05 September 2019
EMA/PRAC/692665/2019
Inspections, Human Medicines Pharmacovigilance and Committees Division

Pharmacovigilance Risk Assessment Committee (PRAC)

Minutes of the meeting on 08-11 July 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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1. Introduction

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

The Chairperson opened the 08 – 11 July 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 the Rules of Procedure (EMA/PRAC/567515/2012 Rev.1). 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.

The PRAC Chairperson welcomed Roberto Frontini, as the new alternate representing Healthcare Professionals. The PRAC Chair also welcomed Ilaria Baldelli as the new alternate for Italy.

Finally, the PRAC welcomed the new Finnish presidency of the Council of the European Union (EU).

1.2. Agenda of the meeting on 08 - 11 July 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 11 – 14 June 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 11-14 June 2019 were published on the EMA website on 13 November 2019 (EMA/PRAC/616893/2019).

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

3.1.1. 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

Cyproterone is a progesterone derivative with anti-androgenic properties authorised for a range of indications across the EU. This includes treatment of severe forms of androgen-induced increased facial and body hair (high-grade hirsutism) and/or forms of androgen-related hair loss, as well as the treatment of prostate cancer subject to certain conditions. In combination with ethinylestradiol, it is also indicated for the treatment of moderate to severe acne related to androgen-sensitivity or hirsutism in women of reproductive age. In combination with estradiol valerate, cyproterone is indicated in hormone replacement therapy (HRT).

The French Medicines Agency[1] (ANSM) sent a letter of notification dated 2 July 2019 of a referral under Article 31 of Directive 2001/83/EC for the review of cyproterone acetate-containing medicine(s) and the risk of meningioma. The risk of meningioma with cyproterone daily doses of 10 mg or more has been known since 2008 and information was included in the prescribing information for these medicine(s) along with a warning that cyproterone should not be used in people who have or have had meningioma. However, there was limited information at the time on the exact magnitude of the risk associated with prolonged use of high cyproterone doses. To further clarify the relationship between cyproterone and the risk of meningioma, the French Health Insurance[2] (CNAM) conducted a pharmacoepidemiology study. The results show that the longer women are treated with high dose of cyproterone, the higher is the risk of meningioma. A strong dose-effect relationship has also been found. A location of the tumour at the anterior skull base appeared to be almost specifically associated with prolonged exposure to cyproterone. In addition, the results of a French pharmacovigilance survey finalised in 2019 completed these results and showed identified cases of meningioma with low dose of cyproterone. While data on cyproterone low dose are limited, the risk cannot be excluded in light of the current knowledge.

[1] Agence Nationale de Sécurité du Médicament et des Produits de Santé
[2] Caisse nationale de l'Assurance Maladie

Therefore, the ANSM considered in the interest of the Union to refer the matter to the PRAC for further evaluation and requested that it gives its recommendation as to whether the marketing authorisations for cyproterone-containing products should be maintained, varied, suspended or revoked.

Discussion

The PRAC noted the notification letter from the ANSM.

The Committee appointed Menno van der Elst as Rapporteur and Adam Przybylkowski as Co-Rapporteur for the procedure.

The PRAC discussed a list of questions (LoQ) to be addressed during the procedure together with a timetable for conducting the review. The PRAC also discussed the need for a public hearing.

Summary of recommendation(s)/conclusions

- The Committee adopted a LoQ to the MAHs for cyproterone-containing products (EMA/PRAC/371762/2019) and a timetable for the procedure (EMA/PRAC/371761/2019).
- The PRAC also discussed the option to conduct a public hearing in the context of the current procedure according to the pre-defined criteria set out in the rules of procedure[3] (EMA/363479/2015). It was agreed by the Committee that at this stage of the procedure, in light of the currently available data and the need to determine the appropriate approach to stakeholder engagement, a public hearing would not be appropriate. The PRAC can reconsider this at a later stage of the procedure, as needed.

See EMA press release (EMA/384708/2019) entitled 'Review of meningioma risk with cyproterone medicines'.

3.2. Ongoing procedures

3.2.1. 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 the 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 is ongoing for Lemtrada (alemtuzumab) following new emerging and serious safety concerns, namely fatal cases, cardiovascular adverse events in close temporal association with infusion of the medicinal product and immune-mediated diseases. The safety profile of the medicinal product is reviewed in light of these safety concerns. For further background, see PRAC minutes April 2019.

Summary of recommendation(s)/conclusions

[3] Rules of procedure on the organisation and conduct of public hearings at the PRAC

- The PRAC discussed the assessment reports produced by the Rapporteurs.
- The PRAC adopted a list of outstanding issues (LoOI), to be addressed by the MAH in accordance with a revised timetable (EMA/PRAC/218954/2019 rev.1).
- The PRAC adopted a list of questions (LoQ) for the Scientific Advisory Group on Neurology (SAG-N) meeting organised on 5 September 2019.
- PRAC members were invited to nominate experts to participate in the SAG-N until 15 August 2019.

Post-meeting note: On 15 August 2019, the PRAC adopted by written procedure the list of experts for the SAG-N.

3.2.2. Estradiol[4] (NAP) - EMEA/H/A-31/1482

Applicant(s): various

PRAC Rapporteur: Eva Jirsova; PRAC Co-rapporteur: Menno van der Elst

Scope: Review of the benefit-risk balance following notification by the European Commission 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 estradiol-containing medicines (0.01% w/w) for topical use, reviewing data showing plasma levels of estradiol similar to those associated with the use of estradiol in systemic hormone replacement therapy (HRT). Undesirable effects known for systemic HRT include venous thromboembolism, stroke, breast and endometrial cancer. This referral procedure follows the partial annulment of the conclusions reached in 2014 in a previous EU review based on procedural grounds and the concerns that the safety risks for those medicinal products are no longer addressed adequately and that patients are put at risk. Therefore, a further review was initiated in April 2019 to review the data assessed in the previous referral procedure for medicinal products containing estradiol for topical use as well as any data that would have become available since 2014. For further background, see PRAC minutes April 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/214200/2019 rev1).
- The PRAC discussed and supported the organisation of an ad-hoc expert group meeting on 17 September 2019. The PRAC adopted a list of questions (LoQ) for the ad-hoc expert group meeting.
- PRAC members were invited to nominate experts to participate in the ad-hoc expert group meeting until 30 August 2019.

3.2.3. Fluorouracil and related substances: capecitabine - CAPECITABINE ACCORD (CAP); CAPECITABINE MEDAC (CAP);

[4] 0.01%, topical use only

Applicants: Accord Healthcare Limited (Capecitabine Accord), Krka, d.d., Novo mesto (Ecansya), Medac Gesellschaft fur klinische Spezialpraparate mbH (Capecitabine medac), Nordic Group B.V. (Teysuno), Roche Registration GmbH (Xeloda), Teva B.V. (Capecitabine Teva), various

PRAC Rapporteur: Jean-Michel Dogné; PRAC Co-rapporteur: Martin Huber

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 fluorouracil-, capecitabine- and tegafur-containing medicines for systemic use in order to review the genotyping and phenotyping methods as well as their availability across the EU for the detection of dihydropyrimidine dehydrogenase (DPD) deficiency responsible for severe and fatal toxicity. The ongoing procedure also reviews the value of the existing screening methods in identifying patients at increased risk of severe side effects as well as the need for updating existing recommendations for pre-treatment evaluation of DPD activity in patients to receive treatment with 5-fluorouracil (5-FU) or related substances. For further background, see PRAC minutes March 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/165647/2019 Rev.2).
- The PRAC discussed and supported the organisation of an ad-hoc inter-Committee Scientific Advisory Group on Oncology (SAG-O) on 11 October 2019. The PRAC adopted a list of questions (LoQ) for the SAG-O.
- The PRAC also adopted a LoQ to the Pharmacogenomics Working Party (PgWP).

Post-meeting note: On 3 September 2019, PRAC members received a request to nominate experts to participate in the SAG-O with a deadline on 13 September 2019.

3.3. Procedures for finalisation

3.3.1. Methotrexate - JYLAMVO (CAP), NORDIMET (CAP); NAP - EMEA/H/A-31/1463

Applicants: Nordic Group B.V. (Nordimet), Therakind Limited (Jylamvo), various

PRAC Rapporteur: Martin Huber; PRAC Co-rapporteur: Željana Margan Koletić

Scope: Review of the benefit-risk balance following notification by Spain 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 for methotrexate-containing medicines (oral and parenteral formulations) is to be concluded. This review was initiated

following reports of overdose toxicity as a consequence of daily intake instead of weekly intake. The procedure also reviewed the risk minimisation measures (RMMs) taken nationally over recent years to fully elucidate the issue and to take appropriate measures. A final assessment of the data submitted was produced by the Rapporteurs according to the agreed timetable. For further background, see PRAC minutes April 2018, PRAC minutes October 2018, PRAC minutes January 2019, PRAC minutes February 2019, PRAC minutes March 2019 and PRAC minutes May 2019.

Discussion

The PRAC discussed the conclusion reached by the Rapporteurs.

The PRAC considered the totality of the data submitted for methotrexate-containing products with regard to the important identified risk of medication errors when methotrexate intended for once weekly use is taken daily by mistake, the root causes for this risk and the effectiveness of the RMMs in place. This included the responses submitted by the MAHs in writing as well as the views of patients and healthcare professionals (HCPs).

The PRAC investigated the root causes for the risk of medication errors and noted that these can occur at all stages of the medication process. The PRAC noted that severe, life-threatening and fatal cases of overdose due to medication errors with methotrexate-containing products continue to be reported and that the RMMs in place have not been sufficiently effective to prevent medication errors, in particular with the oral formulations of methotrexate-containing products. Therefore, the Committee concluded that there is a need to further strengthen the current RMMs by adding warnings in the product information and visual reminders on the outer, intermediate and immediate packaging of methotrexate-containing products with at least one indication requiring a once weekly dosing, for both oral and parenteral use.

In addition, the PRAC recommended other changes to the product information of all methotrexate-containing products with at least one indication requiring once weekly dosing to include that only physicians with expertise in using methotrexate-containing medicines should prescribe them and that HCPs should ensure that patients or their carers will be able to follow the once weekly dosing schedule. In addition, splitting the dose in multiple intakes should no longer be recommended.

Considering the number of reported inadvertent daily administration of methotrexate oral formulations, the PRAC concluded that for these medicinal products, educational materials for HCPs should be developed or updated, if already in place, in accordance with the key elements agreed, as well as a patient card to be provided with the relevant medicinal product, to further increase awareness. It was also agreed that all tablet formulations of methotrexate, bottles and tubes currently used as immediate packaging should be replaced by blisters. These RMMs should be reflected in a new or revised RMP as applicable.

Moreover, the PRAC agreed on targeted follow-up questionnaires to be used for all cases of medication errors reported with methotrexate and resulting in overdose.

The Committee considered that the benefit-risk balance of methotrexate-containing products remains favourable subject to the agreed conditions to the marketing authorisations and taking into account the agreed amendments to the product information and other RMMs.

Summary of recommendation(s)/conclusions

- The PRAC adopted a recommendation to vary[5] the terms of the marketing authorisation(s) for methotrexate-containing products to be considered by CHMP for an opinion – see EMA Press Release (EMA/384938/2019) entitled 'PRAC recommends new measures to avoid dosing errors with methotrexate' published on 12 July 2019.
- The PRAC agreed on the distribution of a direct healthcare professional communication (DHPC) together with a communication plan.

Post-meeting note: the press release entitled 'New measures to avoid potentially fatal dosing errors with methotrexate for inflammatory diseases' (EMA/414775/2019) representing the opinion adopted by the CHMP was published on the EMA website on 23 August 2019.

3.4. Re-examination procedures[6]

None

3.5. Others

None

4. Signals assessment and prioritisation[7]

4.1. New signals detected from EU spontaneous reporting systems

None

4.2. New signals detected from other sources

See Annex I 14.2.

4.3. Signals follow-up and prioritisation

4.3.1. Amino acid, lipid combinations with vitamins or trace elements[8] [9] (NAP)

Applicant(s): various

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of adverse outcomes in neonates treated with solutions not protected from light

EPITT 19423 – Follow-up to May 2019

Background

For background information, see PRAC minutes May 2019.

[5] Update of SmPC section 4.2, labelling and outer, intermediate and inner packaging. The package leaflet is updated accordingly
[6] Re-examination of PRAC recommendation under Article 32 of Directive 2001/83/EC
[7] 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
[8] For parenteral nutrition of neonates only
[9] Including amino acid combinations, glucose, triglyceride combinations (e.g. olive oil, soya bean oil, fish oil), with or without electrolytes, mineral compounds (intravenous (I.V) application)

The MAHs Baxter, B. Braun Melsungen AG, Fresenius Kabi, Noridem, Berlin-Chemie AG (Menarini group), Industria Farmaceutica Galenica Senese S.r.l., Bioindustria and Laboratorios Grifols, S.A. replied to the request for information on the signal of adverse outcomes in neonates treated with solutions not protected from light and the responses were assessed by the Rapporteur.

Discussion

The PRAC considered the data submitted by the MAHs for parenteral nutrition products containing amino acids and/or lipids regarding the risk of toxic degradations of ingredients after exposure to light. Considering the severe clinical outcomes in premature neonates when the medicinal products have been exposed to light, the PRAC agreed on the need for updating the product information with recommendations on light protection when the solution is to be used in neonates and in children below 2 years of age until the administration is completed. The PRAC also agreed to inform healthcare professionals (HCPs) of these new recommendations via a direct healthcare professional communication (DHPC).

Summary of recommendation(s)

- The MAHs for parenteral nutrition products containing amino acids and/or lipids with or without admixture of vitamins and/or trace elements and indicated in neonates and children below 2 years should submit to the relevant National Competent Authorities (NCAs) of the Member States, within 60 days, a variation to update the product information[10].
- The PRAC agreed on the distribution of a DHPC together with a communication plan.

For the full PRAC recommendation, see EMA/PRAC/347675/2019 published on 6 August 2019 on the EMA website.

4.3.2. Mesalazine (NAP)

Applicant(s): various

PRAC Rapporteur: Martin Huber

Scope: Signal of nephrolithiasis

EPITT 19405 – Follow-up to May 2019

Background

For background information, see PRAC minutes May 2019.

