'excipients in the labelling and package leaflet of medicinal products for human use'

15.3.5. Blinatumomab - BLINCYTO (CAP) - EMEA/H/C/003731/II/0030, Orphan

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Eva Jirsová

Scope: Extension of indication to include the treatment of Philadelphia chromosome positive CD19[38] positive B-cell precursor acute lymphoblastic leukaemia (ALL) in adult and paediatric patients with relapsed or refractory ALL and adult patients in first or second complete remission with minimal residual disease (MRD) greater than or equal to 0.1%. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 10.0) are updated accordingly

15.3.6. Canagliflozin - INVOKANA (CAP) - EMEA/H/C/002649/II/0046

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Martin Huber

Scope: Extension of indication to add the treatment of stage 2 or 3 chronic kidney disease (CKD) and albuminuria, as an adjunct to standard of care, in adults with type 2 diabetes mellitus (T2DM), based on new clinical efficacy and safety data from study DNE3001 (CREDENCE): a randomised, double-blind, event-driven, placebo-controlled, multicentre phase 3 study of the effects of canagliflozin on renal and cardiovascular outcomes in subjects with T2DM and diabetic nephropathy. As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 8.1) are updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet

15.3.7. Canagliflozin, metformin - VOKANAMET (CAP) - EMEA/H/C/002656/II/0051

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication to add the treatment of stage 2 or 3 chronic kidney disease

[38] Cluster of differentiation 19

(CKD) and albuminuria, as an adjunct to standard of care, in adults with type 2 diabetes mellitus (T2DM), based on new clinical efficacy and safety data from study DNE3001 (CREDENCE): a randomised, double-blind, event-driven, placebo-controlled, multicentre phase 3 study of the effects of canagliflozin on renal and cardiovascular outcomes in subjects with T2DM and diabetic nephropathy. As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 8.1) are updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet

15.3.8. Darbepoetin alfa - ARANESP (CAP) - EMEA/H/C/000332/II/0150

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Martin Huber

Scope: Update of sections 4.4, 4.8 and 5.1 of the SmPC based on data from: 1) study 20070782: a phase 3, randomised, double-blind, placebo-controlled, non-inferiority study in subjects with chemotherapy-induced anaemia receiving multi-cycle chemotherapy for the treatment of advanced stage non-small cell lung cancer (NSCLC); 2) study EPO-ANE-3010: a randomised, open-label, multicentre, phase 3 study of epoetin alfa plus standard supportive care versus standard supportive care in anaemic patients with metastatic breast cancer receiving standard chemotherapy; 3) the company core data sheet (CCDS). In addition, section 4.6 of the SmPC is revised as requested in the outcome of the PSUR single assessment procedure (PSUSA/00000932/201710) finalised in June 2018. The package leaflet and the RMP (version 9.3) are updated accordingly. Furthermore, the MAH took the opportunity to introduce minor editorial changes, update the information on local representatives and align the product information (PI) with the QRD template (version 10.0)

15.3.9. Dimethyl fumarate - TECFIDERA (CAP) - EMEA/H/C/002601/II/0058

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Martin Huber

Scope: Submission of the final clinical study report (CSR) of study 109MS310 (listed as category 3 study in the RMP): an open-label study to assess the effects of Tecfidera (dimethyl fumarate) on lymphocyte subsets in subjects with relapsing remitting multiple sclerosis (RRMS). The RMP (version 10.1) is updated accordingly, includes updates to reflect safety information available until the data lock point (DLP) of 24 January 2019 and in line with revision 2.01 of the guidance on the format of the risk management plan (RMP) accompanying GVP module V on 'Risk management systems'

15.3.10. Empagliflozin, linagliptin - GLYXAMBI (CAP) - EMEA/H/C/003833/WS1601/0022; Linagliptin, metformin hydrochloride - JENTADUETO (CAP) - EMEA/H/C/002279/WS1601/0051; Linagliptin - TRAJENTA (CAP) - EMEA/H/C/002110/WS1601/0038

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Update of sections 4.2 and 5.1 of the SmPC for Trajenta (linagliptin), update of

sections 4.2, 4.4 and 5.1 of the SmPC for Jentadueto (linagliptin/metformin) and section 5.1 of the SmPC of Glyxambi (empagliflozin/linagliptin) based on the final results from study 1218.74 (CAROLINA) (listed as a category 3 study in the RMP of Jentadueto (linagliptin/metformin) and Trajenta (linagliptin), in fulfilment of Trajenta MEA 008.1 and Jentadueto MEA 001.1): a phase 3 randomised, parallel group, double blind study to evaluate cardiovascular safety of linagliptin versus glimepiride in patients with type 2 diabetes mellitus (T2DM) at high cardiovascular risk. The package leaflet for Trajenta (linagliptin) is updated accordingly. The RMPs (version 13.0 for Jentadueto (linagliptin/metformin) and Trajenta (linagliptin) and version 5.0 for Glyxambi (empagliflozin/linagliptin)) are updated accordingly. In addition, the MAH took the opportunity to make corrections throughout the product information for Glyxambi (empagliflozin/linagliptin) and Jentadueto (linagliptin/metformin) and to introduce corrections to the Bulgarian, French, Swedish translations for Glyxambi (empagliflozin/linagliptin)

15.3.11. Idebenone - RAXONE (CAP) - EMEA/H/C/003834/II/0018, Orphan

Applicant: Santhera Pharmaceuticals (Deutschland) GmbH

PRAC Rapporteur: Amelia Cupelli

Scope: Submission of the final report from study SNT-EAP-001, listed as a specific obligation (SOB11,former SOB4) in Annex II: a follow-up study of patients in the expanded access programme (SNT-EPA-001) for Raxone (idebenone) in the treatment of patients with Leber's hereditary optic neuropathy (LHON) in order to collect further long-term real-world efficacy and safety data. Annex II is updated accordingly. The RMP (version 1.9) is also updated accordingly

15.3.12. Insulin lispro - HUMALOG (CAP) - EMEA/H/C/000088/X/0169

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Annika Folin

Scope: Extension application. The RMP is updated (version 9.3) accordingly and in line with revision 2 of GVP module V on 'Risk management systems'

15.3.13. Insulin lispro - LIPROLOG (CAP) - EMEA/H/C/000393/X/0130

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Annika Folin

Scope: Extension application. The RMP is updated (version 9.3) accordingly and in line with revision 2 of GVP module V on 'Risk management systems'

15.3.14. Lenalidomide - REVLIMID (CAP) - EMEA/H/C/000717/II/0107, Orphan

Applicant: Celgene Europe BV

PRAC Rapporteur: Ghania Chamouni

Scope: Extension of indication to include Revlimid (lenalidomide) in combination with rituximab for the treatment of adult patients with previously treated follicular lymphoma or

marginal zone lymphoma. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 36.2) are updated accordingly

15.3.15. Lumacaftor, ivacaftor - ORKAMBI (CAP) - EMEA/H/C/003954/II/0049

Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Updated of section 4.8 of the SmPC with safety data from study 109: a phase 3, double blind, placebo controlled, parallel group study to evaluate the efficacy and safety of lumacaftor in combination with ivacaftor in subjects aged 6 through 11 years with cystic fibrosis (CF), homozygous for the deletion of phenylalanine in position 508 of the cystic fibrosis transmembrane conductance regulator (F508del-CFTR) mutation; and study 011 Part B (study 011B): a phase 3, open-label study to evaluate the pharmacokinetics, safety, and tolerability of lumacaftor in combination with ivacaftor in subjects 6 through 11 years of age with CF, homozygous for the F508del-CFTR mutation (receiving lumacaftor 200 mg in fixed-dose combination with ivacaftor 250 mg orally q12h for 24 weeks). The RMP (version 7.0) is updated accordingly

15.3.16. Methoxy polyethylene glycol-epoetin beta - MIRCERA (CAP) - EMEA/H/C/000739/II/0068

Applicant: Roche Registration GmbH

PRAC Rapporteur: Eva Segovia

Scope: Submission of the final report for study BH21260 (listed as a category 3 study in the RMP): a randomised, controlled, open-label, multicentre, parallel-group study to assess all-cause mortality and cardiovascular morbidity in patients with chronic kidney disease (CKD) on dialysis and those not on renal replacement therapy under treatment with Mircera (methoxy polyethylene glycol-epoetin beta) or erythropoiesis-stimulating agents (ESAs) of reference (in fulfilment of post-approval commitment MEA 008.5). The RMP (version 12.0) is updated accordingly and in line with revision 2 of the guidance on the format of RMP in the EU (template)

15.3.17. Netupitant, palonosetron - AKYNZEO (CAP) - EMEA/H/C/003728/X/0018

Applicant: Helsinn Birex Pharmaceuticals Limited

PRAC Rapporteur: Ilaria Baldelli

Scope: Extension application to introduce a new pharmaceutical form ‘powder for concentrate for solution for infusion’ and a new strength for the fixed combination of fosnetupitant (pro-drug of netupitant)/palonosetron of 235 mg/0.25 mg, to be administered intravenously (new route of administration). The RMP (version 2.4) is updated accordingly

15.3.18. Nintedanib - OFEV (CAP) - EMEA/H/C/003821/II/0026, Orphan

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Extension of indication to include a new indication for the treatment of systemic

sclerosis associated interstitial lung disease (SSc-ILD). As a consequence, sections 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 7.0) are updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet and to introduce minor linguistic corrections to the Annexes in French and Swedish

15.3.19. Pegfilgrastim - UDENYCA (CAP) - EMEA/H/C/004413/II/0003

Applicant: ERA Consulting GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Update of section 4.6 of the SmPC to amend the safety information based on feasibility data regarding the pregnancy and lactation registry (listed as a category 3 study in the RMP). The package leaflet and the RMP (version 1.5) are updated accordingly