The MAHs Allergan, Astellas, Dr. Falk Pharma, Ferring, Giuliani, Sanofi, Shire, Sofar, Teofarma and Teva replied to the request to provide comments on the proposed updates of product information regarding the signal of nephrolithiasis. The responses were assessed by the Rapporteur.

Discussion

Having considered the review of the evidence on the risk of nephrolithiasis with mesalazine, including cases of stones composed of 100% mesalazine content, and the comments from MAHs of mesalazine-containing products, the PRAC agreed that the MAHs of mesalazine-containing products should update their product information accordingly.

[10] SmPC sections 4.2, 4.4, 6.3 and 6.6. The package leaflet is to be updated accordingly

Summary of recommendation(s)

- The MAHs for mesalazine-containing products should submit to the relevant National Competent Authorities (NCAs) of the Member States, within 60 days, a variation to update the product information[11].

For the full PRAC recommendation, see EMA/PRAC/347675/2019 published on 6 August 2019 on the EMA website.

4.3.3. Natalizumab - TYSABRI (CAP) - EMEA/H/C/000603/SDA/068

Applicant(s): Biogen Netherlands B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Signal of psoriasis

EPITT 19365 – Follow-up to March 2019

Background

For background information, see PRAC minutes March 2019.

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

Discussion

Having considered the available evidence, including case reports from EudraVigilance, literature and the data submitted by the MAH, the PRAC agreed that there is insufficient evidence to establish a causal association between natalizumab and psoriasis. Therefore, the PRAC agreed that no further regulatory actions are warranted at this stage.

Summary of recommendation(s)

- The MAH for Tysabri (natalizumab) should continue to monitor psoriasiform rash, both as new cases and as aggravation of existing cases, in future PSURs[12] as part of its routine safety surveillance.

4.3.4. Ondansetron (NAP)

Applicant(s): various

PRAC Rapporteur: Gabriela Jazbec

Scope: Signal of birth defects following in-utero exposure during the first trimester of pregnancy arising from recent publications

EPITT 19353 – Follow-up to March 2019

Background

For background information, see PRAC minutes March 2019.

Ondansetron is a selective serotonin antagonist indicated for prevention of cytotoxic chemotherapy-/radiotherapy-induced nausea and vomiting (CINV/RINV), and for the

[11] SmPC sections 4.4 and 4.8. The package leaflet is to be updated accordingly
[12] Data lock point (DLP): 07 August 2019

management of postoperative nausea and vomiting (PONV). The product information for ondansetron-containing products states that use in pregnancy is not recommended and that safety in pregnant women has not been established. Based on available literature and treatment guidelines, ondansetron is also used off-label in some Member States for the treatment of nausea and vomiting during pregnancy (NVP) or hyperemesis gravidarum (HG).

Novartis, the MAH for the originator-product containing ondansetron replied to the request for information on the signal of birth defects following in-utero exposure to ondansetron during the first trimester of pregnancy and the responses were assessed by the Rapporteur, together with the responses provided by the authors of the recently published large epidemiological studies by *Zambelli-Weiner A et al.*[13] and *Huybrechts KF et al.*[14].

Discussion

The PRAC considered the available information from the studies by *Zambelli-Weiner A et al.* and *Huybrechts KF et al.* together with the responses from the study authors, the methodological quality of the studies, data from further published epidemiological studies, and the responses from the MAH to the list of questions. The PRAC agreed that the product information of ondansetron-containing products should be updated to provide information on the magnitude of the risk of orofacial malformations and recommendations on the use of ondansetron during pregnancy in its authorised indications.

Summary of recommendation(s)

- The MAHs of ondansetron-containing products should submit to the relevant National Competent Authorities (NCAs) of the Member States, within 60 days, a variation to amend the product information[15].
- The PRAC agreed on key elements for communication. Novartis, the MAH for the originator-product containing ondansetron should agree with NCAs of the Member States where ondansetron-containing products are marketed, on the preferred way of communication according to the agreed key elements.
- The PRAC agreed that MAHs for the following selective serotonin 5-HT_3 receptor antagonists: granisetron-, palonosetron-, palonosetron/netupitant- and tropisetron-containing products should submit a cumulative review on birth defects following in-utero exposure in their next PSURs[16]. This should include a review of published literature, epidemiological studies and post marketing cases.

For the full PRAC recommendation, see EMA/PRAC/347675/2019 published on 6 August 2019 on the EMA website.

Post-meeting note: On 15 October 2019, a teleconference took place between some representatives from the PRAC, EMA and some patients' and healthcare professionals' organisations which had contacted EMA to further clarify the PRAC recommendation and its impact on using ondansetron off label for HG.

[13] Zambelli-Weiner A et al. First trimester ondansetron exposure and risk of structural birth defects. Reprod Toxicol. 2019;83:14-20
[14] Huybrechts KF et al. Association of maternal first-trimester ondansetron use with cardiac malformations and oral clefts in offspring. JAMA. 2018;320(23):2429-2437
[15] SmPC section 4.6. The package leaflet is to be updated accordingly
[16] Granisetron (transdermal patch) data lock point (DLP) 19 October 2019; granisetron (other formulations except for transdermal patch) DLP 18 February 2021; palonosetron DLP 24 July 2019; palonosetron/ netupitant DLP: 10 October 2019;. MAHs for tropisetron-containing products should follow the national PSUR frequency and liaise with the relevant NCAs of the Member States

4.3.5. Vascular endothelial growth factor (VEGF) inhibitors[17]: aflibercept – ZALTRAP (CAP) – EMEA/H/C/002532/SDA/009; axitinib – INLYTA (CAP) – EMEA/H/C/002406/SDA/014; bevacizumab – AVASTIN (CAP) – EMEA/H/C/000582/SDA/087, MVASI (CAP) – EMEA/H/C/004728/SDA/002, ZIRABEV (CAP) – EMEA/H/C/004697/SDA/002; cabozantinib – CABOMETYX (CAP) – EMEA/H/C/004163/SDA/004, COMETRIQ (CAP) – EMEA/H/C/002640/SDA/020; lenvatinib - KISPLYX (CAP) – EMEA/H/C/004224/SDA/015, LENVIMA (CAP) – EMEA/H/C/003727/SDA/017; nintedanib – OFEV (CAP) – EMEA/H/C/003727/SDA/005, VARGATEF (CAP) – EMEA/H/C/002569/SDA/007; pazopanib – VOTRIENT (CAP) – EMEA/H/C/001141/SDA/038; ponatinib – ICLUSIG (CAP) – EMEA/H/C/002695/SDA/017; ramucirumab – CYRAMZA (CAP) – EMEA/H/C/002829/SDA/007; regorafenib – STIVARGA (CAP) – EMEA/H/C/002573/SDA/012; sorafenib – NEXAVAR (CAP) – EMEA/H/C/000690/SDA/040, NAP; sunitinib – SUTENT (CAP) – EMEA/H/C/000687/SDA/054; NAP; tivozanib – FOTIVDA (CAP) – EMEA/H/C/004131/SDA/004; vandetanib – CAPRELSA (CAP) – EMEA/H/C/002315/SDA/021

Applicant(s): Amgen Europe B.V. (Mvasi), Bayer AG (Nexavar, Stivarga), Boehringer Ingelheim (Ofev, Vargatef), Eisai Europe Ltd. (Kisplyx, Lenvima), Eli Lilly Nederland B.V. (Cyramza), EUSA Pharma (UK) Limited (Fotivda), Genzyme Europe BV (Caprelsa), Incyte Biosciences Distribution (Iclusig), Ipsen Pharma (Cabometyx, Cometriq), Novartis Europharm Limited (Votrient), Pfizer Europe MA EEIG (Inlyta, Sutent, Zirabev), PharmaSwiss Ceska Republika (Macugen), Roche Registration GmbH (Avastin), Sanofi-aventis groupe (Zaltrap), various

PRAC Rapporteur: Annika Folin

Scope: Signal of artery dissections and aneurysms

EPITT 19330 – Follow-up to May 2019

Background

For background information, see PRAC minutes May 2019.

The MAHs for Avastin (bevacizumab), for Mvasi (bevacizumab), for Nexavar (sorafenib) and Stivarga (regorafenib), for Ofev (nintedanib) and Vargatef (nintedanib), for Kisplyx (lenvatinib) and Lenvima (lenvatinib), for Cyramza (ramucirumab), for Fotivda (tivozanib), for Caprelsa (vandetanib), for Iclusig (ponatinib), for Cabometyx (lenvatinib) and Cometriq (lenvatinib), for Votrient (pazopanib), for Inlyta (axitinib), Sutent (sunitinib) and Zirabev (bevacizumab), as well as for Zaltrap (aflibercept) replied to the request for comments on the proposed update of the product information on the signal of artery dissections and aneurysms and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence, following the assessment of the EudraVigilance data and consultation with the MAHs, the PRAC agreed that the product information for the vascular endothelial growth factor (VEGF) inhibitors for systemic administration should be updated to include warnings and information regarding the risk of aneurysms and artery dissections.

Summary of recommendation(s)

[17] For systemic use only

- The MAHs for Zaltrap (aflibercept), Inlyta (axitinib), Avastin, Mvasi and Zirabev (bevacizumab), Cabometyx and Cometriq (cabozantinib), Kisplyx and Lenvima (lenvatinib), Ofev and Vargatef (nintedanib), Votrient (pazopanib), Iclusig (ponatinib), Cyramza (ramucirumab), Stivarga (regorafenib), Nexavar (sorafenib) and sorafenib-containing products nationally approved, Sutent (sunitinib[18]) and sunitinib-containing products nationally approved, Fotivda (tivozanib) and Caprelsa (vandetanib) should submit to EMA or the relevant National Competent Authorities of the Member States, within 60 days, a variation to update the product information[19].

For the full PRAC recommendation, see EMA/PRAC/347675/2019 published on 6 August 2019 on the EMA website.

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(s). 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. Esketamine - EMEA/H/C/004535

Scope: Major depressive disorder in adults who have not responded to at least two different treatments with antidepressants in the current moderate to severe depressive episode (treatment-resistant depression)

5.1.2. Osilodrostat - EMEA/H/C/004821, Orphan

Applicant: Novartis Europharm Limited

Scope: Treatment of Cushing's syndrome

5.1.3. Plazomicin - EMEA/H/C/004457

Scope: Treatment of complicated urinary tract infection (cUTI), including treatment of pyelonephritis, treatment of bloodstream infection (BSI) and treatment of infections due to *Enterobacteriaceae*

5.1.4. Solriamfetol - EMEA/H/C/004893

Scope: Improvement of wakefulness in patients with narcolepsy or obstructive sleep apnoea

[18] Including nationally authorised products
[19] Update of SmPC sections 4.4 and 4.8. The package leaflet is to be updated accordingly

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

See Annex I 15.2.

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

See also Annex I 15.3.

5.3.1. Ceftazidime, avibactam - ZAVICEFTA (CAP) - EMEA/H/C/004027/II/0015

Applicant: Pfizer Ireland Pharmaceuticals

PRAC Rapporteur: Rugile Pilviniene

Scope: Extension of indication to include paediatric patients aged 3 months to less than 18 years for Zavicefta (ceftazidime/avibactam) based on data from three paediatric studies namely, study D4280C00014: a phase 1 study to assess the pharmacokinetics, safety and tolerability of a single dose of ceftazidime-avibactam (CAZ-AVI) in children from 3 months of age to <18 years who are receiving systemic antibiotic therapy for suspected or confirmed infection; study C3591004: a single blind, randomised, multicentre, active controlled, trial to evaluate safety, tolerability, pharmacokinetics (PK) and efficacy of ceftazidime and avibactam when given in combination with metronidazole, compared with meropenem, in children from 3 months to less than 18 years of age with complicated intra-abdominal infections (cIAIs); and study C3591005: a single blind, randomised, multicentre, active controlled, trial to evaluate safety, tolerability, pharmacokinetics and efficacy of ceftazidime and avibactam compared with cefepime in children from 3 months to less than 18 years of age with complicated urinary tract infections (CUTIs); as well as population PK modelling/simulation analyses (CAZ-MS-PED-01 and CAZ-MS-PED-02). As a consequence, sections 4.1, 4.2, 4.8, 5.1, 5.2, 6.3 and 6.6 of the SmPC are updated. The package leaflet and the RMP (version 3.0) are updated accordingly. In addition, the MAH took the opportunity to correct sections 2 and 4.4 of the SmPC and the package leaflet with information on sodium content, as well as section 5.2 of the SmPC with information on volumes of distribution of ceftazidime and avibactam. Furthermore, the MAH also introduced minor correction in the Czech product information

Background

Ceftazidime is a bacterial peptidoglycan cell wall synthesis inhibitor and avibactam is a non β-lactam/β-lactamase inhibitor. In combination, ceftazidime/avibactam is indicated, as Zavicefta, in adults for the treatment of complicated intra-abdominal infection (cIAI), complicated urinary tract infection (cUTI) including pyelonephritis and for hospital-acquired pneumonia (HAP) including ventilator associated pneumonia (VAP). It is also indicated for the treatment of infections due to aerobic Gram-negative organisms in adult patients with limited treatment options.

The CHMP is evaluating an extension of the therapeutic indication for Zavicefta, a centrally authorised medicine containing ceftazidime/avibactam, to include paediatric patients aged 3 months to less than 18 years to the existing indications. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this variation.

Summary of advice

- The RMP for Zavicefta (ceftazidime/avibactam) in the context of the variation procedure under evaluation by the CHMP could be considered acceptable provided that an update

to RMP version 3.0 and satisfactory responses to the request for supplementary information (RSI) are submitted.

- The PRAC discussed the issue of off-label use in neonates and infants under 3 months of age and considered that the potential off-label use can be discussed in future PSURs. The PRAC concurred that no other additional pharmacovigilance activities are required in light of the current knowledge. Therefore, the Committee did not support the inclusion of 'neurological disorders related to overdose in off-label use in neonates' as an important potential risk in the RMP.