15.3.20. Pemetrexed - PEMETREXED FRESENIUS KABI (CAP) - EMEA/H/C/003895/X/0009

Applicant: Fresenius Kabi Deutschland GmbH

PRAC Rapporteur: Ghania Chamouni

Scope: Extension application to introduce a new pharmaceutical form (concentrate for solution for infusion) associated with new strength 25 mg/mL. The RMP (version 2.0) is updated accordingly

15.3.21. Ravulizumab - ULTOMIRIS (CAP) - EMEA/H/C/004954/II/0002

Applicant: Alexion Europe SAS

PRAC Rapporteur: Kimmo Jaakkola

Scope: Extension of indication to include the treatment of patients with atypical haemolytic uremic syndrome (aHUS). As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated. The package leaflet and the RMP (version 1.6) are updated accordingly. In addition, Annex II-D on 'Conditions or restrictions with regard to the safe and effective use of the medicinal product' is updated to include in the educational materials the risk of thrombotic microangiopathy (TMA) with the new indication

15.3.22. Saxagliptin, dapagliflozin - QTERN (CAP) - EMEA/H/C/004057/II/0024

Applicant: AstraZeneca AB

PRAC Rapporteur: Ilaria Baldelli

Scope: Update of sections 4.2, 4.4 and 5.1 of the SmPC with information on the glycaemic efficacy and renal safety of dapagliflozin in patients with type 2 diabetes mellitus (T2DM) and moderate renal impairment (chronic kidney disease (CKD) 3A) based on final results from study D1690C00024 (DERIVE) (dapagliflozin): a multicentre, double-blind, placebo-controlled, parallel group, randomised, phase 3 study to evaluate the glycaemic efficacy and renal safety of dapagliflozin in patients with T2DM and CKD 3A who have inadequate glycaemic control, and to reflect a change in renal cut-off value for saxagliptin. The package leaflet and the RMP (version 4.1) are updated accordingly. In addition, the MAH took the opportunity to update section 2, 4.8, 5.2 of the SmPC and Annex II to include the required

excipient information in relation to sodium levels and lactose following the update to the Annex to the European Commission (EC) guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use', as well as to bring the product information in line with the EMA guidance on 'Compilation of quality review of documents (QRD) decisions on stylistic matters in product information' (EMA/25090/2002 Rev.18)

15.3.23. Sonidegib - ODOMZO (CAP) - EMEA/H/C/002839/II/0024

Applicant: Sun Pharmaceutical Industries Europe B.V.

PRAC Rapporteur: Željana Margan Koletić

Scope: Submission of the final report of study CLDE225X2116 (listed as a category 3 study in the RMP): an interventional phase 1b/2, open-label, multicentre, dose-finding study to assess the safety and efficacy of the oral combination of LDE225 (sonidegib) and INC424 (ruxolitinib) in subjects with myelofibrosis. The RMP (version 7.1) is updated accordingly

15.3.24. Ticagrelor - BRILIQUE (CAP) - EMEA/H/C/001241/II/0047/G

Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: Grouped variations consisting of 1) extension of indication to include in co administration with acetylsalicylic acid (ASA) the prevention of atherothrombotic events in adult patients with coronary artery disease (CAD) and type 2 diabetes mellitus (T2DM) without a history of myocardial infarction who have undergone percutaneous coronary intervention (PCI) based on the final results of study D513BC00001 (THEMIS): a phase 3 multinational, randomised, double-blind, placebo controlled study to evaluate the effect of ticagrelor twice daily on the incidence of cardiovascular death, myocardial infarction or stroke in patients with T2DM. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated; 2) update of section 4.8 of the SmPC with new safety information on traumatic haemorrhages based on the final results from study D513BC00001 (THEMIS) and data from the ticagrelor clinical development programme and post-marketing data. The Package Leaflet and the RMP (version 12) are updated accordingly

15.3.25. Turoctocog alfa - NOVOEIGHT (CAP) - EMEA/H/C/002719/II/0030/G

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Grouped variations consisting of submission of: 1) results of study NN7008-3809 (Guardian 4): safety and efficacy of turoctocog alfa in prevention and treatment of bleeds in paediatric previously untreated patients (PUPs) with haemophilia A and; 2) results of study NN7008-4239 (Guardian 9): a multicentre, open-label trial evaluating the pharmacokinetics (PK) of NovoEight (turoctocog alfa) in relation to body mass index (BMI) in subjects with haemophilia A. In addition, the product information is brought in line with revision 3 of the 'Guideline on core SmPC for human plasma derived and recombinant coagulation factor VIII products' (EMA/CHMP/BPWP/1619/1999 rev. 3) and in line with the Annex to the European Commission (EC) guideline on 'excipients in the labelling and package leaflet of medicinal products for human use'. Sections 2, 4.2, 4.4, 4.5, 4.6, 4.8, 5.1 and 5.2 of the SmPC and the package leaflet are updated accordingly. The RMP (version 6) is also updated

accordingly. Furthermore, the MAH took the opportunity to introduce some administrative updates in the product information

15.3.26. Vemurafenib - ZELBORAF (CAP) - EMEA/H/C/002409/II/0054

Applicant: Roche Registration GmbH

PRAC Rapporteur: Annika Folin

Scope: Update of sections 4.4 and 4.5 of the SmPC in order to add information and a precaution regarding concomitant use of strong cytochrome P450 3A4 (CYP3A4) inhibitors based on final results from study GO29475 (MEA-011) (listed as a category 3 study in the RMP): a two-part, phase 1, open-label, multicentre, two-period, one-sequence study to investigate the effect of itraconazole and rifampicin on the pharmacokinetic (PK) of vemurafenib at steady state. The package leaflet and the RMP (version 12.0) are updated accordingly. In addition, the package leaflet is updated to reflect information on sodium content in line with the Annex to the European Commission (EC) guideline on 'excipients in the labelling and package leaflet of medicinal products for human use'

15.3.27. Vernakalant - BRINAVESS (CAP) - EMEA/H/C/001215/II/0035

Applicant: Correvio

PRAC Rapporteur: Menno van der Elst

Scope: Update of sections 4.4 and 4.8 of the SmPC in order to add a warning and update the safety information following updates to the company core safety datasheet (CCDS) based on the results of an integrated safety analysis performed on data of existing clinical studies with a stronger emphasis on treatment-related adverse drug reactions (ADRs) and an incidence rate above one percent. The package leaflet and the RMP (version 7.0) are updated accordingly. In addition, the RMP is updated in line with the results from the completed observational cohort SPECTRUM study (study 6621-049): a prospective observational registry study to characterise normal conditions of use, dosing and safety following administration of vernakalant intravenous (IV) sterile concentrate assessed in variation II/34. Furthermore, the MAH took the opportunity to update sections 4.2, 4.4, 4.6, 4.7, 4.8, 5.1, 5.2, 5.3, 6.4 of the SmPC, Annex II, labelling and package leaflet in order to include editorial changes, to correct typographical errors and to bring the product information in line with the latest quality review of documents (QRD) template (version 10). The package leaflet is also updated in line with the European Commission (EC) guideline on 'excipients in the labelling and package leaflet of medicinal products for human use' and the EMA Annex to the EC guideline

16. Annex I - Periodic safety update reports (PSURs)

Based on the assessment of the following PSURs, the PRAC concluded that the benefit-risk balance of the below mentioned medicines remains favourable in the approved indication(s) and adopted a recommendation to maintain the current terms of the marketing authorisation(s) together with the assessment report. As per agreed criteria, the procedures listed below were finalised at the PRAC level without further plenary discussion.

The next PSURs should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive

2001/83/EC and published on the European medicines web-portal, unless changes apply as stated in the outcome of the relevant PSUR/PSUSA procedure(s).

16.1. PSUR single assessment (PSUSA) procedures including centrally authorised products (CAPs) only

16.1.1. Abemaciclib - VERZENIOS (CAP) - PSUSA/00010724/201903

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Evaluation of a PSUSA procedure

16.1.2. Alogliptin – VIPIDIA (CAP); alogliptin, metformin - VIPDOMET (CAP); alogliptin, pioglitazone - INCRESYNC (CAP) - PSUSA/00010061/201904

Applicant(s): Takeda Pharma A/S

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.3. Aprepitant - EMEND (CAP) - PSUSA/00000229/201903

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

16.1.4. Bezlotoxumab - ZINPLAVA (CAP) - PSUSA/00010576/201904

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.5. Cariprazine - REAGILA (CAP) - PSUSA/00010623/201904

Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.1.6. Chenodeoxycholic acid[39] - CHENODEOXYCHOLIC ACID LEADIANT (CAP) - PSUSA/00010590/201904

Applicant: Leadiant GmbH

PRAC Rapporteur: Adam Przybylkowski

[39] Indicated for the treatment of inborn errors of primary bile acid synthesis due to sterol 27 hydroxylase deficiency (presenting as cerebrotendinous xanthomatosis (CTX)) in infants, children and adolescents aged 1 month to 18 years and adults – centrally authorised product(s) only

Scope: Evaluation of a PSUSA procedure

16.1.7. Defibrotide - DEFITELIO (CAP) - PSUSA/00010086/201904

Applicant: Gentium S.r.l.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.8. Diphtheria, tetanus, pertussis antigens (pertussis toxoid, filamentous haemagglutinin) (acellular, component), hepatitis b (rDNA40), poliomyelitis (inactivated), haemophilus type b conjugate vaccines (adsorbed) – HEXAXIM (Art 5841); HEXACIMA (CAP); HEXYON (CAP) - PSUSA/00010091/201904