5.3.2. Dulaglutide - TRULICITY (CAP) - EMEA/H/C/002825/II/0040

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Amelia Cupelli

Scope: Extension of indication to include a new indication to reduce the risk of major adverse cardiovascular events (MACE) (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in adults with type 2 diabetes mellitus (T2DM) who have multiple cardiovascular risk factors without established cardiovascular disease, and in adults with T2DM with established cardiovascular disease. The data supporting this new indication is derived from study GBDJ (researching cardiovascular events with a weekly incretin in diabetes (REWIND)): a single pivotal phase 3 long-term cardiovascular outcomes study, which assessed the efficacy and safety of treatment with once-weekly injection of dulaglutide 1.5 mg when added to glucose-lowering regimen of patients with T2DM, compared to the addition of a once weekly placebo injection (in fulfilment of post-authorisation measure (PAM) (MEA 004)). 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 3.1) are updated accordingly. In addition, the MAH took the opportunity to update the wording of the existing indication in section 4.1 of the SmPC and to implement a minor change in section 5.1 of the SmPC, in the glycaemic control summary subsection based on the results from the dulaglutide study as add-on to sodium-glucose co-transporter 2 (SGLT2) inhibitor therapy which was assessed as part of variation II/25 concluded in April 2018

Background

Dulaglutide is a long-acting glucagon-like peptide 1 (GLP-1) receptor agonist. It is indicated, as Trulicity, in adults with type 2 diabetes mellitus (T2DM) to improve glycaemic control when diet and exercise alone do not provide adequate glycaemic control in patients for whom the use of metformin is considered inappropriate due to intolerance or contraindications. It is also indicated in combination with other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control.

The CHMP is evaluating an extension of the therapeutic indication for Trulicity, a centrally authorised medicine containing dulaglutide, to include a new indication to reduce the risk of major adverse cardiovascular events (MACE) in adults with T2DM who have multiple cardiovascular risk factors without established cardiovascular disease, and in adults with T2DM with established cardiovascular disease. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this variation.

Summary of advice

- The RMP for Trulicity (dulaglutide) in the context of the variation procedure under evaluation by the CHMP could be considered acceptable provided that an update to RMP version 3.1 and satisfactory responses to the request for supplementary information (RSI) are submitted.
- The PRAC agreed that gastrointestinal events and hypersensitivity including anaphylactic reaction should be retained as important identified risks considering that monitoring the occurrence of these events is amongst the primary objectives of ongoing study H9X-MC-B009[20] due for completion in March 2020. In addition, cardiovascular effects should be removed as an important potential risk following assessment of the data from completed study H9X-MC-GBDJ[21] and the reassuring outcome relating to cardiovascular safety. Finally, use in children and adolescents under 18 years, use in patients with end stage renal disease, use in patients with hepatic impairment and use in patients over 75 years old should be also removed from missing information in line with the principles and definitions of risks and missing information of revision 2 of GVP module V on 'Risk management systems'.

5.3.3. Fingolimod - GILENYA (CAP) - EMEA/H/C/002202/II/0053

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ghania Chamouni

Scope: Update of sections 4.3, 4.4, 4.6 and 4.8 of the SmPC to add a contraindication on use during pregnancy and in women of childbearing potential not using effective contraception with further warning and detailed information, a warning for women stopping treatment for the purpose of becoming pregnant and for pregnant women and to add information to prescribers on 'severe exacerbation of disease after Gilenya (fingolimod) discontinuation', timing of reported events and further recommendations on monitoring of patients. The package leaflet is updated accordingly

Background

Fingolimod is a sphingosine 1-phosphate receptor modulator. It is indicated, as Gilenya, as a single disease modifying therapy (DMT) in highly active relapsing remitting multiple sclerosis (RRMS) for adult patients and paediatric patients aged 10 years and older under certain conditions.

The CHMP is evaluating a type II variation for Gilenya, a centrally authorised product containing fingolimod, to update the product information in order to include a contraindication on use during pregnancy and in women of childbearing potential not using effective contraception, the timing of reported events and further recommendations on monitoring of patients. The product information is also updated in order to add a warning for women stopping treatment for the purpose of becoming pregnant and for pregnant women. In addition, a new undesirable effect on severe exacerbation of disease after treatment discontinuation with Gilenya (fingolimod) is added. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this variation. For further background, see PRAC minutes May 2019.

Summary of advice

[20] Dulaglutide modified-prescription-event monitoring and network database study in the EU
[21] A long-term, phase 3, randomised, double-blind, placebo-controlled, parallel-arm, event-driven, multicentre, international, cardiovascular outcomes trial with Trulicity (dulaglutide)

- The RMP for Gilenya (fingolimod) in the context of the variation procedure under evaluation by the CHMP could be considered acceptable provided that an update to RMP version 16.1 and satisfactory responses to the request for supplementary information (RSI) are submitted.
- The PRAC agreed on the distribution of a direct healthcare professional communication (DHPC) according to a defined communication plan in pregnant women and in women of childbearing potential not using effective contraception.

5.3.4. Infliximab - REMSIMA (CAP) - EMEA/H/C/002576/X/0062

Applicant: Celltrion Healthcare Hungary Kft.

PRAC Rapporteur: Kimmo Jaakkola

Scope: Extension application to introduce a solution for injection as a new pharmaceutical form, 120 mg as a new strength and subcutaneous use as a new route of administration. The RMP (version 9.1) is updated accordingly

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 Remsima, a biosimilar product containing infliximab, 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 CHMP is evaluating an extension of application for Remsima (infliximab) to introduce a subcutaneous (SC) formulation. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this procedure. For further background, see PRAC minutes March 2019.

Summary of advice

- The RMP for Remsima (infliximab) in the context of the extension of application procedure under evaluation by the CHMP could be considered acceptable provided that an update to RMP version 9.3 and satisfactory responses to the request for supplementary information (RSI) are submitted.
- The PRAC discussed the MAH's responses to the request for supplementary information (RSI). The PRAC supported including study CT-P13 SC 4.8[22] as a category 3 study in the RMP. The MAH should provide updates with regards to studies conducted with the SC formulation as part of future PSURs.

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.

[22] A non-interventional single arm safety study, 288 rheumatoid arthritis (RA) patients exposed to Remsima (biosimilar infliximab) (CT-P13) SC for up to 18 months (comparison to historical data with intravenous (IV) Remsima (infliximab))

6.1.1. Ingenol mebutate - PICATO (CAP) - PSUSA/00010035/201901

Applicant: LEO Laboratories Ltd

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

Background

Ingenol mebutate has shown *in vivo* and *in vitro* models a dual mechanism of action for the effects of induction of local lesion cell death and for promoting an inflammatory response characterised by local production of pro-inflammatory cytokines and chemokines and infiltration of immunocompetent cells. Ingenol mebutate is indicated, as Picato, for the cutaneous treatment of non-hyperkeratotic, non-hypertrophic actinic keratosis in adults.

The PRAC is currently reviewing the benefit-risk balance of Picato, a centrally authorised medicine containing ingenol mebutate, in the framework of the assessment of a PSUR single assessment (PSUSA) procedure due for PRAC recommendation at the September 2019 PRAC meeting.

Summary of conclusions

- The PRAC Rapporteur presented the preliminary assessment of the currently ongoing PSUSA procedure, which is due to be completed at the next PRAC meeting. Further discussion and adoption of a recommendation is planned at the September 2019 PRAC meeting.

6.1.2. Inotersen - TEGSEDI (CAP) - PSUSA/00010697/201901

Applicant: Akcea Therapeutics Ireland Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

Background

Inotersen is an antisense oligonucleotide (ASO) inhibitor of human transthyretin (TTR) production. It is indicated, as Tegsedi, for the treatment of stage 1 or stage 2 polyneuropathy in adult patients with hereditary transthyretin amyloidosis (hATTR).

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Tegsedi, a centrally authorised medicine containing inotersen 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 Tegsedi (inotersen) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a warning on liver transplant rejection. Therefore, the current terms of the marketing authorisation(s) should be varied[23].

[23] 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

- In the next PSUR, the MAH should monitor cases of liver rejection and provide a detailed discussion on patient characteristics and on potential risk factors for liver rejection including disease severity.

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. Liraglutide - SAXENDA (CAP); VICTOZA (CAP) - PSUSA/00001892/201812

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

Background

Liraglutide is a glucagon-like peptide 1 (GLP-1) analogue. It is indicated, as Saxenda, as an adjunct to a reduced-calorie diet and increased physical activity for weight management in adult patients with an initial body mass index (BMI) of ≥30 kg/m² (obese), or ≥27 kg/m² to <30 kg/m² (overweight) in the presence of at least one weight-related comorbidity. It is also indicated, as Victoza, 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 Saxenda and Victoza, a centrally authorised medicine containing liraglutide 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 Saxenda and Victoza (liraglutide) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include delayed gastric emptying as an undesirable effect with a frequency 'uncommon'. Therefore, the current terms of the marketing authorisations should be varied[24].
- In the next PSUR, the MAH should monitor cases of neoplasms and evaluate the difference in reporting rates of neoplasms between liraglutide used in T2DM and for liraglutide in weight management.

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. Nivolumab - OPDIVO (CAP) - PSUSA/00010379/201901

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

[24] 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

Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody (HuMAb), which binds to the programmed death-1 (PD-1) receptor and blocks its interaction with programmed death-ligand 1 (PD-L1) and PD-L2. It is indicated, as Opdivo, for the treatment of melanoma as monotherapy or in combination with ipilimumab and as monotherapy for the treatment of adults with locally advanced or metastatic non-small cell lung cancer after prior chemotherapy, advanced renal cell carcinoma after prior therapy, relapsed or refractory classical Hodgkin lymphoma after autologous stem cell transplant (ASCT) and treatment with brentuximab vedotin, recurrent or metastatic squamous cell cancer of the head and neck progressing on or after platinum based therapy and locally advanced unresectable or metastatic urothelial carcinoma after failure of prior platinum-containing therapy.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Opdivo, a centrally authorised medicine containing nivolumab 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 Opdivo (nivolumab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to revise the existing warning on immune-related colitis to include cytomegalovirus (CMV) infection/reactivation. Therefore, the current terms of the marketing authorisation(s) should be varied[25].

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. The frequency of submission of the subsequent PSURs should be changed from 6-monthly to yearly and the list of Union reference dates (EURD list) will be updated accordingly.

6.1.5. Secukinumab - COSENTYX (CAP) - PSUSA/00010341/201812

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

Background

Secukinumab is a fully human immunoglobulin G, subclass 1, κ light chain (IgG1/κ) monoclonal antibody that selectively binds to and neutralises the pro-inflammatory cytokine interleukin-17A (IL-17A). It is indicated, as Cosentyx, for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy as well as for the treatment of active ankylosing spondylitis in adults who have responded inadequately to conventional therapy. It is also indicated alone or in combination with methotrexate (MTX) for the treatment of active psoriatic arthritis in adult patients when the response to previous disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate.

[25] Update of SmPC section 4.4. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Cosentyx, a centrally authorised medicine containing secukinumab, 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 Cosentyx (secukinumab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include lower respiratory tract infections and inflammatory bowel disease as undesirable effects with a frequency 'uncommon'. Therefore, the current terms of the marketing authorisation(s) should be varied[26].
- In the next PSUR, the MAH should provide a cumulative review of cases of sepsis, and of skin infections, particularly focussed on serious cutaneous infections as well as of urinary tract infections (UTIs) and cases of fatal infection. In addition, the MAH should provide cumulative reviews of cases of asthenic conditions, paraesthesia and peripheral neuropathy, as well as of gastroesophageal reflux. Moreover, the MAH should provide a comprehensive discussion on malignancies, including a review of the available literature suggesting that IL-17A has a role as pro-tumour and anti-tumour activity. The MAH should propose amendments of the product information as appropriate.
- The MAH should submit to EMA, within 60 days, a cumulative review of cases of inflammatory bowel disease (IBD) in order to revise the existing warning on IBD in the product information.

The PRAC agreed that further to the recommendation for secukinumab, MAHs of other anti-IL-17A (i.e. brodalumab- and ixekizumab-containing products) should review and discuss in the next PSURs all available data from clinical trials, spontaneous reports and published literature relating to the risk of inflammatory bowel disease associated with these medicinal products. The MAHs should propose amendments of the product information as appropriate.

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.

6.1.6. Sofosbuvir, velpatasvir - EPCLUSA (CAP) - PSUSA/00010524/201812

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

Background

Sofosbuvir is a pan-genotypic inhibitor of the hepatitis C virus (HCV) non-structural protein 5B (NS5B) ribonucleic acid (RNA)-dependent RNA polymerase. Velpatasvir is a HCV inhibitor targeting the HCV non-structural protein 5A (NS5A) protein. In combination, sofosbuvir/velpatasvir is indicated, as Epclusa, for the treatment of chronic HCV infection in adults.

[26] 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

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Epclusa, a centrally authorised medicine containing sofosbuvir/velpatasvir 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 Epclusa (sofosbuvir/velpatasvir) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include new information on the impact of direct-acting antiviral (DAAV) therapy on drugs metabolised by the liver and on the potential need for dose adjustment of those drugs when they are co-administered with DAAV therapy. Therefore, the current terms of the marketing authorisation(s) should be varied[27].
- In the next PSUR, the MAH should perform a cumulative review of rash events and propose to update the product information as appropriate. The MAH should also provide a cumulative safety review of all cases of bradyarrhythmia involving drug-drug interaction with sofosbuvir and amiodarone, and propose to update the product information as appropriate. The MAH should continue to closely monitor cases of hyperglycaemia and discuss them in the next PSUR.

As agreed in the outcome of procedure PSUSA/00010306/201810 for Harvoni (sofosbuvir/ledipasvir) adopted in May 2019, and procedure PSUSA/00010134/201812 for Sovaldi (sofosbuvir) adopted in June 2019, the PRAC considered that the above recommendation for updating the product information to reflect the risk of DAAV therapy affecting other drugs metabolised by the liver is also relevant for other medicinal products within the same therapeutic class (DAAV therapy for HCV). Therefore, the MAHs of centrally authorised products of the same class should update their product information accordingly. Therefore, the MAHs of centrally authorised products of the same class should submit to EMA, within 60 days of the European Commission Decision (CD) a variation to update their product information respectively.

The PRAC also considered that the information regarding the impact of DAAV therapy on tacrolimus and ciclosporin is also relevant for tacrolimus- and ciclosporin-containing products. Therefore, the MAHs of tacrolimus- and ciclosporin-containing products should review the need to update their product information in an upcoming regulatory procedure or at the latest within 60 days of the European Commission (EC) decision. Further consideration should be given at the level of CHMP and CMDh. For further background, see PRAC minutes May 2019 and PRAC minutes June 2019.

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. The frequency of submission of the subsequent PSURs should be changed from 6-monthly to yearly and the list of Union reference dates (EURD list) will be updated accordingly.