Applicants: Sanofi Pasteur (Hexaxim, Hexacima), Sanofi Pasteur Europe (Hexyon)

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.9. Dupilumab - DUPIXENT (CAP) - PSUSA/00010645/201903

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

16.1.10. Empagliflozin – JARDIANCE (CAP); empagliflozin, metformin - SYNJARDY (CAP) - PSUSA/00010388/201904

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

16.1.11. Emtricitabine - EMTRIVA (CAP) - PSUSA/00001209/201904

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.1.12. Emtricitabine, tenofovir alafenamide - DESCOVY (CAP) - PSUSA/00010515/201904

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

[40] Ribosomal deoxyribonucleic acid
[41] Article 58 of Regulation (EC) No 726/2004 allows the Committee for Medicinal Products for Human Use (CHMP) to give opinions, in co-operation with the World Health Organisation (WHO) on medicinal products for human use that are intended exclusively for markets outside of the European Union (EU)

16.1.13. Emtricitabine, tenofovir disoproxil - TRUVADA (CAP) - PSUSA/00001210/201904

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.1.14. Exenatide - BYDUREON (CAP); BYETTA (CAP) - PSUSA/00009147/201903

Applicant: AstraZeneca AB

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

16.1.15. Febuxostat - ADENURIC (CAP) - PSUSA/00001353/201904

Applicant: Menarini International Operations Luxembourg S.A.

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.1.16. Fenofibrate, pravastatin - PRAVAFENIX (CAP) - PSUSA/00001363/201904

Applicant: Laboratoires SMB s.a.

PRAC Rapporteur: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

16.1.17. Florbetapir (^{18}F) - AMYVID (CAP) - PSUSA/00010032/201904

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.18. Fosaprepitant - IVEMEND (CAP) - PSUSA/00001471/201903

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

16.1.19. Glycopyrronium bromide, formoterol fumarate dihydrate - BEVESPI AEROSPHERE (CAP) - PSUSA/00010739/201904 (with RMP)

Applicant: AstraZeneca AB

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.1.20. Herpes zoster vaccine (recombinant, adjuvanted) - SHINGRIX (CAP) - PSUSA/00010678/201904

Applicant: GlaxoSmithkline Biologicals SA

PRAC Rapporteur: Sonja Hrabcik

Scope: Evaluation of a PSUSA procedure

16.1.21. Histamine[42] - CEPLENE (CAP) - PSUSA/00001610/201904

Applicant: Noventia Pharma Srl

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

16.1.22. Insulin glulisine - APIDRA (CAP) - PSUSA/00001752/201904

Applicant: Sanofi-Aventis Deutschland GmbH

PRAC Rapporteur: Hans Christian Siersted

Scope: Evaluation of a PSUSA procedure

16.1.23. Irinotecan[43] - ONIVYDE (CAP) - PSUSA/00010534/201904

Applicant: Les Laboratoires Servier

PRAC Rapporteur: David Olsen

Scope: Evaluation of a PSUSA procedure

16.1.24. Mannitol[44] - BRONCHITOL (CAP) - PSUSA/00009226/201904

Applicant: Pharmaxis Europe Limited

PRAC Rapporteur: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

16.1.25. Meningococcal group A, C, W-135, Y conjugate vaccine (conjugated to tetanus toxoid carrier protein) - NIMENRIX (CAP) - PSUSA/00010044/201904

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: David Olsen

Scope: Evaluation of a PSUSA procedure

16.1.26. Methylnaltrexone bromide - RELISTOR (CAP) - PSUSA/00002023/201903

Applicant: PharmaSwiss Ceska Republika s.r.o

[42] Indicated for the treatment of acute myeloid leukaemia (AML)
[43] Liposomal formulation(s) only
[44] Indicated for the treatment of cystic fibrosis

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.27. Mogamulizumab - POTELIGEO (CAP) - PSUSA/00010741/201903

Applicant: Kyowa Kirin Holdings B.V.

PRAC Rapporteur: Hans Christian Siersted

Scope: Evaluation of a PSUSA procedure

16.1.28. Oestrogens conjugated, bazedoxifene - DUAVIVE (CAP) - PSUSA/00010321/201904

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.29. Parathyroid hormone - NATPAR (CAP) - PSUSA/00010591/201904

Applicant: Shire Pharmaceuticals Ireland Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

16.1.30. Patiromer - VELTASSA (CAP) - PSUSA/00010618/201904

Applicant: Vifor Fresenius Medical Care Renal Pharma France

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

16.1.31. Propranolol[45] - HEMANGIOL (CAP) - PSUSA/00010250/201904

Applicant: Pierre Fabre Dermatologie

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

16.1.32. Ramucirumab - CYRAMZA (CAP) - PSUSA/00010323/201904

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.33. Regadenoson - RAPISCAN (CAP) - PSUSA/00002616/201904

Applicant: GE Healthcare AS

[45] Centrally authorised product(s) only

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

16.1.34. Siltuximab - SYLVANT (CAP) - PSUSA/00010254/201904

Applicant: EUSA Pharma (Netherlands) B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.35. Tocilizumab - ROACTEMRA (CAP) - PSUSA/00002980/201904

Applicant: Roche Registration GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.36. Vandetanib - CAPRELSA (CAP) - PSUSA/00009327/201904

Applicant: Genzyme Europe BV

PRAC Rapporteur: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

16.2. PSUR single assessment (PSUSA) procedures including centrally authorised products (CAPs) and nationally authorised products (NAPs)

16.2.1. Enoxaparin[46] - INHIXA (CAP); NAP - PSUSA/00010553/201904

Applicant(s): Techdow Europe AB (Inhixa), various

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.2.2. Travoprost - IZBA (CAP); TRAVATAN (CAP); NAP - PSUSA/00003011/201902

Applicant(s): Novartis Europharm Limited (Izba, Travatan), various

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

16.2.3. Zonisamide - ZONEGRAN (CAP); NAP - PSUSA/00003152/201903

Applicant(s): Eisai GmbH (Zonegran), various

PRAC Rapporteur: Ronan Grimes

Scope: Evaluation of a PSUSA procedure

[46] Biosimilar(s) only

16.3. PSUR single assessment (PSUSA) procedures including nationally authorised products (NAPs) only

16.3.1. Ambrosia artemisiifolia[47] [48] [49] [50] (NAP) - PSUSA/00010693/201904

Applicant(s): various

PRAC Lead: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.3.2. Alprazolam (NAP) - PSUSA/00000109/201903

Applicant(s): various

PRAC Lead: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

16.3.3. Amifostine (NAP) - PSUSA/00000142/201903

Applicant(s): various

PRAC Lead: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

16.3.4. Dermatophagoides pteronyssinus, Dermatophagoides farina[51] [52] [53] (NAP) - PSUSA/00010582/201903

Applicant(s): various

PRAC Lead: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.3.5. Enoxaparin[54] (NAP) - PSUSA/00010560/201904

Applicant(s): various

PRAC Lead: Nikica Mirošević Skvrce

Scope: Evaluation of a PSUSA procedure

16.3.6. Germanium (^{68}Ge) chloride, gallium (^{68}Ga) chloride (NAP) - PSUSA/00010364/201903

Applicant(s): various

PRAC Lead: Eva Jirsová

[47] 302
[48] Allergen for therapy
[49] For sublingual use only
[50] Medicinal product(s) authorised via decentralised procedure only
[51] Allergen for therapy
[52] For oromucosal use only
[53] Medicinal product(s) authorised via mutual recognition procedure and decentralised procedure only
[54] Except biosimilar(s)

Scope: Evaluation of a PSUSA procedure

16.3.7. Influenza vaccine (split virion, inactivated)[55] (NAP) - PSUSA/00010298/201903

Applicant(s): various

PRAC Lead: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.3.8. Influenza vaccine (split virion, inactivated, prepared in cell cultures) (NAP) - PSUSA/00010299/201903

Applicant(s): various

PRAC Lead: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.3.9. Influenza vaccine (surface antigen, inactivated) (NAP) - PSUSA/00001744/201903

Applicant(s): various

PRAC Lead: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.3.10. Influenza vaccine (surface antigen, inactivated, adjuvanted) (NAP) - PSUSA/00010300/201903

Applicant(s): various

PRAC Lead: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.3.11. Nicorandil (NAP) - PSUSA/00002152/201902

Applicant(s): various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.4. Follow-up to PSUR/PSUSA procedures

16.4.1. Saxagliptin - ONGLYZA (CAP) - EMEA/H/C/001039/LEG 040

Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: Discussion on the association between bullous pemphigoid and saxagliptin/metformin and saxagliptin as a single active substance as requested in the conclusions of PSUSA/00002686/201811 for saxagliptin/metformin adopted in June 2019

[55] Non centrally authorised product(s) only

16.4.2. Saxagliptin, metformin hydrochloride - KOMBOGLYZE (CAP) - EMEA/H/C/002059/LEG 018

Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: Discussion on the association between bullous pemphigoid and saxagliptin/metformin and saxagliptin as a single active substance as requested in the conclusions of PSUSA/00002686/201811 for saxagliptin/metformin adopted in June 2019

17. Annex I – Post-authorisation safety studies (PASS)

Based on the assessment of the following PASS protocol(s), result(s), interim result(s) or feasibility study(ies), and following endorsement of the comments received, the PRAC adopted the conclusion of the Rapporteurs on their assessment for the medicines listed below without further plenary discussion.

17.1. Protocols of PASS imposed in the marketing authorisation(s)[56]

17.1.1. Axicabtagene ciloleucel - YESCARTA (CAP) - EMEA/H/C/PSP/S/0079.2

Applicant: Kite Pharma EU B.V., ATMP[57]

PRAC Rapporteur: Anette Kirstine Stark

Scope: MAH's response to PSP/S/0079.1 [protocol for a long-term, non-interventional study in patients taking Yescarta (axicabtagene ciloleucel) for the treatment of relapsed or refractory diffuse large B-cell lymphoma and primary mediastinal B-cell lymphoma to evaluate the safety of patients, including secondary malignancies, cytokine release syndrome (CRS), neurologic events, serious infections, prolonged cytopenias, hypogammaglobulinaemia and pregnancy outcomes in female patients of childbearing potential] as per the request for supplementary information (RSI) adopted in October 2019

17.1.2. Ketoconazole - KETOCONAZOLE HRA (CAP) - EMEA/H/C/PSA/S/0043

Applicant: Laboratoire HRA Pharma

PRAC Rapporteur: Željana Margan Koletić

Scope: Substantial amendment to a protocol previously endorsed in September 2017 for a prospective, multi-country, observational registry to collect clinical information on patients with endogenous Cushing's syndrome exposed to ketoconazole using the existing European Registry on Cushing's Syndrome (ERCUSYN) in order to assess drug utilisation pattern and to document the safety (e.g. hepatotoxicity, QT prolongation) and effectiveness of ketoconazole

17.1.3. Levonorgestrel (NAP) - EMEA/H/N/PSA/S/0044

Applicant: Bayer Pharma AG (Jaydess, Luadei)

[56] In accordance with Article 107n of Directive 2001/83/EC
[57] Advanced therapy medicinal product

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Substantial amendment to a protocol previously endorsed in February 2018 for study EURAS-LCS12: a European active surveillance study of LCS-12 (levonorgestrel intrauterine contraceptive system releasing 12 µg levonorgestrel/24h in vitro), an intra-uterine device (IUD) for Jaydess and Luadei (levonorgestrel) to investigate whether LCS-12 is associated with an increased risk of unintended pregnancy compared to Mirena (levonorgestrel-releasing intrauterine system) and to copper IUDs

17.1.4. Nonacog beta pegol - REFIXIA (CAP) - EMEA/H/C/PSA/S/0041.1

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: MAH's response to PSA/S/0041 [amendment to a protocol previously endorsed in June 2018 (PSP/S/0059) for a non-interventional PASS in male patients with haemophilia B receiving nonacog beta pegol (N9-GP) prophylaxis treatment to investigate safety of N9-GP during long-term routine use] as per the request for supplementary information (RSI) adopted in September 2019

17.1.5. Oral retinoids: acitretin (NAP), alitretinoin (NAP), isotretinoin (NAP) - EMEA/H/N/PSP/J/0069.2

Applicant(s): F. Hoffmann-La Roche Ltd. (on behalf of a consortium)

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: MAH's response to PSP/J/0069 [protocol for a joint drug utilisation study (DUS) to describe the prescribing practices before and after the update of the pregnancy prevention programme (PPP) for the following oral retinoids: acitretin, alitretinoin and isotretinoin in order to assess the effectiveness of the updated risk minimisation measures (RMMs) in women of childbearing potential, as required in the outcome of the referral procedure under Article 31 of Directive 2001/83/EC for retinoids for oral use completed in 2018 (EMEA/H/A-31/1446)] as per the request for supplementary information (RSI) adopted in June 2019

17.1.6. Tisagenlecleucel - KYMRIAH (CAP) - EMEA/H/C/PSP/S/0066.3

Applicant: Novartis Europharm Ltd, ATMP[58]

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: MAH's response to PSA/S/0066.2 [protocol for non-interventional study CCTL019B2401 with secondary use of data from two registries conducted by the 'European Society for Blood and Marrow Transplantation' (EBMT) and 'Centre for International Blood and Marrow Transplant Research' (CIBMTR) to evaluate the long term safety of patients with B lymphocyte malignancies treated with tisagenlecleucel (chimeric antigen receptor (CAR)-T cell therapy) in a real-world setting] as per the request for supplementary information (RSI) adopted in October 2019

[58] Advanced therapy medicinal product

17.1.7. Umeclidinium bromide – INCRUSE ELLIPTA (CAP), ROLUFTA ELLIPTA (CAP); umeclidinium bromide, vilanterol – ANORO ELLIPTA (CAP), LAVENTAIR ELLIPTA (CAP) - EMEA/H/C/PSA/S/0032.3

Applicant: Glaxo Group Limited

PRAC Rapporteur: Ilaria Baldelli

Scope: MAH's response to PSA/S/0032.1 [substantial amendment to a protocol previously endorsed by PRAC in March 2015 (EMEA/H/C/PSP/J/003.1) for study 201038: a post-authorisation safety (PAS) observational cohort study to quantify the incidence of selected cardiovascular and cerebrovascular events in chronic obstructive pulmonary disease (COPD) patients using inhaled umeclidinium bromide/vilanterol (UMEC/VI) combination, inhaled UMEC, or tiotropium] as per the request for supplementary information (RSI) adopted in March 2019

17.1.8. Valproate (NAP) - EMEA/H/N/PSP/J/0074.1

Applicant(s): Sanofi-aventis Recherche & Development (on behalf of a consortium)

PRAC Rapporteur: Jean-Michel Dogné

Scope: MAH's response to PSP/J/0074 [protocol for an observational study to evaluate and identify the best practices for switching of valproate in clinical practice, as required in the outcome of the referral procedure under Article 31 of Directive 2001/83/EC on valproate-containing products completed in February 2018 (EMEA/H/A-31/1454)] as per the request for supplementary information (RSI) adopted in February 2019

17.2. Protocols of PASS non-imposed in the marketing authorisation(s)[59]

17.2.1. Dimethyl fumarate - TECFIDERA (CAP) - EMEA/H/C/002601/MEA 008.3

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Martin Huber

Scope: MAH's response to MEA 008.2 [updated protocol for study 109MS402: Biogen multiple sclerosis (MS) pregnancy exposure registry to prospectively evaluate pregnancy outcomes in women with MS who were exposed to a registry-specified Biogen MS product during the eligibility window for that product] as per the request for supplementary information (RSI) adopted in June 2019

17.2.2. Epoetin zeta - RETACRIT (CAP) - EMEA/H/C/000872/MEA 033

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Martin Huber

Scope: Substantial amendment to a protocol previously agreed in September 2015 (MEA 031.1) for study PMS-830-09-0082 (PASCO II): a post-authorisation safety cohort observation of Retacrit (epoetin zeta) administered subcutaneously for the treatment of renal anaemia

[59] In accordance with Article 107m of Directive 2001/83/EC, supervised by PRAC in accordance with Article 61a (6) of Regulation (EC) No 726/2004

17.2.3. Epoetin zeta - SILAPO (CAP) - EMEA/H/C/000760/MEA 033

Applicant: Stada Arzneimittel AG

PRAC Rapporteur: Martin Huber

Scope: Substantial amendment to a protocol previously agreed in September 2015 (Retacrit, MEA 031.1) for study PMS-830-09-0082 (PASCO II): a post-authorisation safety cohort observation of Silapo (epoetin zeta) administered subcutaneously for the treatment of renal anaemia

17.2.4. Hydrocortisone - PLENADREN (CAP) - EMEA/H/C/002185/MEA 009.1

Applicant: Shire Services BVBA

PRAC Rapporteur: Annika Folin

Scope: Amendment to protocol for study SHP617-400 (EU AIR) (0918-400): a non-interventional (PASS) registry study: A European multicentre, multi-country, post-authorisation observational study (registry) of patients with chronic adrenal insufficiency

17.2.5. Inotersen - TEGSEDI (CAP) - EMEA/H/C/004782/MEA 001.2

Applicant: Akcea Therapeutics Ireland Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: MAH's response to MEA 001.1 [protocol for a long-term observational study to evaluate and further characterise the events of thrombocytopenia, glomerulonephritis and retinal toxicity/eye disease related to vitamin A deficiency when Tegsedi (inotersen) is prescribed in normal clinical practice, consisting of a protocol for a cohort of inotersen-exposed patients (TEG4001) and a protocol for an external comparator cohort (TEG4003)] as per the request for supplementary information (RSI) adopted in June 2019

17.2.6. Inotersen - TEGSEDI (CAP) - EMEA/H/C/004782/MEA 002.2

Applicant: Akcea Therapeutics Ireland Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: MAH's response to MEA 002.1 [protocol for study TEG4002: a retrospective chart review for evaluating adherence to and effectiveness of the proposed platelet monitoring schedule, proposed cut-off points, dose adaptation, and initiation of corticosteroids on thrombocyte recovery] as per the request for supplementary information (RSI) adopted in June 2019

17.2.7. Niraparib - ZEJULA (CAP) - EMEA/H/C/004249/MEA 003.3

Applicant: Tesaro Bio Netherlands B.V.