6.1.7. Sofosbuvir, velpatasvir, voxilaprevir - VOSEVI (CAP) - PSUSA/00010619/201901

Applicant: Gilead Sciences Ireland UC

[27] Update of SmPC section 4.5. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

Background

Sofosbuvir is a pan-genotypic inhibitor of the hepatitis C virus (HCV) non-structural protein 5B (NS5B) ribonucleic acid (RNA)-dependent RNA polymerase. Velpatasvir is a HCV inhibitor targeting the HCV non-structural protein 5A (NS5A) protein and voxilaprevir is a pan-genotypic inhibitor of the HCV non-structural protein 3/4A (NS3/4A) protease. In combination sofosbuvir/velpatasvir/voxilaprevir is indicated, as Vosevi, for the treatment of chronic HCV infection in adults.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Vosevi, a centrally authorised medicine containing sofosbuvir/velpatasvir/voxilaprevir 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 Vosevi (sofosbuvir/velpatasvir/voxilaprevir in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include new information on the impact of direct-acting antiviral (DAAV) therapy on drugs metabolised by the liver and on the potential need for dose adjustment of those drugs when they are co-administered with DAAV therapy. Therefore, the current terms of the marketing authorisation(s) should be varied[28].
- In the next PSUR, the MAH should continue to closely monitor cases of hyperglycaemia and present and discuss them in the next PSUR.

As agreed in the outcome of procedure PSUSA/00010306/201810 for Harvoni (sofosbuvir/ledipasvir) adopted in May 2019, and procedure PSUSA/00010134/201812 for Sovaldi (sofosbuvir) adopted in June 2019, the PRAC considered that the above recommendation for updating the product information to reflect the risk of DAAV therapy affecting other drugs metabolised by the liver is also relevant for other medicinal products within the same therapeutic class (DAAV therapy for HCV). Therefore, the MAHs of centrally authorised products of the same class should update their product information accordingly. Therefore, the MAHs of centrally authorised products of the same class should submit to EMA, within 60 days of the European Commission Decision (CD) a variation to update their product information respectively.

The PRAC also considered that the information regarding the impact of DAAV therapy on tacrolimus and ciclosporin is also relevant for tacrolimus- and ciclosporin-containing products. Therefore, the MAHs of tacrolimus- and ciclosporin-containing products, should review the need to update their product information in an upcoming regulatory procedure or at the latest within 60 days of the European Commission (EC) decision. Further consideration should be given at the level of CHMP and CMDh. For further background, see PRAC minutes May 2019 and PRAC minutes June 2019.

[28] Update of SmPC section 4.5. 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. The frequency of submission of the subsequent PSURs should be changed from 6-monthly to yearly and the list of Union reference dates (EURD list) will be updated accordingly.

6.1.8. Thyrotropin alfa - THYROGEN (CAP) - PSUSA/00002940/201811

Applicant: Genzyme Europe BV

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

Background

Thyrotropin alfa is a recombinant human thyroid stimulating hormone. It is indicated, as Thyrogen, for use with serum thyroglobulin (Tg) testing with or without radioiodine imaging for the detection of thyroid remnants and well-differentiated thyroid cancer in post-thyroidectomy patients maintained on hormone suppression therapy and for the pre-therapeutic stimulation in combination with a range of 30 mCi[29] (1.1 GBq[30]) to 100 mCi (3.7 GBq) radioiodine for ablation of thyroid tissue remnants in patients who have undergone a near-total or total thyroidectomy for well-differentiated thyroid cancer and who do not have evidence of distant metastatic thyroid cancer.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Thyrogen, a centrally authorised medicine containing thyrotropin alfa 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 Thyrogen (thyrotropin alfa) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to delete the descriptive information regarding stroke from the description of selected adverse reactions, in order to align with currently available evidence on this adverse drug reaction. Therefore, the current terms of the marketing authorisation(s) should be varied[31].
- In the next PSUR, the MAH should review and discuss events of medication error.

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.

6.1.9. Umeclidinium bromide - INCRUSE ELLIPTA (CAP); ROLUFTA ELLIPTA (CAP) - PSUSA/00010263/201812

Applicant(s): GlaxoSmithKline (Ireland) Limited (Incruse Ellipta), GlaxoSmithKline Trading Services Limited (Rolufta Ellipta)

[29] Millicurie
[30] Gigabecquerel
[31] 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

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

Background

Umeclidinium bromide is a long acting muscarinic receptor antagonist. It is indicated, as Incruse Ellipta and Rolufta Ellipta, as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Incruse Ellipta and Rolufta Ellipta, centrally authorised medicines containing umeclidinium bromide 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 Incruse Ellipta and Rolufta Ellipta (umeclidinium bromide) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include dizziness as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[32].

The frequency of PSUR submission should be revised from yearly to three-yearly and the next PSUR should be submitted to the EMA within 90 days of the data lock point. The list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC is updated accordingly.

6.1.10. Umeclidinium bromide, vilanterol - ANORO ELLIPTA (CAP); LAVENTAIR ELLIPTA (CAP) - PSUSA/00010264/201812

Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

Background

Umeclidinium is a long acting muscarinic receptor antagonist and vilanterol, a selective long-acting, beta2-adrenergic receptor agonist. In combination, umeclidinium bromide/vilanterol is indicated, as Anoro Ellipta and Laventair Ellipta, as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Anoro Ellipta and Laventair Ellipta, centrally authorised medicines containing umeclidinium bromide/vilanterol 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 Anoro Ellipta and Laventair Ellipta (umeclidinium bromide/vilanterol) in the approved indication(s) remains unchanged.

[32] 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

- Nevertheless, the product information should be updated to include dizziness as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[33].
- In the next PSUR, the MAH should provide a cumulative review of cases of anxiety and propose amendments to the product information as appropriate.

The frequency of PSUR submission should be revised from yearly to three-yearly and the next PSUR should be submitted to the EMA within 90 days of the data lock point. The list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC is updated accordingly.

6.1.11. Ustekinumab - STELARA (CAP) - PSUSA/00003085/201812

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

Background

Ustekinumab is a fully human immunoglobulin (Ig) G1κ[34] monoclonal antibody that binds with specificity to the shared p40 protein subunit of human cytokines interleukin (IL)-12 and IL-23. It is indicated, as Stelara, for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a tumour necrosis factor alfa (TNFα) antagonist or have medical contraindications to such therapies; for the treatment of moderate to severe plaque psoriasis in adults who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including ciclosporin, methotrexate (MTX) or PUVA (psoralen and ultraviolet A). It is also indicated for the treatment of moderate to severe plaque psoriasis in adolescent patients from the age of 12 years and older, who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies. Furthermore, it is indicated alone or in combination with MTX for the treatment of active psoriatic arthritis (PsA) in adult patients when the response to previous non-biological disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Stelara, a centrally authorised medicine containing ustekinumab, 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 Stelara (ustekinumab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the existing warning on systemic and respiratory hypersensitivity reactions to reflect reported cases of non-infectious organising pneumonia and to add organising pneumonia as an undesirable

[33] 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
[34] Immunoglobulin G, subclass 1, κ light chain

effect with a frequency 'very rare'. Therefore, the current terms of the marketing authorisation(s) should be varied[35].

- In the next PSUR, the MAH should provide a cumulative review on infusion related reactions (IRRs) and comment on the need for measures to minimise the risk of IRRs. The MAH should comment on the need to update the product information in relation to use in patients with a history of active hepatitis B and hepatitis C. The MAH should also provide a cumulative review of demyelinating events, serious hepatic events, and discuss whether the warning on serious infections needs to be updated to reflect the fact that fatal cases of serious infection have occurred. In addition, the MAH should provide a cumulative review of the potential association with *Clostridium difficile* infection. Finally, the MAH should comment whether the product information warrants an update in relation to human papillomavirus (HPV) infection, considering the potential for immunosuppression and several cases of possibly HPV-related malignancies.

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. Bimatoprost, timolol - GANFORT (CAP); NAP - PSUSA/00002961/201811

Applicant(s): Allergan Pharmaceuticals Ireland (Ganfort), various

PRAC Rapporteur: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

Background

Bimatoprost is a synthetic prostamide, structurally related to prostaglandin F2α and timolol is a beta-1 and beta-2 non-selective adrenergic receptor blocking agent. In combination, bimatoprost/timolol is indicated for the reduction of intraocular pressure (IOP) in adult patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to topical beta-blockers or prostaglandin analogues.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Ganfort, a centrally authorised medicine containing bimatoprost/timolol, and nationally authorised medicine(s) containing bimatoprost/timolol 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 bimatoprost/timolol-containing medicinal products in the approved indication(s) remains unchanged.

[35] 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

- Nevertheless, the product information should be updated to include hallucination as an undesirable effect with a frequency 'not known', and to remove a note related to the undesirable effect superior sulcus deepening. Therefore, the current terms of the marketing authorisations should be varied[36].

The PRAC considered that the undesirable effect of hallucination in patients with open-angle glaucoma or ocular hypertension indication is also relevant to be included as an undesirable effect in the product information of single agent and fixed-dose combinations containing timolol as this effect is related to the systemic action of timolol. Further considerations should be given at the level of 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.

6.2.2. Levetiracetam - KEPPRA (CAP); NAP - PSUSA/00001846/201811

Applicant(s): UCB Pharma S.A. (Keppra), various

PRAC Rapporteur: Laurence de Fays

Scope: Evaluation of a PSUSA procedure

Background

Levetiracetam is a pyrrolidone derivative indicated as monotherapy in the treatment of partial onset seizures with or without secondary generalisation in adults and adolescents from 16 years of age with newly diagnosed epilepsy. As an adjunctive treatment, levetiracetam is indicated for the treatment of partial onset seizures with or without secondary generalisation in adults, adolescents, children and infants from 1 month of age with epilepsy; for the treatment of myoclonic seizures in adults and adolescents from 12 years of age with juvenile myoclonic epilepsy as well as for the treatment of primary generalised tonic-clonic seizures in adults and adolescents from 12 years of age with idiopathic generalised epilepsy.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Keppra, a centrally authorised medicine containing levetiracetam, and nationally authorised medicine(s) containing levetiracetam 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 levetiracetam-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a warning on the risk of abnormal and aggressive behaviours in patients treated with levetiracetam. Therefore, the current terms of the marketing authorisations should be varied[37].

[36] 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
[37] 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

- In the next PSUR, the MAHs should provide a cumulative review of cases of 'hypoglycaemia' in association with levetiracetam and include a discussion on the potential hypoglycaemic role of levetiracetam, while distinguishing patients with or without underlying diabetes.
- The MAH UCB Pharma should submit to EMA, within 90 days, a cumulative review of cases of 'cardiac arrhythmia' and 'Torsade de pointes/QT prolongation' in association with levetiracetam as well as cases in relation to the important potential risk 'seizure worsening'. The MAH should propose amendments to the product information as appropriate.

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.

6.2.3. Lutetium (^{177}Lu) chloride - ENDOLUCINBETA (CAP); LUMARK (CAP); NAP - PSUSA/00010391/201812

Applicant(s): ITG Isotope Technologies Garching GmbH (EndolucinBeta), I.D.B. Holland B.V. (Lumark), various

PRAC Rapporteur: Ronan Grimes

Scope: Evaluation of a PSUSA procedure

Background

Lutetium (^{177}Lu) chloride is a radiopharmaceutical precursor indicated for radiolabelling of carrier molecules, which have been specifically developed and authorised for radiolabelling with this radionuclide.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of EndolucinBeta and Lumark, centrally authorised medicines containing lutetium (^{177}Lu) chloride, and nationally authorised medicine(s) containing lutetium (^{177}Lu) chloride 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 containing lutetium (^{177}Lu) chloride-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a warning on tumour lysis syndrome (TLS) and to add TLS as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisations should be varied[38].
- In the next PSUR, the MAH should provide a cumulative review on the possible association between lutetium (^{177}Lu) chloride and hypotension, and to comment on the role of the radiopharmaceutical agent.

[38] 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.

6.2.4. Paclitaxel – APEALEA (CAP); NAP - PSUSA/00002264/201812

Applicant(s): Oasmia Pharmaceutical AB (Apealea), various

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

Background

Paclitaxel is an anti-microtubule agent indicated for the treatment of adult patients with first relapse of platinum-sensitive epithelial ovarian cancer, primary peritoneal cancer and fallopian tube cancer.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Apealea, a centrally authorised medicine containing paclitaxel, and nationally authorised medicine(s) containing paclitaxel 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 paclitaxel-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include information about persistence of neuropathy after discontinuation of paclitaxel treatment and to include palmar-plantar erythrodysesthesia syndrome as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisations should be varied[39].

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.

6.2.5. Sufentanil - DZUVEO (CAP); ZALVISO (CAP); NAP - PSUSA/00002798/201811

Applicant(s): FGK Representative Service GmbH (Dzuveo), Grunenthal GmbH (Zalviso), various

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

Background

Sufentanil is a synthetic, potent opioid with highly selective binding to μ-opioid receptors indicated for the management of acute moderate to severe pain in adult patients, and the management of acute moderate to severe post-operative pain in adult patients, respectively.

[39] 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

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Dzuveo and Zalviso, centrally authorised medicines containing sufentanil, and nationally authorised medicine(s) containing sufentanil 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 sufentanil-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include information on interaction with serotoninergic agents and the risk of serotonin syndrome. Therefore, the current terms of the marketing authorisations should be varied[40].

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. Azathioprine (NAP) - PSUSA/00000275/201812

Applicant(s): various

PRAC Lead: Hans Christian Siersted

Scope: Evaluation of a PSUSA procedure

Background

Azathioprine is a pro-drug of 6-mercaptopurine indicated in immunosuppressive regimens as an adjunct to immunosuppressive agents that form the mainstay of treatment (basis immunosuppression) and indicated either alone or in combination with corticosteroids and/or other drugs in severe cases (patients who are intolerant to steroids or who are dependent on steroids and in whom the therapeutic response is inadequate) of inflammatory bowel disease (IBD), severe rheumatoid arthritis, systemic lupus erythematosus (SLE), dermatomyositis and polymyositis, auto-immune chronic active hepatitis and other inflammatory diseases, subject to certain conditions.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing azathioprine 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 azathioprine-containing products in the approved indication(s) remains unchanged.

[40] Update of SmPC section 4.5. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

- Nevertheless, the product information should be updated to include a warning on interaction between azathioprine and neuromuscular blocking agents and to amend the existing warning on co-administration with xanthine oxidase inhibitors to add additional text. In addition, acute febrile neutrophilic dermatosis (Sweet's syndrome) should be added as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[41].
- In the next PSUR, the MAH(s) should provide a cumulative review and discussion of the safety issue of 'posterior reversible encephalopathy syndrome (PRES)'. The MAH(s) should discuss whether the safety issue is adequately addressed in the product information and should propose an update of the product information as warranted.

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.

6.3.2. Iron[42] (NAP) - PSUSA/00010236/201901

Applicant(s): various

PRAC Lead: Zane Neikena

Scope: Evaluation of a PSUSA procedure

Background

Iron is an essential micronutrient. Iron complexes[43] include iron sucrose, iron carboxymaltose, iron (III) isomaltoside and sodium ferric gluconate for parenteral preparation(s). It is indicated for the treatment of iron deficiency anaemia and other types of anaemias.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing iron 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 iron-containing medicinal product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include, for all intravenous (IV) iron-containing medicinal products, information that cases of foetal bradycardia related to maternal hypersensitivity have been reported and add recommendation that unborn babies should be carefully monitored during IV administration of parenteral iron-containing medicinal products to pregnant women. Additionally, the undesirable effects section should be updated for IV formulations of medicinal products containing sodium ferric gluconate complex to add superficial thrombophlebitis at injection site, with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[44].

[41] Update of SmPC sections 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
[42] Parenteral preparation(s) only, except iron dextran
[43] Iron dextran evaluated in a separate procedure, see under 6.3.3.
[44] Update of SmPC sections 4.6 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

- In the next PSUR, the MAHs should provide for all IV iron-containing products a detailed discussion on the reported cases of hypersensitivity reactions (HSR) with respect to the dose and infusion rate, together with the need to update the product information and to specify within it the current methods of administration (i.e. administration rate and dilution volume) in order to prevent HSR. All MAHs should provide a discussion of severity of reported cases of HSR and propose to update the product information as applicable. The MAH Pharmacosmos should provide an analysis of safety data regarding HSR from ongoing and finished clinical trials and published literature, in the context of the results from the currently ongoing PASS (EUPAS20720)[45] imposed as an outcome of the referral procedure under Article 31 of Directive 2001/83/EC concluded in 2013 (EMA/H/A31/1322). Moreover, the MAHs should provide a discussion on all fatal cases and fatal cases associated with HSR. Finally, MAHs should continue to submit within PSURs the data previously submitted with annual cumulative reviews. These data sets should maintain consistency in presentation across the class, including continuing to use the same data lock point (DLP), exposure and event definitions and classification of severity for the different medicinal products.

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. Iron dextran (NAP) - PSUSA/00010696/201901

Applicant(s): various

PRAC Lead: Zane Neikena

Scope: Evaluation of a PSUSA procedure

Background

Iron dextran is analogous to the physiological form of iron (ferritin) and is indicated for the treatment of anaemias.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing iron dextran 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 iron dextran-containing medicinal product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include information that cases of foetal bradycardia related to maternal hypersensitivity have been reported and to add recommendation that unborn babies should be carefully monitored during intravenous (IV) administration of parenteral iron-containing medicinal products to pregnant women. Therefore, the current terms of the marketing authorisation(s) should be varied[46].

[45] Intravenous iron post-authorisation safety study (PASS): evaluation of the risk of severe hypersensitivity reactions
[46] Update of SmPC section 4.6. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

- In the next PSUR, the MAH(s) should provide a detailed discussion on the reported cases of hypersensitivity reactions (HSR) with respect to the dose and infusion rate, together with the need to update the product information and to specify the current methods of administration (i.e. administration rate and dilution volume) in the product information in order to prevent HSR. The MAH(s) should also provide a discussion of severity of reported cases of HSR and propose to update the product information as applicable. Finally, MAH(s) should continue to submit within PSURs the data previously submitted with annual cumulative reviews. These data sets should maintain consistency in presentation across the class, including continuing to use the same data lock point (DLP), exposure and event definitions and classification of severity for the different medicinal products.

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.

6.3.4. Ketamine (NAP) - PSUSA/00001804/201812

Applicant(s): various

PRAC Lead: Laurence de Fays

Scope: Evaluation of a PSUSA procedure

Background

Ketamine is a rapid-acting, non-barbiturate, general anaesthetic indicated for induction of anaesthesia prior to the administration of other general anaesthetic agents. It is also indicated as the sole anaesthetic agent for diagnostic and surgical procedures that do not require skeletal muscle relaxation. Additionally, it is indicated to supplement low-potency agents, such as nitrous oxide.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing ketamine 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 ketamine-containing medicinal product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to revise the existing warnings on long term use and on drug abuse and dependence regarding the occurrence of acute kidney injury, hydronephrosis and ureteral disorders. Therefore, the current terms of the marketing authorisation(s) should be varied[47].

[47] Update of SmPC section 4.4. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

- In the next PSUR, the MAH(s) should provide a cumulative review of diabetes insipidus, following recent publications[48]. The MAH(s) should continue to monitor cases of off-label use with ketamine for sleep disorder, depression/anxiety, or mood disorder.

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.

6.3.5. Metoclopramide (NAP) - PSUSA/00002036/201811

Applicant(s): various

PRAC Lead: Karen Pernille Harg

Scope: Evaluation of a PSUSA procedure

Background

Metoclopramide is a dopamine-receptor (D2) antagonist. It is indicated in adults for the prevention of delayed chemotherapy-induced nausea and vomiting (CINV), the prevention of radiotherapy induced nausea and vomiting (RINV), as well as for the symptomatic treatment of nausea and vomiting, including acute migraine-induced nausea and vomiting under certain conditions.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing metoclopramide 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 metoclopramide-containing medicinal product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include visual disturbances and oculogyric crisis as undesirable effects with a frequency 'uncommon'. Therefore, the current terms of the marketing authorisation(s) should be varied[49].
- In the next PSUR, the MAH(s) should closely monitor cases of off label use in paediatric patients, and discuss if any risk minimisation measures (RMMs) are warranted. In addition, MAH(s) should perform a cumulative review of cases of off-label use in breastfeeding women to increase milk production, discuss how frequently this occurs in the EU, and review the potential risks to women and breastfed infants.

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.

[48] Including Gaffar S et al. A case of central diabetes insipidus after ketamine infusion during an external to internal carotid artery bypass. J Clin Anesth. 2017;36:72-75; Kataria V et al. Ketamine-induced diabetes insipidus. J Pain Palliat Care Pharmacother. 2018;32(2-3):165-169

[49] 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

6.3.6. Tapentadol (NAP) - PSUSA/00002849/201811

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

Tapentadol is a centrally acting synthetic analgesic indicated for the relief of moderate to severe acute pain, and for the management of severe chronic pain in adults, which can be adequately managed only with opioid analgesics.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing tapentadol 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 tapentadol-containing medicinal product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include delirium as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[50].

The frequency of PSUR submission should be revised from yearly to three-yearly and the next PSUR should be submitted to the EMA within 90 days of the data lock point. The list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC is updated accordingly.

6.3.7. Valaciclovir (NAP) - PSUSA/00003086/201812

Applicant(s): various

PRAC Lead: Jana Lukačišinová

Scope: Evaluation of a PSUSA procedure

Background

Valaciclovir is a prodrug of acyclovir and it is rapidly and almost completely converted to acyclovir, which is a purine (guanine) nucleoside analogue which acts as a specific inhibitor of herpes viruses. It is indicated for the treatment of varicella and herpes zoster, treatment of herpes labialis, treatment and prevention of recurrent herpes simplex infection of the skin and mucous membranes, including genital herpes and for prophylaxis of cytomegalovirus (CMV) infection following organ transplantation.

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

Summary of recommendation(s) and conclusions

[50] 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

- Based on the review of the data on safety and efficacy, the benefit-risk balance of valaciclovir-containing medicinal product(s) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAHs should provide a cumulatively review of new cases of severe cutaneous adverse reactions (SCARs), including a literature review. The MAH(s) should closely monitor cases of overdose in patients with renal impairment/elderly. In addition, MAH(s) should provide a detailed review of new cases of acute kidney injury in patients taking concomitantly valaciclovir and non-steroidal anti-inflammatory drugs (NSAID). Moreover, MAH(s) should provide a cumulative review of cross-reactivity between valaciclovir and other antivirals intended for the treatment of herpes virus infections and a literature review should be presented. As a consequence, MAH(s) should propose to update the product information as appropriate.
- The PRAC considered that the MAH for the originator product containing valaciclovir (GlaxoSmithKline) should be requested to provide detailed reviews on cases of severe cutaneous reactions, including blister, skin exfoliation and skin erosion, on drug reaction with eosinophilia and systemic symptoms (DRESS) as well as a detailed review of cases of acute kidney, including a disproportionality analysis and a literature search. Further consideration will be given at the level of 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.

6.4. Follow-up to PSUR/PSUSA procedures

See Annex I 16.4.

7. Post-authorisation safety studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)[51]

See Annex I 17.1.

7.2. Protocols of PASS non-imposed in the marketing authorisation(s)[52]

See also Annex I 17.1.

7.2.1. Neratinib - NERLYNX (CAP) - EMEA/H/C/004030/MEA 002

Applicant: Puma Biotechnology B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Protocol for study PUMA-NER-6202: a randomised study to characterise the incidence and severity of diarrhoea in patients with early stage epidermal growth factor

[51] In accordance with Article 107n of Directive 2001/83/EC
[52] 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

receptor 2 + (HER2+) breast cancer treated with neratinib and intensive loperamide prophylaxis versus neratinib and intensive loperamide prophylaxis plus a bile acid sequestrant in the first month of treatment [final study results expected in December 2021] (from the initial opinion/MA)

Background

Nerlynx is a centrally authorised medicine containing neratinib, an irreversible pan-erythroblastic leukaemia viral oncogene homolog (ERBB) tyrosine kinase inhibitor (TKI) indicated for the extended adjuvant treatment of adult patients with early-stage hormone receptor positive epidermal growth factor receptor 2 (HER2)-overexpressed/amplified breast cancer and who completed adjuvant trastuzumab-based therapy less than one year ago.

As part of the RMP of Nerlynx (neratinib), the MAH is requested to conduct a randomised study to characterise the incidence and severity of diarrhoea in patients with early stage HER2+ breast cancer treated with neratinib The MAH submitted a protocol for study PUMA-NER-6202 for the evaluation of the risk of diarrhoea which was assessed by the Rapporteur. The PRAC was requested to provide advice to CHMP on the protocol submitted by the MAH.

Summary of advice

- The study protocol version 1.1 for study PUMA-NER-6202 could be considered acceptable provided an updated protocol and satisfactory responses to the request for supplementary information (RSI) are submitted.
- The PRAC considered that the research questions and objectives as well as variables should be revised. In particular, the MAH should include the systematic collection of gastrointestinal adverse events, other than diarrhoea. In addition, the MAH should amend the definition of intention-to-treat (ITT) population. More information is requested on handling of missing data, randomization methods, clinical difference for the patient reported outcomes, sample size of the control cohort, and limitations of the research methods.

7.2.2. Neratinib - NERLYNX (CAP) - EMEA/H/C/004030/MEA 003

Applicant: Puma Biotechnology B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Protocol for study PUMA-NER-7402: a non-interventional study exploring the safety of neratinib among breast cancer patients to characterise the incidence and duration of diarrhoea in a real world setting, to describe patient characteristics, incidence rates and duration of diarrhoea, to describe use of loperamide and other concomitant anti-diarrhoeal medication, describe adherence to neratinib therapy, assess the impact of neratinib therapy on patient self-reported, health related quality of life and their ability to perform their activities of daily living and to further assess and characterise adverse events hepatic, cardiac, pulmonary, reproductive and developmental toxicity [final study results expected in December 2023] (from the initial opinion/MA)

Background

Nerlynx is a centrally authorised medicine containing neratinib, an irreversible pan-erythroblastic leukaemia viral oncogene homolog (ERBB) tyrosine kinase inhibitor (TKI) indicated for the extended adjuvant treatment of adult patients with early-stage hormone

receptor positive epidermal growth factor receptor 2 (HER2)-overexpressed/amplified breast cancer and who completed adjuvant trastuzumab-based therapy less than one year ago.

As part of the RMP of Nerlynx (neratinib), the MAH is requested to conduct an observational study to evaluate the incidence of treatment discontinuation due to diarrhoea at three months in patients receiving neratinib for the treatment of early-stage HER2+ and hormone receptor-positive breast cancer and who are participating in the patient support programme. The MAH submitted a protocol for study PUMA-NER-7402 which was assessed by the Rapporteur. The PRAC was requested to provide advice to CHMP on the protocol submitted by the MAH.

Summary of advice

- The study protocol version 1.1 for study PUMA-NER-7402 could be considered acceptable provided an updated protocol and satisfactory responses to the request for supplementary information (RSI) are submitted.
- The MAH should further justify that patients and treatments are comparable within and outside the patient support programme (PSP) and dose reductions due to diarrhoea should be included as a secondary endpoint. In addition, more information is requested on adverse events (AEs) of special interest, patient reported outcomes, justification of the sample size, data analysis and limitations of the research methods. Moreover, a variable related to the receipt of the educational materials should be included.

7.2.3. Neratinib - NERLYNX (CAP) - EMEA/H/C/004030/MEA 004

Applicant: Puma Biotechnology B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Protocol for study PUMA-NER-7403: a study to evaluate the availability, interpretability, and impact of Nerlynx (neratinib) educational materials [final study results expected in December 2021] (from the initial opinion/MA)

Background

Nerlynx is a centrally authorised medicine containing neratinib, an irreversible pan-erythroblastic leukaemia viral oncogene homolog (ERBB) tyrosine kinase inhibitor (TKI) indicated for the extended adjuvant treatment of adult patients with early-stage hormone receptor positive epidermal growth factor receptor 2 (HER2)-overexpressed/amplified breast cancer and who completed adjuvant trastuzumab-based therapy less than one year ago.

As part of the RMP of Nerlynx (neratinib), the MAH is requested to conduct a study to assess the interpretability and accessibility of educational materials for patients receiving Nerlynx (neratinib) and for healthcare providers prescribing Nerlynx (neratinib) in the European Union (EU). The MAH submitted a protocol for study PUMA-NER-7403 which was assessed by the Rapporteur. The PRAC was requested to provide advice to CHMP on the protocol submitted by the MAH.