PRAC Rapporteur: Jan Neuhauser

Scope: MAH's response to MEA 003.2 [protocol and statistical analysis plan for a non-interventional non-imposed PASS: a pooled analysis of the incidence of acute myelogenous leukaemia, myelodysplastic syndrome, and other secondary primary malignancies in

patients treated with niraparib] as per the request for supplementary information (RSI) adopted in May 2019

17.2.8. Risankizumab - SKYRIZI (CAP) - EMEA/H/C/004759/MEA 001

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Protocol for study P19-633: a post-marketing registry-based prospective cohort study of long-term safety of risankizumab in real world setting in Denmark and Sweden [final study report due in December 2031]

17.2.9. Risankizumab - SKYRIZI (CAP) - EMEA/H/C/004759/MEA 002

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Protocol for study P16-751 on pregnancy exposures and outcomes in psoriasis patients treated with risankizumab: a cohort study utilising large healthcare databases with mother-baby linkage in the United States [final study report due in Q3 2026]

17.2.10. Sotagliflozin - ZYNQUISTA (CAP) - EMEA/H/C/004889/MEA 004

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Martin Huber

Scope: Protocol for a PASS to evaluate the risk of malignancies (bladder, renal, breast, Leydig cell, pancreatic, thyroid, and prostate cancers) in adult patients with type 1 diabetes mellitus (T1DM) using sotagliflozin [final clinical study report (CSR) expected in April 2030] (from initial opinion/MA)

17.2.11. Ulipristal acetate - ESMYA (CAP) - EMEA/H/C/002041/MEA 028.2

Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Annika Folin

Scope: MAH's response to MEA 028.1 [protocol for study PGL18-001: a retrospective drug utilisation study (DUS) through a chart review across four major EU countries [final study report expected by Q2 2020], as requested in the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 completed in May 2018 (EMEA/H/A-20/1460)] as per the request for supplementary information (RSI) adopted in June 2019

17.3. Results of PASS imposed in the marketing authorisation(s)[60]

None

[60] In accordance with Article 107p-q of Directive 2001/83/EC

17.4. Results of PASS non-imposed in the marketing authorisation(s)[61]

17.4.1. Canagliflozin - INVOKANA (CAP) - EMEA/H/C/002649/II/0045/G

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Martin Huber

Scope: Grouped variations consisting of the submission of the final reports for three non-interventional studies (listed as category 3 studies in the RMP): 1) study RRA-21410: an epidemiology study to characterise the risk of lower limb amputations (LLA) in subjects in the overall type 2 diabetes mellitus (T2DM) population and in a subpopulation with established cardiovascular disease (CVD); 2) study NAP4001: a meta-analysis from studies DIA3008 (CANVAS: a randomised, multicentre, double-blind, parallel, placebo-controlled study of the effects of JNJ-28431754 (canagliflozin) on cardiovascular outcomes in adult subjects with type 2 diabetes mellitus (T2DM)), DIA4003 (CANVAS-R: a randomised, multicentre, double-blind, parallel, placebo-controlled study of the effects of canagliflozin on renal endpoints in adult subjects with T2DM), and DNE3001 (CREDENCE: a randomised, double-blind, event-driven, placebo-controlled, multicentre study of the effects of canagliflozin on renal and cardiovascular outcomes in subjects with T2DM and diabetic nephropathy) to characterise the risk of LLA in subjects at high risk for cardiovascular (CV) events and/or progression of kidney disease; 3) meta-analysis from CANVAS, CANVAS-R and CREDENCE to evaluate the incidence of bladder cancer in the canagliflozin group compared to the placebo group

17.4.2. Canagliflozin, metformin - VOKANAMET (CAP) - EMEA/H/C/002656/II/0050/G

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Menno van der Elst

Scope: Grouped variations consisting of the submission of the final reports for three non-interventional studies (listed as category 3 studies in the RMP): 1) study RRA-21410: an epidemiology study to characterise the risk of lower limb amputations (LLA) in subjects in the overall type 2 diabetes mellitus (T2DM) population and in a subpopulation with established cardiovascular disease (CVD); 2) study NAP4001: a meta-analysis from studies DIA3008 (CANVAS: a randomised, multicentre, double-blind, parallel, placebo-controlled study of the effects of JNJ-28431754 (canagliflozin) on cardiovascular outcomes in adult subjects with type 2 diabetes mellitus (T2DM)), DIA4003 (CANVAS-R: a randomised, multicentre, double-blind, parallel, placebo-controlled study of the effects of canagliflozin on renal endpoints in adult subjects with T2DM), and DNE3001 (CREDENCE: a randomised, double-blind, event-driven, placebo-controlled, multicentre study of the effects of canagliflozin on renal and cardiovascular outcomes in subjects with T2DM and diabetic nephropathy) to characterise the risk of LLA in subjects at high risk for cardiovascular (CV) events and/or progression of kidney disease; 3) meta-analysis from CANVAS, CANVAS-R and CREDENCE to evaluate the incidence of bladder cancer in the canagliflozin group compared to the placebo group

[61] In accordance with Article 61a (6) of Regulation (EC) No 726/2004, in line with the revised variations regulation for any submission as of 4 August 2013

17.4.3. Colistimethate sodium - COLOBREATHE (CAP) - EMEA/H/C/001225/II/0044/G

Applicant: Teva B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Grouped variations consisting of the submission of the final report for study CLB-MD-05 (listed as a category 3 study in the RMP): an observational safety study of Colobreathe (colistimethate sodium dry powder for inhalation) compared with other inhaled anti-pseudomonal antibiotics in cystic fibrosis patients using cystic fibrosis registries. The RMP (version 9.0) is updated accordingly, together with the results from study CLB-MD-08: (listed as a category 3 study in the RMP): a non-interventional PASS cross-sectional survey study to evaluate the effectiveness of Colobreathe (colistimethate sodium) risk minimisation educational programme among healthcare professionals and patients, as per the outcome of variation II/39 adopted in February 2019

17.4.4. Etanercept - ENBREL (CAP) - EMEA/H/C/000262/WS1654/0228; LIFMIOR (CAP) - EMEA/H/C/004167/WS1654/0022

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Eva Segovia

Scope: Submission of the final report from study B1801311 (British Association of Dermatologists Biologics and Immunomodulators Register (BADBIR)) (listed as a category 3 study in the RMP): a prospective cohort study that compared patients treated with biologic interventions (etanercept, adalimumab and ustekinumab) and patients with similar disease characteristics but exposed only to conventional non-biologic systemic therapies

17.4.5. Lenalidomide - REVLIMID (CAP) - EMEA/H/C/000717/II/0110, Orphan

Applicant: Celgene Europe BV

PRAC Rapporteur: Ghania Chamouni

Scope: Submission of the final results of study CC-5013-PASS-001: a non-interventional PASS to characterise and determine the incidence of adverse events of special interest specifically neutropenia, thrombocytopenia, acute and opportunistic infections, bleeding events, venous thromboembolism, cardiac disorders, neuropathy, rash, hypersensitivity, hypothyroidism and renal failure in subjects treated with lenalidomide in a naturalistic setting

17.4.6. Nalmefene - SELINCRO (CAP) - EMEA/H/C/002583/II/0025

Applicant: H. Lundbeck A/S

PRAC Rapporteur: Martin Huber

Scope: Submission for the final study reports for: 1) study 15649A on the use of Selincro (nalmefene) using European databases: a cohort design study using longitudinal electronic medical records or claims databases; 2) study 14910A: a non-interventional multi-country prospective cohort study to investigate the pattern of use of Selincro (nalmefene) and frequency of selected adverse reactions in routine clinical practice

17.4.7. Riociguat - ADEMPAS (CAP) - EMEA/H/C/002737/II/0030, Orphan

Applicant: Bayer AG

PRAC Rapporteur: Kimmo Jaakkola

Scope: Submission of the final report for study 16657, EXPERT (EXPosurE Registry RiociguaT in patients with pulmonary hypertension) (listed as a category 3 study in the RMP) to collect information about the long term use of Adempas (riociguat) in real clinical practice. The RMP (version 7.1) is updated accordingly

17.4.8. Teriflunomide - AUBAGIO (CAP) - EMEA/H/C/002514/II/0025

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Martin Huber

Scope: Submission of the final survey reports (listed as a category 3 study in the RMP) for patients and healthcare professionals (HCPs) to assess the effectiveness of the education materials. As part of the submission, the MAH proposes a revised patient card

17.5. Interim results of imposed and non-imposed PASS submitted before the entry into force of the revised variation regulation

17.5.1. Alglucosidase alfa - MYOZYME (CAP) - EMEA/H/C/000636/MEA 024.11

Applicant: Genzyme Europe BV

PRAC Rapporteur: Adrien Inoubli

Scope: MAH's response to MEA 024.10 [Annual report on adverse events and/or lack of efficacy, immunological data, follow-up growth disturbances in children and data on urinary hexose tetrasaccharide (Hex4) from the Pompe registry: a global, observational and voluntary programme designed to collect uniform and meaningful clinical data related to the onset, progression, and treated course of patients with Pompe disease. The registry aims at detecting adverse events and/or lack of efficacy in patients, and at collecting immunological data, and follow-up growth disturbances in children] as per the request for supplementary information (RSI) as adopted in April 2019

17.5.2. Alglucosidase alfa - MYOZYME (CAP) - EMEA/H/C/000636/MEA 025.11

Applicant: Genzyme Europe BV

PRAC Rapporteur: Adrien Inoubli

Scope: MAH's response to MEA 025.10 [annual report on data on patients with renal or hepatic insufficiency from the Pompe registry: a global, observational and voluntary programme designed to collect uniform and meaningful clinical data related to the onset, progression, and treated course of patients with Pompe disease. The registry aims at detecting adverse events and/or lack of efficacy in patients, and at collecting immunological data, and follow-up growth disturbances in children] as per the request for supplementary information (RSI) adopted in April 2019

17.5.3. Autologous CD34+ enriched cell fraction that contains CD34+ cells transduced with retroviral vector that encodes for the human adenosine deaminase (ADA) cDNA sequence - STRIMVELIS (CAP) - EMEA/H/C/003854/ANX 004.2

Applicant: Orchard Therapeutics (Netherlands) BV, ATMP[62]