Summary of advice

- The study protocol version 1.1 for study PUMA-NER-7403 could be acceptable provided an updated protocol and satisfactory responses to a list of questions agreed by the PRAC are submitted to the EMA within 60 days.

- The PRAC noted that within this study the effectiveness of the educational materials is only evaluated through process indicators and not on outcome indicators. Therefore, the MAH should discuss whether and how the effectiveness of the educational materials can be studied within study PUMA-NER-7402.

See also under 7.2.2.

7.3. Results of PASS imposed in the marketing authorisation(s)[53]

None

7.4. Results of PASS non-imposed in the marketing authorisation(s)[54]

See also Annex I 17.4.

7.4.1. Bosentan - STAYVEER (CAP) - EMEA/H/C/002644/II/0027

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Adrien Inoubli

Scope: Submission of the final report from study AC-052-516 (listed as a category 1 study in Annex II and the RMP): a non-interventional observational study of the disease characteristics and outcomes of pulmonary arterial hypertension (PAH) in children and adolescents in real-world clinical settings. The RMP (version 10) is updated accordingly and in line with revision 2 of GVP module V on 'Risk management systems'

Background

Stayveer is a centrally authorised medicine containing bosentan, a dual endothelin receptor antagonist (ERA) with affinity for both endothelin A and B (ETA and ETB) receptors. Stayveer (bosentan) is indicated for the treatment of pulmonary arterial hypertension (PAH) to improve exercise capacity and symptoms in patients with WHO[55] functional class III. It is also indicated to reduce the number of new digital ulcers in patients with systemic sclerosis and ongoing digital ulcer disease.

As stated in the RMP of Stayveer (bosentan) and in Annex II-D on 'Conditions or restrictions with regard to the safe and effective use of the medicinal product', the MAH conducted study AC-052-516, a non-interventional PASS, to assess the disease characteristics and outcomes of PAH in children and adolescents in real-world clinical settings. The Rapporteur assessed the MAH's final study report. The PRAC is responsible for producing an assessment report to be further considered at the level of the CHMP, which is responsible for adopting an opinion on this variation.

Summary of advice

- Based on the available data and the Rapporteur's review, the PRAC considered that the ongoing variation assessing the final study report can be concluded positively. The PRAC advised for a positive opinion.
- The PRAC agreed that despite follow-up until puberty has not been completely fulfilled,

[53] In accordance with Article 107p-q of Directive 2001/83/EC
[54] 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
[55] World Health Organization

future reporting is unlikely to provide significant additional information of demographics, disease characteristics and PAH safety outcomes. The PRAC advised to remove the study from the 'Conditions or restrictions with regard to the safe and effective use of the medicinal product'.

7.4.2. Bosentan - TRACLEER (CAP) - EMEA/H/C/000401/II/0091

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Adrien Inoubli

Scope: Submission of the final report from study AC-052-516 (listed as a category 1 study in Annex II and the RMP): a non-interventional observational study of the disease characteristics and outcomes of pulmonary arterial hypertension (PAH) in children and adolescents in real-world clinical settings. The RMP (version 10) is updated accordingly and in line with revision 2 of GVP module V on 'Risk management systems'

Background

Tracleer is a centrally authorised medicine containing bosentan, a dual endothelin receptor antagonist (ERA) with affinity for both endothelin A and B (ETA and ETB) receptors. Tracleer (bosentan) is indicated for the treatment of pulmonary arterial hypertension (PAH) to improve exercise capacity and symptoms in patients with WHO[56] functional class III. It is also indicated to reduce the number of new digital ulcers in patients with systemic sclerosis and ongoing digital ulcer disease.

As stated in the RMP of Tracleer (bosentan) and in Annex II-D on 'Conditions or restrictions with regard to the safe and effective use of the medicinal product', the MAH conducted study AC-052-516, a non-interventional PASS, to assess the disease characteristics and outcomes of PAH in children and adolescents in real-world clinical settings. The Rapporteur assessed the MAH's final study report. The PRAC is responsible for producing an assessment report to be further considered at the level of the CHMP, which is responsible for adopting an opinion on this variation.

Summary of advice

- Based on the available data and the Rapporteur's review, the PRAC considered that the ongoing variation assessing the final study report can be concluded positively. The PRAC advised for a positive opinion.
- The PRAC agreed that despite follow-up until puberty has not been completely fulfilled, future reporting is unlikely to provide significant additional information of demographics, disease characteristics and PAH safety outcomes. The PRAC advised to remove the study from the 'Conditions or restrictions with regard to the safe and effective use of the medicinal product'.

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.

[56] World Health Organization

7.6. Others

See Annex I 17.6.

7.7. New Scientific Advice

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

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. Ospemifene - SENSHIO (CAP) - EMEA/H/C/002780/R/0028 (without RMP)

Applicant: Shionogi B.V.

PRAC Rapporteur: Kirsti Villikka

Scope: 5-year renewal of the marketing authorisation

Background

Ospemifene is a selective oestrogen receptor modulator indicated for the treatment of moderate to severe symptomatic vulvar and vaginal atrophy (VVA) in post-menopausal women who are not candidates for local vaginal oestrogen therapy.

Senshio, a centrally authorised medicine containing ospemifene, 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 Senshio (ospemifene) and the CHMP Rapporteur's assessment report, the PRAC considered that a second five-year renewal of the marketing authorisation(s) is warranted based on pharmacovigilance grounds.

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

12.3.1. Guideline on the clinical investigation of recombinant and human plasma-derived factor VIII products on requirements for previously untreated patients (PUPs) - PRAC and PDCO flow for paediatric investigation plans (PIPs) of authorised medicinal products with studies on PUPs

In order to manage changes to the 'Guideline on the clinical investigation of recombinant and human plasma-derived factor VIII products on requirements for previously untreated patients (PUPs)', the EMA Secretariat presented to the PRAC a proposal for information flow between the Paediatric Committee (PDCO) and the PRAC for paediatric investigation plans (PIPs) of authorised medicinal products with studies involving PUPs for factor VIII-containing products. The PRAC supported the proposal to be kept informed about changes to agreed PIPs regarding studies in PUPs in order to ensure a full regulatory oversight and to facilitate future planning while following criteria for RMPs.

12.4. Cooperation within the EU regulatory network

None

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

12.6.1. International Conference on Harmonisation (ICH) E2B(R3) on electronic transmission of individual case safety reports - data elements and message specification - stakeholder readiness for mandatory use

The PRAC was presented with the results of the stakeholder readiness survey on the implementation of the ISO[57]/ICH[58] E2B(R3) standard for electronic transmission of

[57] International Organization for Standardization
[58] International Conference on Harmonisation

individual case safety reports (ICSRs).

Follow-up discussion is scheduled in October 2019.

12.7. PRAC work plan

None

12.8. Planning and reporting

12.8.1. Marketing authorisation applications (MAA) forecast for 2019 – planning update dated Q2 2019

The EMA Secretariat presented to PRAC for information a quarterly updated report on marketing authorisation applications planned for submission (the business 'pipeline'). For previous update, see PRAC minutes April 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 PRAC was updated on the activities of the Granularity and Periodicity Advisory Group (GPAG), focussing on harmonising and streamlining the EURD list, and noted the GPAG progress highlights. In particular, the PRAC was updated on the development of the EURD tool.

12.10.3. PSURs repository

None

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

The PRAC endorsed the draft revised EURD list, version July 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 July 2019, the updated EURD list was adopted by the CHMP and CMDh at their July 2019 meetings and published on the EMA website on 5 August 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 outcome of the SMART Working Group (SMART WG) processes meeting held on 8 July 2019. The SMART WG discussed about the evaluation of the pilot of monitoring EudraVigilance data by MAHs, in preparation of the discussion at PRAC, and practical arrangements for future meeting frequency.

See also under 12.11.2.

12.11.2. Signal management - monitoring of EudraVigilance data by MAHs – experience from the pilot period

The EMA Secretariat presented to PRAC a summary of the evaluation of the monitoring of EudraVigilance (EV) data by MAHs, in the context of the pilot period which started on 22 February 2018. Approximately 300 active substances and combinations were included in the pilot. A limited number of signal notifications were received during the pilot period and only one was confirmed for PRAC evaluation.

Further discussion is planned in September 2019.

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 31 July 2019 on the EMA website, see:

Home>Human Regulatory>Human medicines>Pharmacovigilance>Signal management>List of medicines under additional monitoring).

12.13. EudraVigilance database

12.13.1. Activities related to the confirmation of full functionality

None

12.13.2. EudraVigilance – EMA data management and quality activities

The EMA Secretariat provided PRAC with an overview of the data management and quality assurance activities performed by the EMA on information of suspected adverse reactions and medicinal products reported to and held in EudraVigilance (EV) and the extended EV medicinal product dictionary (XEVMPD) in line with revision 2 of GVP module VI on 'Collection, management and submission of reports of suspected adverse reactions to medicinal products'. The EMA and the National competent Authorities (NCAs) work towards ensuring collaboration on assuring quality of data in EV to maximise the use of resources available within the European Union (EU).

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. EMA policy on handling of competing interests for scientific committees' members and experts – reminder training

The PRAC was provided with a re-fresher training on the 'EMA policy on the handling of competing interests for scientific committees' members and experts' (EMA/626261/2014,Rev. 1), which requires the declaration and evaluation of any competing interests that a committee member or participating experts may have. For further background, see PRAC minutes December 2016.

12.20.2. EMA reimbursement rules for delegates - update

The PRAC was informed of the updated reimbursement rules for delegates participating in EMA meetings, further to their adoption by the EMA Management Board (MB) in June 2019.

12.20.3. Rapid data analytical process - pilot

The EMA Secretariat presented to PRAC a pilot for a collaborative rapid data analytical process, tested by the EMA in 2019, to provide rapid identification, analysis and reporting of results for questions identified during regulatory procedures and which could be answered in electronic healthcare databases (EHDs) in support of topics currently discussed by PRAC. The PRAC supported the initiative. PRAC members were invited to send nominations by 31 July 2019 in order to volunteer to participate in the pilot. The evaluation of the pilot will be presented to PRAC in Q1 2020.

Post-meeting note: Jean-Michel Dogné, Nikica Mirošević Skvrce, Daniel Morales and Antoine Pariente volunteered to participate in the pilot.

13. Any other business

None

14. Annex I – Signals assessment and prioritisation[59]

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[60].

14.2. New signals detected from other sources

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

Applicant(s): Meda AB, various

PRAC Rapporteur: To be appointed

Scope: Signal of pemphigus, new onset and relapse

EPITT 19441 – New signal

Lead Member State(s): PL

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. Arsenic trioxide - EMEA/H/C/005175

Scope: Treatment of relapsed acute promyelocytic leukaemia (APL)

[59] 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

[60] 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

15.1.2. Clofarabine - EMEA/H/C/005039

Scope: Treatment of acute lymphoblastic leukaemia

15.1.3. Lidocaine, prilocaine - EMEA/H/C/005298

Scope: Treatment of primary premature ejaculation in adult men

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. Cobimetinib - COTELLIC (CAP) - EMEA/H/C/003960/II/0016

Applicant: Roche Registration GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Submission of an updated RMP (version 4) in order to revise safety concerns in line with revision 2 of GVP module V on 'Risk management systems'. In addition, the outcome of procedure MEA 003.3 adopted at the November 2018 PRAC meeting (held on 29-31 October 2018) is implemented as requested

15.2.2. Exenatide - BYETTA (CAP) - EMEA/H/C/000698/II/0069

Applicant: AstraZeneca AB

PRAC Rapporteur: Annika Folin

Scope: Submission of a justification for extrapolating exenatide once weekly clinical data (previously assessed for Bydureon) to exenatide twice daily (Byetta) in order to include the latest agreed RMP versions for Bydureon (v30, v31s2 and v32s2) also in the dossier for Byetta. As a consequence, the removal of the important potential risk 'Cardiac Events' is proposed also for Byetta

15.2.3. Filgrastim - FILGRASTIM HEXAL (CAP) - EMEA/H/C/000918/WS1608/0049; Filgrastim - ZARZIO (CAP) - EMEA/H/C/000917/WS1608/0050

Applicant: Sandoz GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Submission of an updated RMP (version 12.0) in order to align the due dates and deliverables for post-authorisation measure MEA 007 relating to study EP06-501: a non-interventional, prospective, long-term safety data collection of Zarzio/Filgrastim Hexal (filgrastim) in healthy unrelated stem cell donors undergoing peripheral blood progenitor cell mobilisation. The due date is extended from December 2019 to March 2020, to combine the annual safety report (ASR) with the 5-year interim clinical study report (CSR) in 2020 and the final CSR in 2024 and for the MEA to cover the entire duration of study EP06-501

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. Natalizumab - TYSABRI (CAP) - EMEA/H/C/000603/II/0114

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Submission of an update of the RMP (version 25.0) with information related to extended interval dosing that will be added to the educational materials. Annex II-D on 'Conditions or restrictions with regard to the safe and effective use of the medicinal product' of the product information is updated accordingly

15.2.6. Pembrolizumab - KEYTRUDA (CAP) - EMEA/H/C/003820/II/0068

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Update of the RMP (version 23.1) in order to discuss the effectiveness of the educational materials put in place for Keytruda (pembrolizumab) at the time of the initial marketing authorisation, to provide a proposal to update these materials and to revise the safety specification as requested in the outcome of the PSUR single assessment procedure (PSUSA/00010403/201803) finalised in October 2018

15.2.7. Posaconazole - NOXAFIL (CAP) - EMEA/H/C/000610/II/0057

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Adrien Inoubli

Scope: Submission of an updated RMP (version 15.1) in order to bring it in line with revision 2 of GVP module V on 'Risk management systems' with the consequent applicable re-evaluation of some safety concerns. In addition, the MAH took the opportunity to include data from the completed clinical trial in paediatric subjects PN097: a phase 1B study of the safety, tolerability, and pharmacokinetics of intravenous (IV) and powder for oral suspension formulations of posaconazole (POS) in immunocompromised paediatric subjects, and update the due date for submission changed from December 2019 to Q4 2020 for the final report of the ongoing post-marketing efficacy trial PN069: a phase 3 randomised study on the efficacy and safety of posaconazole versus voriconazole for the treatment of invasive aspergillosis in adults and adolescents

15.2.8. Pregabalin - PREGABALIN MYLAN (CAP) - EMEA/H/C/004078/WS1603/0013; PREGABALIN MYLAN PHARMA (CAP) - EMEA/H/C/003962/WS1603/0011

Applicant: Mylan S.A.S

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Submission of an updated RMP (version 6) to get adjusted to the RMP of the originator medicinal product containing pregabalin. In addition, the RMP is updated in line with revision 2 of the guidance on the format of RMP in the EU (template)

15.2.9. Ribavirin - REBETOL (CAP) - EMEA/H/C/000246/II/0086

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Adrien Inoubli

Scope: Submission of an updated RMP (version 5.1) in order to revise safety concerns for ribavirin in line with revision 2 of GVP module V on 'Risk management systems'. In addition, the MAH took the opportunity to revise the safety concerns of ribavirin in light of the current era of interferon (IFN) free regimen, as requested in a previous PSUSA procedure (EMEA/H/C/PSUSA/00010007/201707) concluded in March 2018

15.2.10. Saxagliptin, metformin hydrochloride - KOMBOGLYZE (CAP) - EMEA/H/C/002059/II/0046

Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: Submission of an updated RMP (version 15) in order to bring it in line with revision 2 of the guidance on the format of RMP in the EU (template). As a result, the list of safety concerns has been revised and a number of important identified risks, important potential risks and missing information have been reclassified or removed from the RMP

15.2.11. Talimogene laherparepvec - IMLYGIC (CAP) - EMEA/H/C/002771/II/0034

Applicant: Amgen Europe B.V., ATMP[61]

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Submission of an updated RMP (version 7.0) in order to add 2 category 3 studies, namely: 1) study 20180062: a cross-sectional survey to evaluate patient knowledge of safety messages included in the patient safety brochure and patient alert card and; 2) study 20180099: a cross-sectional survey to evaluate physician knowledge of safety messages included in the physician education booklet; as well as an internal evaluation of managed distribution process metrics, to evaluate the effectiveness of additional risk minimisation measures (aRMM)

[61] Advanced therapy medicinal product

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. Afatinib - GIOTRIF (CAP) - EMEA/H/C/002280/II/0031

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Annika Folin

Scope: Update of sections 4.4 and 4.8 of the SmPC in order to add gastrointestinal (GI) perforation as an additional side effect based on summaries of clinical trial and post-marketing safety data. The package leaflet is updated accordingly. In addition, the RMP (version 8.0) is updated accordingly and in line with revision 2 of the guidance on the format of RMP in the EU (template), taking also into consideration recommendations part of the conclusions of renewal procedure R/0026 adopted in March 2018. Furthermore, the MAH took the opportunity to correct some typographical errors in the German, Austrian and Spanish product information and to update the list of the local representatives for Austria in the package leaflet

15.3.2. Buprenorphine, naloxone - SUBOXONE (CAP) - EMEA/H/C/000697/X/0042

Applicant: Indivior Europe Limited

PRAC Rapporteur: Martin Huber

Scope: Extension application to introduce a new pharmaceutical form (sublingual film) associated with four new strengths (2/0.5 mg, 4/1 mg, 8/2 mg and 16/4 mg) and a new route of administration (either sublingual or buccal administration). The RMP (version 14.0) is updated accordingly

15.3.3. Cariprazine - REAGILA (CAP) - EMEA/H/C/002770/II/0010

Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Submission of in vitro metabolism study report for study R188-A15. The RMP (version 1.6) is updated accordingly

15.3.4. Daratumumab - DARZALEX (CAP) - EMEA/H/C/004077/II/0029, Orphan

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Extension of indication to extend the existing therapeutic indication for Darzalex (daratumumab) in combination with lenalidomide and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant (ASCT). As a consequence, sections 4.1, 4.2, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 6.0 s1) are updated accordingly

15.3.5. Daratumumab - DARZALEX (CAP) - EMEA/H/C/004077/II/0030, Orphan

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Extension of indication to extend the existing therapeutic indication for Darzalex (daratumumab) in combination with bortezomib, thalidomide and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma who are eligible for autologous stem cell transplant (ASCT). As a consequence, sections 4.1, 4.2, 4.5, 4.8 and 5.1 of the SmPC are updated. The package leaflet and RMP (version 6.0 s1) are updated accordingly

15.3.6. 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 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 quality review of documents (QRD) template (version 10.0)

15.3.7. Deferiprone - FERRIPROX (CAP) - EMEA/H/C/000236/II/0128

Applicant: Apotex B.V.

PRAC Rapporteur: Ghania Chamouni

Scope: Update of section 4.4 of the SmPC and the patient/carer reminder card in order to update and change the recommended frequency of absolute neutrophil count (ANC) monitoring throughout Ferriprox (deferiprone) treatment from a weekly basis to every week for the first six months of therapy, once every two weeks after six months and to monthly after one year of therapy. The package leaflet and the RMP (version 13.2) are updated accordingly. In addition, the MAH took the opportunity to introduce minor linguistic amendments in the Hungarian and Maltese product information

15.3.8. 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'

15.3.9. Eculizumab - SOLIRIS (CAP) - EMEA/H/C/000791/II/0105, Orphan

Applicant: Alexion Europe SAS

PRAC Rapporteur: Eva Segovia

Scope: Extension of indication to include treatment of adult patients with neuromyelitis optica spectrum disorder (NMOSD) who are anti-aquaporin-4 (AQP4) antibody (Ab) positive with a relapsing course of the disease. As a consequence the SmPC sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2, Annex II are updated. The package leaflet and the RMP (version 19) are updated accordingly

15.3.10. Empagliflozin, linagliptin - GLYXAMBI (CAP) - EMEA/H/C/003833/WS1601/0022; Linagliptin, metformin - 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. Fluciclovine (^{18}F) - AXUMIN (CAP) - EMEA/H/C/004197/II/0011

Applicant: Blue Earth Diagnostics Ireland Limited

PRAC Rapporteur: Rugile Pilviniene

Scope: Extension of indication to include diagnosis and continuing assessment of glioma in adult patients. As a consequence, sections 4.1, 4.2, 4.4, 4.6, 5.1, 5.2 and 11 of the SmPC and Annex II are updated. The package leaflet and the RMP (version 3.0) are updated accordingly

15.3.12. Insulin human - ACTRAPHANE (CAP) - EMEA/H/C/000427/WS1582/0076; ACTRAPID (CAP) - EMEA/H/C/000424/WS1582/0070; INSULATARD (CAP) - EMEA/H/C/000441/WS1582/0073; MIXTARD (CAP) - EMEA/H/C/000428/WS1582/0077; PROTAPHANE (CAP) - EMEA/H/C/000442/WS1582/0072

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Hans Christian Siersted

Scope: Submission of an updated RMP (version 3.0) for insulin human-containing products to reclassify the risk of 'medication errors' from an important potential risk to an important identified risk as requested in the outcome of the PSUR single assessment procedure PSUSA/00001753/201710 finalised in June 2018 and in line with the 'Good practice guide on risk minimisation and prevention of medication errors' dated 2015. However, the RMP is also brought in line with revision 2 of GVP module V on 'Risk management systems' and revision 2 of the guidance on the format of RMP in the EU (template). As a consequence, the MAH proposes to remove this risk as it is fully characterised and managed through routine pharmacovigilance and routine risk minimisation measures. In addition, section 4.4 of the SmPC is updated in order to add a warning on accidental mix-ups/medication. The package leaflet is updated accordingly. Furthermore, the MAH took the opportunity to include minor updates to Annex III-A on 'labelling' and to bring the package leaflet in line with the latest quality review document (QRD) template (version 10.0)

15.3.13. Insulin human - INSUMAN (CAP) - EMEA/H/C/000201/II/0130

Applicant: Sanofi-Aventis Deutschland GmbH

PRAC Rapporteur: Jean-Michel Dogné

Scope: Submission of the final clinical study report (CSR) from study HUBIN_L_05335 (listed as a category 3 study in the RMP): a phase 3 study covering the evaluation of Insuman Implantable 400 IU/mL (insulin human) in patients with type 1 diabetes treated with the Medtronic MiniMed Implantable Pump System using Insuplant 400 IU/mL (in fulfilment of post-authorisation measure (PAM) MEA040). The RMP (version 4.0) is updated accordingly and includes the amended protocol (version 2) of the ongoing study HUBIN_C_06380: an European observational cohort of patients with type 1 diabetes treated via intraperitoneal route with Insuman Implantable 400 IU/mL (insulin human) in Medtronic MiniMed implantable pump as endorsed by PRAC in procedure MEA 047.5 in May 2018

15.3.14. Ivacaftor - KALYDECO (CAP) - EMEA/H/C/002494/X/0075/G, Orphan

Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Grouped applications consisting of: 1) extension application to add a new strength of 25 mg granules in sachet in the treatment of cystic fibrosis in children aged 6 to less than 12 months old; 2) update of sections 4.2, 4.8, 5.1, 5.2 and 5.3 of the SmPC, and sections 2 and 3 of the package leaflet for the 150 mg film-coated tablet presentation to bring it in line with the new dosage form (25 mg granules). The RMP (version 8.3) is updated accordingly. In addition, the MAH took the opportunity to implement minor updates in the product information

15.3.15. Ixazomib - NINLARO (CAP) - EMEA/H/C/003844/II/0014/G, Orphan

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Annika Folin

Scope: Grouped variations consisting of 1) submission of the final report of progression free survival (PFS) in fulfilment of study C16019 (SOB004): a phase 3, randomised, placebo-controlled, double-blind study of oral ixazomib citrate maintenance therapy in patients with multiple myeloma following autologous stem cell transplant; 2) request for an extension of the due date for study C16014 (SOB003): a phase 3, randomised, double-blind, multicentre study comparing oral ixazomib plus lenalidomide and dexamethasone versus placebo plus lenalidomide and dexamethasone in adult patients with newly diagnosed multiple myeloma (NDMM). As a result, Annex II is amended. The RMP (version 4.0) is updated accordingly

15.3.16. Lapatinib - TYVERB (CAP) - EMEA/H/C/000795/II/0062

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Annika Folin

Scope: Submission of the final report from study EGF117165/LAP016A2206 (listed as an obligation in the Annex II of the product information): an open-label, phase 2 study to evaluate biomarkers associated with response to subsequent therapies in subjects with epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer receiving treatment with trastuzumab in combination with lapatinib or chemotherapy. Annex II and the RMP (version 36.0) are updated accordingly

15.3.17. Meningococcal group B vaccine (recombinant, adsorbed) - TRUMENBA (CAP) - EMEA/H/C/004051/II/0013

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Jean-Michel Dogné

Scope: Extension of indication to include active immunisation of children 1-9 years old. As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated based on the results from the two pivotal studies, namely B1971017: a phase 2, randomised, controlled, observer-blinded study to describe the immunogenicity, safety, and tolerability of *Neisseria meningitidis* serogroup b bivalent recombinant lipoprotein 2086 vaccine (bivalent rLP2086 (Trumenba)) in healthy subjects aged ≥24 months to <10 years; and study B1971035: a phase 2, randomised, controlled, observer-blinded study conducted to describe the immunogenicity, safety, and tolerability of a *Neisseria meningitidis* serogroup B bivalent recombinant lipoprotein 2086 vaccine (bivalent rLP2086 (Trumenba)) when administered to healthy toddlers aged 12 to <18 months or 18 to <24 months, and the safety and immunogenicity of a booster dose of bivalent rLP2086. The package leaflet and the RMP (version 2.0) are updated accordingly. In addition, the MAH took the opportunity to submit a corrected version of the final report of study B1971016: a phase 3, randomised, placebo-controlled, observer-blinded, trial to assess the safety, tolerability, and immunogenicity of bivalent rLP2086 vaccine (Trumenba) when administered as a 3-dose regimen in healthy young adults aged >=18 to <26 years, which was included in the initial marketing authorisation application (MAA)/opinion

15.3.18. Naltrexone hydrochloride, bupropion hydrochloride - MYSIMBA (CAP) - EMEA/H/C/003687/II/0029/G

Applicant: Orexigen Therapeutics Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: Grouped variations consisting of: 1) update of section 4.8 to adjust the list of adverse drug reactions and their corresponding frequencies in line with the outcome of the PSUSA procedure (PSUSA/00010366/201709) finalised in April 2018; 2) update of sections 4.2, 4.4 and 5.2 of the SmPC to add results from a phase 1 open label parallel study to evaluate the pharmacokinetics of a single oral dose of extended-release combination of naltrexone and bupropion in subjects with normal hepatic function or varying degrees of impaired hepatic function and remove the recommendation to not use naltrexone/bupropion in patients with mild hepatic impairment. The existing warning is updated accordingly. The warning related to contraindications is aligned to section 4.3 to add end-stage renal failure patients. As a consequence, the RMP (version 11) is updated accordingly. In addition, the MAH took the opportunity to update the warning on lactose in accordance with the European Commission (EC) guideline on 'excipients in the labelling and package leaflet of medicinal products for human use'

15.3.19. Nelarabine - ATRIANCE (CAP) - EMEA/H/C/000752/II/0046/G

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Anette Kirstine Stark

Scope: Grouped variations consisting of: 1) update to Annex II to remove the specific obligation (SOB) based on the final results from study NLR506AUS02T (COG-AALL0434): 'intensified methotrexate, nelarabine and augmented Berlin-Frankfurt-Munster (BFM) therapy for children and young adults with newly diagnosed T-cell acute lymphoblastic leukaemia (T-ALL) and T-cell lymphoblastic lymphoma (T-LBL)'. As a consequence, sections 4.8 and 5.1 of the SmPC are updated; 2) update of section 4.6 of the SmPC to revise information on male and female contraception taking into consideration available non-clinical and clinical safety data as well as internal MAH's guidelines based on information from literature, health authority and working group guidelines. Furthermore, the MAH took the opportunity to update details of the local representatives and introduced minor editorial changes in the package leaflet. The RMP (version 10) is updated accordingly

15.3.20. Obinutuzumab - GAZYVARO (CAP) - EMEA/H/C/002799/II/0034, Orphan

Applicant: Roche Registration GmbH

PRAC Rapporteur: Annika Folin

Scope: Submission of the final results of the pivotal study BO21005/GOYA: a phase 3, multicentre, open-label randomised trial comparing the efficacy of obinutuzumab (GA101 (RO5072759)) in combination with cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP) (G-CHOP) versus rituximab and CHOP (R-CHOP) in previously untreated patients with CD20-positive diffuse large B-cell lymphoma (DLBCL), to address the additional pharmacovigilance activities required in the EU RMP. The RMP (version 5.0) is updated accordingly

15.3.21. Panitumumab - VECTIBIX (CAP) - EMEA/H/C/000741/II/0093

Applicant: Amgen Europe B.V.