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to ANX 004.1 [biennial progress report for study GSK2696273 entitled 'adenosine deaminase severe combined immunodeficiency (ADA-SCID) registry for patients treated with Strimvelis gene therapy: long-term prospective, non-interventional follow-up of safety and effectiveness' (PSP/004) [final clinical study report (CSR) after the 50th patient has 15 year follow-up visit - Q4 2037] as per the request for supplementary information (RSI) adopted in June 2019

17.5.4. Dapagliflozin - EDISTRIDE (CAP) - EMEA/H/C/004161/MEA 006.2

Applicant: AstraZeneca AB

PRAC Rapporteur: Annika Folin

Scope: Second interim results for study MB102-103 ST/D1690R00008 - (EUPAS12113): a pharmacoepidemiology study assessing the risk of severe complications of urinary tract infections (UTIs) and evaluating severe complications of UTIs [final clinical study report (CSR) due in 2020]

17.5.5. Dapagliflozin - EDISTRIDE (CAP) - EMEA/H/C/004161/MEA 007.2

Applicant: AstraZeneca AB

PRAC Rapporteur: Annika Folin

Scope: Second interim results for study MB102-110 ST/D1690R00004 - (EUPAS11684): a pharmacoepidemiology observational study assessing the risk of acute renal failure and evaluating the risk of acute kidney injury [final clinical study report (CSR) due in 2020]

17.5.6. Dapagliflozin - EDISTRIDE (CAP) - EMEA/H/C/004161/MEA 008.2

Applicant: AstraZeneca AB

PRAC Rapporteur: Annika Folin

Scope: Second interim results for study MB102-104 ST/D1690R00005 - (EUPAS12110): a pharmacoepidemiology observational study assessing the risk of acute hepatic failure and evaluating the risk of acute liver injury [final clinical study report (CSR) due in 2020]

17.5.7. Dapagliflozin - EDISTRIDE (CAP) - EMEA/H/C/004161/MEA 009.2

Applicant: AstraZeneca AB

PRAC Rapporteur: Annika Folin

Scope: Second interim results for study MB102-118 ST/D1690R00007 - (EUPAS12116): a pharmacoepidemiology study assessing the risk of cancer [final clinical study report (CSR)

[62] Advanced therapy medicinal product

due in 2024]

17.5.8. Dapagliflozin - FORXIGA (CAP) - EMEA/H/C/002322/MEA 001.7

Applicant: AstraZeneca AB

PRAC Rapporteur: Annika Folin

Scope: Second interim results for study MB102-103 ST/D1690R00008 - (EUPAS12113): a pharmacoepidemiology study assessing the risk of severe complications of urinary tract infections (UTIs) and evaluating severe complications of UTIs [final clinical study report (CSR) due in 2020]

17.5.9. Dapagliflozin - FORXIGA (CAP) - EMEA/H/C/002322/MEA 002.7

Applicant: AstraZeneca AB

PRAC Rapporteur: Annika Folin

Scope: Second interim results for study MB102-110 ST/D1690R00004 - (EUPAS11684): a pharmacoepidemiology observational study assessing the risk of acute renal failure and evaluating the risk of acute kidney injury [final clinical study report (CSR) due in 2020]

17.5.10. Dapagliflozin - FORXIGA (CAP) - EMEA/H/C/002322/MEA 003.6

Applicant: AstraZeneca AB

PRAC Rapporteur: Annika Folin

Scope: Second interim results for study MB102-104 ST/D1690R00005 - (EUPAS12110): a pharmacoepidemiology observational study assessing the risk of acute hepatic failure and evaluating the risk of acute liver injury [final clinical study report (CSR) due in 2020]

17.5.11. Dapagliflozin - FORXIGA (CAP) - EMEA/H/C/002322/MEA 004.7

Applicant: AstraZeneca AB

PRAC Rapporteur: Annika Folin

Scope: Second interim results for study MB102-118 ST/D1690R00007 - (EUPAS12116): a pharmacoepidemiology study assessing the risk of cancer [final clinical study report (CSR) due in 2024]

17.5.12. Dapagliflozin, metformin - EBYMECT (CAP) - EMEA/H/C/004162/MEA 005.2

Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: Second interim results for study MB102-103 ST/D1690R00008 - (EUPAS12113): a pharmacoepidemiology study assessing the risk of severe complications of urinary tract infections (UTIs) and evaluating severe complications of UTIs [final clinical study report (CSR) due in 2020]

17.5.13. Dapagliflozin, metformin - EBYMECT (CAP) - EMEA/H/C/004162/MEA 006.2

Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: Second interim results for study MB102-110 ST/D1690R00004 - (EUPAS11684): a pharmacoepidemiology observational study assessing the risk of acute renal failure and evaluating the risk of acute kidney injury [final clinical study report (CSR) due in 2020]

17.5.14. Dapagliflozin, metformin - EBYMECT (CAP) - EMEA/H/C/004162/MEA 007.2

Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: Second interim results for study MB102-104 ST/D1690R00005 - (EUPAS12110): a pharmacoepidemiology observational study assessing the risk of acute hepatic failure and evaluating the risk of acute liver injury [final clinical study report (CSR) due in 2020]

17.5.15. Dapagliflozin, metformin - EBYMECT (CAP) - EMEA/H/C/004162/MEA 008.2

Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: Second interim results for study MB102-118 ST/D1690R00007 - (EUPAS12116): a pharmacoepidemiology study assessing the risk of cancer [final clinical study report (CSR) due in 2024]

17.5.16. Dapagliflozin, metformin - XIGDUO (CAP) - EMEA/H/C/002672/MEA 008.2

Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: Second interim results for study MB102-103 ST/D1690R00008 - (EUPAS12113): a pharmacoepidemiology study assessing the risk of severe complications of urinary tract infections (UTIs) and evaluating severe complications of UTIs [final clinical study report (CSR) due in 2020]

17.5.17. Dapagliflozin, metformin - XIGDUO (CAP) - EMEA/H/C/002672/MEA 009.2

Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: Second interim results for study MB102-110 ST/D1690R00004 - (EUPAS11684): a pharmacoepidemiology observational study assessing the risk of acute renal failure and evaluating the risk of acute kidney injury [final clinical study report (CSR) due in 2020]

17.5.18. Dapagliflozin, metformin - XIGDUO (CAP) - EMEA/H/C/002672/MEA 010.2

Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: Second interim results for study MB102-104 ST/D1690R00005 - (EUPAS12110): a pharmacoepidemiology observational study assessing the risk of acute hepatic failure and evaluating the risk of acute liver injury [final clinical study report (CSR) due in 2020]

17.5.19. Dapagliflozin, metformin - XIGDUO (CAP) - EMEA/H/C/002672/MEA 011.2

Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: Second interim results for study MB102-118 ST/D1690R00007 - (EUPAS12116): a pharmacoepidemiology study assessing the risk of cancer [final clinical study report (CSR) due in 2024]

17.5.20. Dimethyl fumarate - SKILARENCE (CAP) - EMEA/H/C/002157/MEA 001.3

Applicant: Almirall S.A

PRAC Rapporteur: Annika Folin

Scope: Interim results for study M-41008-40 (listed as a category 3 study in the RMP): an observational PASS in European psoriasis registers to evaluate the long-term safety of Skilarence (dimethyl fumarate) used for the treatment of patients with moderate to severe psoriasis [future due date(s): end of data collection: Q1 2027; final study report expected within a year of availability of the final data set]

17.5.21. Hydrocortisone - PLENADREN (CAP) - EMEA/H/C/002185/MEA 009

Applicant: Shire Services BVBA

PRAC Rapporteur: Annika Folin

Scope: Interim report for study SHP617-400 (EU AIR): a non-interventional (PASS) registry study: A European multicentre, multi-country, post-authorisation observational study (registry) of patients with chronic adrenal insufficiency

17.5.22. Saxagliptin, dapagliflozin - QTERN (CAP) - EMEA/H/C/004057/MEA 003

Applicant: AstraZeneca AB

PRAC Rapporteur: Ilaria Baldelli

Scope: Second interim results for study MB102-103 ST/D1690R00008 - (EUPAS12113): a pharmacoepidemiology study assessing the risk of severe complications of urinary tract infections (UTIs) and evaluating severe complications of UTIs [final clinical study report (CSR) due in 2020]

17.5.23. Saxagliptin, dapagliflozin - QTERN (CAP) - EMEA/H/C/004057/MEA 004

Applicant: AstraZeneca AB

PRAC Rapporteur: Ilaria Baldelli

Scope: Second interim results for study MB102-110 ST/D1690R00004 - (EUPAS11684): a pharmacoepidemiology observational study assessing the risk of acute renal failure and

evaluating the risk of acute kidney injury [final clinical study report (CSR) due in 2020]

17.5.24. Saxagliptin, dapagliflozin - QTERN (CAP) - EMEA/H/C/004057/MEA 005

Applicant: AstraZeneca AB

PRAC Rapporteur: Ilaria Baldelli

Scope: Second interim results for study MB102-104 ST/D1690R00005 - (EUPAS12110): a pharmacoepidemiology observational study assessing the risk of acute hepatic failure and evaluating the risk of acute liver injury [final clinical study report (CSR) due in 2020]

17.5.25. Saxagliptin, dapagliflozin - QTERN (CAP) - EMEA/H/C/004057/MEA 006

Applicant: AstraZeneca AB

PRAC Rapporteur: Ilaria Baldelli

Scope: Second interim results for study MB102-118 ST/D1690R00007 - (EUPAS12116): a pharmacoepidemiology study assessing the risk of cancer [final clinical study report (CSR) due in 2024]

17.5.26. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/MEA 044.6

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Rhea Fitzgerald

Scope: MAH's response to MEA 044.3 [first interval safety report for study CNTO1275PSO4056: an observational PASS of ustekinumab in the treatment of paediatric patients aged 12 years and older with moderate to severe plaque psoriasis (adolescent registry)] as per the request for supplementary information (RSI) adopted in June 2019

17.6. Others

17.6.1. Deferasirox - EXJADE (CAP) - EMEA/H/C/000670/MEA 075

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ghania Chamouni

Scope: Interim study results for study CICL670F2202: a randomised, open-label, multicentre, two arm, phase 2 study allowing to evaluate the safety of deferasirox granules in paediatric patients with iron overload [final clinical study report (CSR) due in June 2021] (from X/54)

17.6.2. Eribulin - HALAVEN (CAP) - EMEA/H/C/002084/MEA 022.1

Applicant: Eisai GmbH

PRAC Rapporteur: Annika Folin

Scope: MAH's response to MEA 022 relating to the statistical analysis plan (SAP) [SAP and protocol for study E7389-M044-504: an observational post-authorisation, single-arm, prospective, multicentre cohort study to investigate the frequency of and time to resolution of eribulin-induced or aggravated peripheral neuropathy (PN) in patients with locally

advanced or metastatic breast cancer in a real-life setting (from variation II/33)] as per the request for supplementary information (RSI) adopted in April 2019

17.6.3. Reslizumab - CINQAERO (CAP) - EMEA/H/C/003912/MEA 005.5

Applicant: Teva B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: MAH's response to MEA 005.4 [feasibility assessment conducted in US and non-US healthcare databases for study C38072-AS-50027 (listed as category 3 study in the RMP): a long-term non-interventional cohort study comparing the risk of malignancy in severe asthma patients treated with reslizumab and patients not treated with reslizumab using secondary administrative healthcare data [final clinical study report (CSR) expected January 2020]] as per the request for supplementary information (RSI) adopted in February 2019

17.7. New Scientific Advice

Information related to this section cannot be released at the present time as it is deemed to contain commercially confidential information.

17.8. Ongoing Scientific Advice

Information related to this section cannot be released at the present time as it is deemed to contain commercially confidential information.

17.9. Final Scientific Advice (Reports and Scientific Advice letters)

Information related to this section cannot be released at the present time as it is deemed to contain commercially confidential information.

18. Annex I – Renewals of the marketing authorisation, conditional renewals and annual reassessments

Based on the review of the available pharmacovigilance data for the medicines listed below and the CHMP Rapporteur's assessment report, the PRAC considered that either the renewal of the marketing authorisation procedure could be concluded - and supported the renewal of their marketing authorisations for an unlimited or additional period, as applicable - or no amendments to the specific obligations of the marketing authorisation under exceptional circumstances for the medicines listed below were recommended. As per agreed criteria, the procedures were finalised at the PRAC level without further plenary discussion.

18.1. Annual reassessments of the marketing authorisation

18.1.1. Cerliponase alfa - BRINEURA (CAP) - EMEA/H/C/004065/S/0018 (without RMP)

Applicant: BioMarin International Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Annual reassessment of the marketing authorisation

18.1.2. Ex vivo expanded autologous human corneal epithelial cells containing stem cells - HOLOCLAR (CAP) - EMEA/H/C/002450/R/0026 (without RMP)

Applicant: Chiesi Farmaceutici S.p.A., ATMP[63]

PRAC Rapporteur: Rhea Fitzgerald

Scope: Annual reassessment of the marketing authorisation

18.1.3. Galsulfase - NAGLAZYME (CAP) - EMEA/H/C/000640/S/0078 (without RMP)

Applicant: BioMarin International Limited

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Annual reassessment of the marketing authorisation

18.1.4. Lomitapide - LOJUXTA (CAP) - EMEA/H/C/002578/S/0036 (without RMP)

Applicant: Amryt Pharmaceuticals DAC

PRAC Rapporteur: Menno van der Elst

Scope: Annual reassessment of the marketing authorisation

18.1.5. Smallpox vaccine (live modified vaccinia virus Ankara) - IMVANEX (CAP) - EMEA/H/C/002596/S/0041 (without RMP)

Applicant: Bavarian Nordic A/S

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Annual reassessment of the marketing authorisation

18.1.6. Vestronidase alfa - MEPSEVII (CAP) - EMEA/H/C/004438/S/0007 (without RMP)

Applicant: Ultragenyx Germany GmbH

PRAC Rapporteur: Eva Segovia

Scope: Annual reassessment of the marketing authorisation

18.1.7. Vandetanib - CAPRELSA (CAP) - EMEA/H/C/002315/R/0041 (without RMP)

Applicant: Genzyme Europe BV

PRAC Rapporteur: Ghania Chamouni

Scope: Annual reassessment of the marketing authorisation

18.2. Conditional renewals of the marketing authorisation

18.2.1. Bedaquiline - SIRTURO (CAP) - EMEA/H/C/002614/R/0035 (without RMP)

Applicant: Janssen-Cilag International NV

[63] Advanced therapy medicinal product(s)

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Conditional renewal of the marketing authorisation

18.2.2. Cabozantinib - COMETRIQ (CAP) - EMEA/H/C/002640/R/0032 (with RMP)

Applicant: Ipsen Pharma

PRAC Rapporteur: Menno van der Elst

Scope: Conditional renewal of the marketing authorisation

18.3. Renewals of the marketing authorisation

18.3.1. Ciclosporin - IKERVIS (CAP) - EMEA/H/C/002066/R/0017 (without RMP)

Applicant: Santen Oy

PRAC Rapporteur: Jan Neuhauser

Scope: 5-year renewal of the marketing authorisation

18.3.2. Denosumab - PROLIA (CAP) - EMEA/H/C/001120/R/0082 (without RMP)

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: 5-year renewal of the marketing authorisation

18.3.3. Empagliflozin, metformin - SYNJARDY (CAP) - EMEA/H/C/003770/R/0044 (with RMP)

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Eva Segovia

Scope: 5-year renewal of the marketing authorisation

18.3.4. Netupitant, palonosetron - AKYNZEO (CAP) - EMEA/H/C/003728/R/0024 (without RMP)

Applicant: Helsinn Birex Pharmaceuticals Limited

PRAC Rapporteur: Ilaria Baldelli

Scope: 5-year renewal of the marketing authorisation

18.3.5. Human papillomavirus vaccine [types 6, 11, 16, 18, 31, 33, 45, 52, 58] (recombinant, adsorbed) - GARDASIL 9 (CAP) - EMEA/H/C/003852/R/0035 (without RMP)

Applicant: MSD Vaccins

PRAC Rapporteur: Jean-Michel Dogné

Scope: 5-year renewal of the marketing authorisation

18.3.6. Naltrexone hydrochloride, bupropion hydrochloride - MYSIMBA (CAP) - EMEA/H/C/003687/R/0033 (without RMP)

Applicant: Orexigen Therapeutics Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: 5-year renewal of the marketing authorisation

18.3.7. Oritavancin - ORBACTIV (CAP) - EMEA/H/C/003785/R/0027 (without RMP)

Applicant: Menarini International Operations Luxembourg S.A.

PRAC Rapporteur: Adam Przybylkowski

Scope: 5-year renewal of the marketing authorisation

19. Annex II – List of participants

including any restrictions with respect to involvement of members / alternates / experts following evaluation of declared interests for the 28-31 October 2019 meeting.

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Sabine Straus	Chair	The Netherlands	No interests declared	Full involvement
Jan Neuhauser	Member	Austria	No interests declared	Full involvement
Sonja Hrabcik	Alternate	Austria	No interests declared	Full involvement
Jean-Michel Dogné	Member	Belgium	No interests declared	Full involvement
Yuliyan Eftimov	Alternate	Bulgaria	No interests declared	Full involvement
Nikica Mirošević Skvrce	Member	Croatia	No interests declared	Full involvement
Željana Margan Koletić	Alternate	Croatia	No interests declared	Full involvement
Panagiotis Psaras	Alternate	Cyprus	No interests declared	Full involvement
Jana Lukacisinova	Alternate	Czech Republic	No interests declared	Full involvement
Anette Stark	Member	Denmark	No interests declared	Full involvement
Hans Christian Siersted	Alternate	Denmark	No restrictions applicable to this meeting	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Maia Uusküla	Member	Estonia	No interests declared	Full involvement
Kirsti Villikka	Member	Finland	No interests declared	Full involvement
Kimmo Jaakkola	Alternate	Finland	No interests declared	Full involvement
Ghania Chamouni	Member	France	No participation in discussion, final deliberations and voting on:	17.4.3. Colistimethate sodium - COLOBREATHE (CAP)
Adrien Inoubli	Alternate	France	No interests declared	Full involvement
Martin Huber	Member (Vice-Chair)	Germany	No interests declared	Full involvement
Brigitte Keller-Stanislawski	Alternate	Germany	No interests declared	Full involvement
Sophia Trantza	Alternate	Greece	No participation in discussion, final deliberations and voting on:	4.3.4. Ibuprofen – PEDEA (CAP); NAP; ketoprofen (NAP) and fixed-dose combinations
Julia Pallos	Member	Hungary	No interests declared	Full involvement
Guðrún Stefánsdóttir	Member	Iceland	No participation in discussion, final deliberations and voting on:	3.2.2. Leuprorelin (NAP) 14.1.1. Adalimumab – AMGEVITA (CAP), HALIMATOZ (CAP), HEFIYA (CAP), HULIO (CAP), HUMIRA (CAP), HYRIMOZ (CAP), IDACIO (CAP), IMRALDI (CAP),

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				KROMEYA (CAP) 15.3.5. Blinatumomab - BLINCYTO (CAP) 15.3.8. Darbepoetin alfa - ARANESP (CAP) 18.3.2. Denosumab - PROLIA (CAP)
Rhea Fitzgerald	Member	Ireland	No restrictions applicable to this meeting	Full involvement
Ronan Grimes	Alternate	Ireland	No interests declared	Full involvement
Amelia Cupelli	Member	Italy	No interests declared	Full involvement
Ilaria Baldelli	Alternate	Italy	No interests declared	Full involvement
Zane Neikena	Member	Latvia	No interests declared	Full involvement
Rugile Pilviniene	Member	Lithuania	No interests declared	Full involvement
Ruta Kerpauskiene	Alternate	Lithuania	No interests declared	Full involvement
Marcel Bruch	Member	Luxembourg	No interests declared	Full involvement
John Joseph Borg	Member (CHMP member)	Malta	No interests declared	Full involvement
Menno van der Elst	Member	Netherlands	No interests declared	Full involvement
Liana Gross-Martirosyan	Alternate	Netherlands	No interests declared	Full involvement
David Olsen	Member	Norway	No participation in discussion, final deliberations and voting on:	3.2.1. Cyproterone acetate (NAP) 3.4.1. Estradiol (NAP) 4.3.3. Ferric carboxymaltose

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				(NAP); iron (NAP); iron dextran (NAP); iron (III) isomaltoside (NAP); iron sucrose (NAP); sodium ferric gluconate (NAP) 4.3.4. Ibuprofen – PEDEA (CAP); NAP; ketoprofen(NAP) and fixed-dose combinations 4.3.7. Vascular endothelial growth factor (VEGF) inhibitors : aflibercept – EYLEA (CAP), ranibizumab – LUCENTIS (CAP) 5.1.3. Darolutamide - NUBEQA (CAP MAA) 17.1.3. Levonorgestrel (NAP) 17.4.7. Riociguat - ADEMPAS (CAP)
Karen Pernille Harg	Alternate	Norway	No interests declared	Full involvement
Adam Przybylkowski	Member	Poland	No interests declared	Full involvement
Ana Diniz Martins	Member	Portugal	No interests declared	Full involvement
Alexandra - Maria Spurni	Alternate	Romania	No interests declared	Full involvement
Michal Radik	Member	Slovakia	No	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			restrictions applicable to this meeting	
Gabriela Jazbec	Member	Slovenia	No interests declared	Full involvement
Eva Segovia	Member	Spain	No interests declared	Full involvement
Maria del Pilar Rayon	Alternate	Spain	No interests declared	Full involvement
Ulla Wändel Liminga	Member	Sweden	No interests declared	Full involvement
Annika Folin	Alternate	Sweden	No interests declared	Full involvement
Patrick Batty	Alternate	United Kingdom	No interests declared	Full involvement
Daniel Morales	Member	Independent scientific expert	No interests declared	Full involvement
Hedvig Nordeng	Member	Independent scientific expert	No interests declared	Full involvement
Livia Puljak	Member	Independent scientific expert	No interests declared	Full involvement
Stefan Weiler	Member	Independent scientific expert	No participation in discussion, final deliberations and voting on:	7.2.11. Ulipristal acetate - ESMYA (CAP)
Raymond Anderson	Member	Healthcare Professionals' Representative	No interests declared	Full involvement
Roberto Frontini	Alternate	Healthcare Professionals' Representative	No restrictions applicable to this meeting	Full involvement
Cathalijne van Doorne	Member	Patients' Organisation Representative	No interests declared	Full involvement
Virginie Hivert	Alternate	Patients' Organisation Representative	No restrictions applicable to this meeting	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Ivona Bahnik Biševac	Expert - via telephone*	Croatia	No restrictions applicable to this meeting	Full involvement
Ivana Kosier	Expert - via telephone*	Croatia	No interests declared	Full involvement
Barbara Kovačić	Expert - via telephone*	Croatia	No interests declared	Full involvement
Ivana Ljubičić	Expert - via telephone*	Croatia	No restrictions applicable to this meeting	Full involvement
Martin Ainsworth	Expert - via telephone*	Denmark	No restrictions applicable to this meeting	Full involvement
Helle Marie Esbjørn Kristensen	Expert - via telephone*	Denmark	No interests declared	Full involvement
Emma Louise Nautrup Ravn Stadsbjerg	Expert - via telephone*	Denmark	No interests declared	Full involvement
Päivi Susanna Worsøe	Expert - via telephone*	Denmark	No restrictions applicable to this meeting	Full involvement
Krõõt Aab	Expert - in person*	Estonia	No interests declared	Full involvement
Malak Abou-Taam	Expert - in person*	France	No interests declared	Full involvement
Pauline Dayani	Expert - in person*	France	No restrictions applicable to this meeting	Full involvement
Sylvain Gueho	Expert - in person*	France	No interests declared	Full involvement
Tiphaine Vaillant	Expert - in person*	France	No interests declared	Full involvement
Isabelle Yoldjian	Expert - via telephone*	France	No interests declared	Full involvement
Dennis Lex	Expert - in person*	Germany	No restrictions applicable to this meeting	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Ruchika Sharma	Expert - via telephone*	Ireland	No restrictions applicable to this meeting	Full involvement
Gerry Wilson	Expert - via telephone*	Ireland	No restrictions applicable to this meeting	Full involvement
Joan Deckers	Expert - in person*	Netherlands	No interests declared	Full involvement
Bianca Mulder	Expert - in person*	Netherlands	No restrictions applicable to this meeting	Full involvement
Virginie Seelen	Expert - in person*	Netherlands	No interests declared	Full involvement
Johannes Petrus Theodorus (Jan) Span	Expert - in person*	Netherlands	No interests declared	Full involvement
Lies van Vlijmen	Expert - in person*	Netherlands	No interests declared	Full involvement
Inge Zomerdijk	Expert - in person*	Netherlands	No interests declared	Full involvement
Dolores Montero Corominas	Expert - via telephone*	Spain	No interests declared	Full involvement
Charlotte Backman	Expert - in person*	Sweden	No interests declared	Full involvement
Rickard Ljung	Expert - in person*	Sweden	No restrictions applicable to this meeting	Full involvement
Darius Matusevicius	Expert - via telephone*	Sweden	No restrictions applicable to this meeting	Full involvement
Karin Nylén	Expert - via telephone*	Sweden	No interests declared	Full involvement
A representative from the European Commission attended the meeting				
Meeting run with support from relevant EMA staff				

* Experts were only evaluated against the agenda topics or activities they participated in

20. Annex III - List of acronyms and abbreviations

For a list of acronyms and abbreviations used in the PRAC minutes, see:
Home>Committees>PRAC>Agendas, minutes and highlights

21. Explanatory notes

The Notes give a brief explanation of relevant minute's items and should be read in conjunction with the minutes.

EU Referral procedures for safety reasons: Urgent EU procedures and Other EU referral procedures

(Items 2 and 3 of the PRAC minutes)

A referral is a procedure used to resolve issues such as concerns over the safety or benefit-risk balance of a medicine or a class of medicines. In a referral, the EMA is requested to conduct a scientific assessment of a particular medicine or class of medicines on behalf of the European Union (EU). For further detailed information on safety related referrals please see:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000150.jsp&mid=WC0b01ac05800240d0

Signals assessment and prioritisation

(Item 4 of the PRAC minutes)

A safety signal is information on a new or incompletely documented adverse event that is potentially caused by a medicine and that warrants further investigation. Signals are generated from several sources such as spontaneous reports, clinical studies and the scientific literature. The evaluation of safety signals is a routine part of pharmacovigilance and is essential to ensuring that regulatory authorities have a comprehensive knowledge of a medicine's benefits and risks.
The presence of a safety signal does not mean that a medicine has caused the reported adverse event. The adverse event could be a symptom of another illness or caused by another medicine taken by the patient. The evaluation of safety signals is required to establish whether or not there is a causal relationship between the medicine and the reported adverse event.
The evaluation of safety signals may not necessarily conclude that the medicine caused the adverse event in question. In cases where a causal relationship is confirmed or considered likely, regulatory action may be necessary and this usually takes the form of an update of the summary of product characteristics and the package leaflet.

Risk Management Plans (RMPs)

(Item 5 of the PRAC minutes)

The RMP describes what is known and not known about the side effects of a medicine and states how these risks will be prevented or minimised in patients. It also includes plans for studies and other activities to gain more knowledge about the safety of the medicine and risk factors for developing side effects. RMPs are continually modified and updated throughout the lifetime of the medicine as new information becomes available.

Assessment of Periodic Safety Update Reports (PSURs)

(Item 6 of the PRAC minutes)

A PSUR is a report providing an evaluation of the benefit-risk balance of a medicine, which is submitted by marketing authorisation holders at defined time points following a medicine's authorisation.

PSURs summarises data on the benefits and risks of a medicine and includes the results of all studies carried out with this medicine (in the authorised and unauthorised indications).

Post-authorisation Safety Studies (PASS)

(Item 7 of the PRAC minutes)

A PASS is a study of an authorised medicinal product carried out to obtain further information on its safety, or to measure the effectiveness of risk management measures. The results of a PASS help regulatory agencies to evaluate the safety and benefit-risk profile of a medicine.

Product related pharmacovigilance inspections

(Item 9 of the PRAC minutes)

Inspections carried out by regulatory agencies to ensure that marketing authorisation holders comply with their pharmacovigilance obligations.

More detailed information on the above terms can be found on the EMA website:
http://www.ema.europa.eu/ema/