PRAC Rapporteur: David Olsen

Scope: Submission of an updated RMP (version 23) brought in line with revision 2 of GVP module V on 'Risk management systems'. In addition, the MAH proposed the removal of some additional risk minimisation measures (aRMM). As a result Annex II is updated. The MAH took the opportunity to update sections 4.2 and 4.4 of the SmPC to include the table on dose modification previously located in section 4.4. In addition, section 4.4 is updated to implement the statement on 'sodium' content in accordance with the European Commission (EC) guideline on 'excipients in the labelling and package leaflet of medicinal products for human use'. Furthermore, minor corrections are introduced in section 4.8 of the SmPC and in the list of the local representatives

15.3.22. Pegfilgrastim - PELGRAZ (CAP) - EMEA/H/C/003961/II/0005

Applicant: Accord Healthcare S.L.U.

PRAC Rapporteur: Menno van der Elst

Scope: Change in the immediate packaging of Pelgraz (pegfilgrastim) finished product solution for injection 6mg/0.6 mL to add an additional presentation as a solution for injection in pre-filled injector in addition to the existing approved solution for injection in Pre-filled syringe. The RMP (version 1.4) is updated accordingly

15.3.23. Pitolisant - WAKIX (CAP) - EMEA/H/C/002616/II/0017, Orphan

Applicant: Bioprojet Pharma

PRAC Rapporteur: Kirsti Villikka

Scope: Update of sections 4.4, 4.5 and 4.6 of the SmPC in order to reflect available information of co-administration of pitolisant with cytochrome P450 3A4 (CYP3A4) substrates based on the results from the following studies: 1) study R-B478-2.649: a drug-drug interaction in-vitro study of CYP450 3A induction: effect of BF2.649 (pitolisant), BP2.951 (pitolisant metabolite), BP1.8054 (pitolisant metabolite) and BP1.4787 (modafinil); 2) study R.BF2.649-SK-005: evaluation of the induction potential of CYP3A4 by BF2.649, P2.951 and BP1.8054 gene expression analysis in human primary hepatocytes; 3) study R-B472-1.11413: quantification of 4β-hydroxycholesterol (BP1.11413) in human serum from a two-part, open label, one sequence, cross-over pharmacokinetic study to evaluate: study part I: at steady-state, the pitolisant (40 mg) interaction (as inducer) on both a single dose of midazolam and of bupropion in eighteen healthy male volunteers; study to assess the tolerance and pharmacokinetic profile of repeated 20 mg oral doses of BF2.649, in healthy elderly subjects and a young adult control group; a study to assess the potential impact of drug-drug interaction of rifampicin on the relative bioavailability of BF2.649 in healthy male subjects; B28-day repeated dose study, to evaluate pharmacokinetic parameters and accumulation rate of BF2.649, administered once a day, in six ambulatory healthy male volunteers. The MAH took the opportunity to update section 5.2 of the SmPC to more accurately reflect information previously assessed during procedure II/0004/G finalised in 2017. The RMP (version 6.0) is updated accordingly. In addition, the MAH took the opportunity to clarify details on the manufacturers of the finished product in the package

leaflet

15.3.24. Ranibizumab - LUCENTIS (CAP) - EMEA/H/C/000715/II/0074/G

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Grouped variations consisting of: 1) extension of indication to include a new indication for the vial presentation 'treatment of retinopathy of prematurity (ROP) in preterm infants'. As a consequence, sections 2, 4.1, 4.2, 4.5, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated. The package leaflet, labelling and the RMP (version 18.0) are updated accordingly; 2) introduction of a low volume high accuracy syringe, as a stand-alone medical device for the administration of the Lucentis (ranibizumab) 0.2 mg paediatric dose (corresponding to 0.02 mL of the Lucentis 10 mg/mL solution for injection in vial presentation)

15.3.25. Telotristat ethyl - XERMELO (CAP) - EMEA/H/C/003937/II/0015, Orphan

Applicant: Ipsen Pharma

PRAC Rapporteur: Adam Przybylkowski

Scope: Update of section 5.1 of the SmPC based on final results from study LX1606.1-302.CS (TELEPATH) (listed as a category 3 study in the RMP): a multicentre, phase 3, long-term extension study to further evaluate the safety and tolerability of telotristat etiprate in patients with carcinoid syndrome (CS). The RMP (version 4.0) is updated accordingly and in line with revision 2 of GVP module V on 'Risk management systems'

15.3.26. Tenofovir alafenamide - VEMLIDY (CAP) - EMEA/H/C/004169/II/0020

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Amelia Cupelli

Scope: Update of sections 4.8 and 5.1 of the SmPC based on safety information from interim results at week 48 of study GS-US-320-4018 (listed as a category 3 study in the RMP): a phase 3, randomised, double blind study conducted to evaluate the efficacy and safety of switching from tenofovir disoproxil fumarate (TDF) 300 mg once a day (QD) to tenofovir alafenamide (TAF) 25 mg QD in subjects with chronic Hepatitis B (CHB) who are virologically suppressed. The package leaflet and the RMP (version 4.1) are updated accordingly

15.3.27. Vedolizumab - ENTYVIO (CAP) - EMEA/H/C/002782/X/0040

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Adam Przybylkowski

Scope: Extension application to introduce a new pharmaceutical form (solution for injection) associated with a new strength (108 mg) and a new route of administration (subcutaneous use). The RMP (version 5.0) is updated accordingly

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. Adalimumab[62] - AMGEVITA (CAP); HALIMATOZ (CAP); HEFIYA (CAP); HULIO (CAP); HYRIMOZ (CAP); IMRALDI (CAP) - PSUSA/00010589/201812

Applicant(s): Amgen Europe B.V. (Amgevita), Mylan S.A.S (Hulio), Sandoz GmbH (Halimatoz, Hefiya, Hyrimoz), Samsung Bioepis NL B.V. (Imraldi)

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.2. Afamelanotide - SCENESSE (CAP) - PSUSA/00010314/201812

Applicant: Clinuvel Europe Limited

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.3. Alectinib - ALECENSA (CAP) - PSUSA/00010581/201901

Applicant: Roche Registration GmbH

PRAC Rapporteur: Jana Lukacisinova

Scope: Evaluation of a PSUSA procedure

16.1.4. Allopurinol, lesinurad - DUZALLO (CAP) - PSUSA/00010704/201812

Applicant: Grunenthal GmbH

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

[62] Biosimilar medicinal product(s) only

16.1.5. Amifampridine - FIRDAPSE (CAP) - PSUSA/00000141/201812

Applicant: BioMarin International Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.6. Asfotase alfa - STRENSIQ (CAP) - PSUSA/00010421/201901

Applicant: Alexion Europe SAS

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

16.1.7. Asparaginase[63] - SPECTRILA (CAP) - PSUSA/00010445/201901

Applicant: Medac Gesellschaft fur klinische Spezialpraparate mbH

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.1.8. Beclometasone, formoterol, glycopyrronium bromide - RIARIFY (CAP); TRIMBOW (CAP); TRYDONIS (CAP) - PSUSA/00010617/201901

Applicant(s): Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.1.9. Binimetinib - MEKTOVI (CAP) - PSUSA/00010717/201812

Applicant: Pierre Fabre Medicament

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Evaluation of a PSUSA procedure

16.1.10. Birch bark extract[64] - EPISALVAN (CAP) - PSUSA/00010446/201901

Applicant: Amryt AG

PRAC Rapporteur: Zane Neikena

Scope: Evaluation of a PSUSA procedure

16.1.11. Brodalumab - KYNTHEUM (CAP) - PSUSA/00010616/201901

Applicant: LEO Pharma A/S

PRAC Rapporteur: Eva Segovia

[63] Centrally authorised product(s) only
[64] Centrally authorised product(s) only

Scope: Evaluation of a PSUSA procedure

16.1.12. Budesonide[65] - JORVEZA (CAP) - PSUSA/00010664/201901

Applicant: Dr. Falk Pharma GmbH

PRAC Rapporteur: Zane Neikena

Scope: Evaluation of a PSUSA procedure

16.1.13. Cenegermin - OXERVATE (CAP) - PSUSA/00010624/201901

Applicant: Dompe farmaceutici S.p.A.

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.1.14. Cholic acid[66] - ORPHACOL (CAP) - PSUSA/00010208/201809

Applicant: Laboratoires CTRS

PRAC Rapporteur: Sofia Trantza

Scope: Evaluation of a PSUSA procedure

16.1.15. Cladribine[67] - MAVENCLAD (CAP) - PSUSA/00010634/201901

Applicant: Merck Europe B.V.

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Evaluation of a PSUSA procedure

16.1.16. Clofarabine - EVOLTRA (CAP) - PSUSA/00000805/201812

Applicant: Genzyme Europe BV

PRAC Rapporteur: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

16.1.17. Concentrate of proteolytic enzymes enriched in bromelain - NEXOBRID (CAP) - PSUSA/00010028/201812

Applicant: MediWound Germany GmbH

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

[65] Centrally authorised product(s) only
[66] Treatment of inborn errors in primary bile acid synthesis due to 3β-hydroxy-Δ5-C27-steroid oxidoreductase deficiency or Δ4-3-oxosteroid-5β-reductase indication(s) only
[67] Treatment of multiple sclerosis (MS) only

16.1.18. Dasabuvir - EXVIERA (CAP) - PSUSA/00010363/201901

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

16.1.19. Dimethyl fumarate[68] - SKILARENCE (CAP) - PSUSA/00010647/201812

Applicant: Almirall S.A

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

16.1.20. Encorafenib - BRAFTOVI (CAP) - PSUSA/00010719/201812

Applicant: Pierre Fabre Medicament

PRAC Rapporteur: Rugile Pilviniene

Scope: Evaluation of a PSUSA procedure

16.1.21. Ertugliflozin - STEGLATRO (CAP) - PSUSA/00010682/201812

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.22. Ertugliflozin, metformin - SEGLUROMET (CAP) - PSUSA/00010680/201812

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.23. Ertugliflozin, sitagliptin - STEGLUJAN (CAP) - PSUSA/00010681/201812

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.24. Guselkumab - TREMFYA (CAP) - PSUSA/00010652/201901

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

[68] Treatment of psoriasis only

16.1.25. Human papillomavirus vaccine [types 6, 11, 16, 18, 31, 33, 45, 52, 58] (recombinant, adsorbed) - GARDASIL 9 (CAP) - PSUSA/00010389/201812

Applicant: MSD Vaccins

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

16.1.26. Inotuzumab ozogamicin - BESPONSA (CAP) - PSUSA/00010659/201812

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.27. Lamivudine[69] - EPIVIR (CAP); lamivudine, zidovudine - COMBIVIR (CAP) - PSUSA/00009207/201811

Applicant(s): ViiV Healthcare B.V. (Combivir, Epivir)

PRAC Rapporteur: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

16.1.28. Lesinurad - ZURAMPIC (CAP) - PSUSA/00010470/201812

Applicant: Grunenthal GmbH

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

16.1.29. Lonoctocog alfa - AFSTYLA (CAP) - PSUSA/00010559/201901

Applicant: CSL Behring GmbH

PRAC Rapporteur: Sonja Hrabcik

Scope: Evaluation of a PSUSA procedure

16.1.30. Lutetium (^{177}Lu) oxodotreotide - LUTATHERA (CAP) - PSUSA/00010643/201812

Applicant: Advanced Accelerator Applications

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.31. Neratinib - NERLYNX (CAP) - PSUSA/00010712/201901

Applicant: Puma Biotechnology B.V.

PRAC Rapporteur: Menno van der Elst

[69] Treatment of human immunodeficiency virus (HIV) infections only

Scope: Evaluation of a PSUSA procedure

16.1.32. Olaparib - LYNPARZA (CAP) - PSUSA/00010322/201812

Applicant: AstraZeneca AB

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.1.33. Ombitasvir, paritaprevir, ritonavir - VIEKIRAX (CAP) - PSUSA/00010367/201901

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

16.1.34. Peramivir - ALPIVAB (CAP) - PSUSA/00010687/201812

Applicant: BioCryst Ireland Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.35. Ponatinib - ICLUSIG (CAP) - PSUSA/00010128/201812

Applicant: Incyte Biosciences Distribution B.V.

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

16.1.36. Sarilumab - KEVZARA (CAP) - PSUSA/00010609/201901

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

16.1.37. Saxagliptin, dapagliflozin - QTERN (CAP) - PSUSA/00010520/201901

Applicant: AstraZeneca AB

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.1.38. Selexipag - UPTRAVI (CAP) - PSUSA/00010503/201812

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

16.1.39. Sonidegib - ODOMZO (CAP) - PSUSA/00010408/201812

Applicant: Sun Pharmaceutical Industries Europe B.V.

PRAC Rapporteur: Željana Margan Koletić

Scope: Evaluation of a PSUSA procedure

16.1.40. Spheroids of human autologous matrix-associated chondrocytes - SPHEROX (CAP) - PSUSA/00010630/201901 (with RMP)

Applicant: CO.DON AG, ATMP[70]

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.41. Tasimelteon - HETLIOZ (CAP) - PSUSA/00010394/201901

Applicant: Vanda Pharmaceuticals Germany GmbH

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.42. Vonicog alfa - VEYVONDI (CAP) - PSUSA/00010714/201812

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.43. Ziconotide - PRIALT (CAP) - PSUSA/00003142/201812

Applicant: Riemser Pharma GmbH

PRAC Rapporteur: Jean-Michel Dogné

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. Caspofungin - CANCIDAS (CAP); CASPOFUNGIN ACCORD (CAP); NAP - PSUSA/00000576/201812

Applicant(s): Merck Sharp & Dohme B.V. (Cancidas), Accord Healthcare S.L.U. (Caspofungin Accord), various

PRAC Rapporteur: Laurence de Fays

Scope: Evaluation of a PSUSA procedure

[70] Advanced therapy medicinal product

16.2.2. Edotreotide - SOMAKIT TOC (CAP); NAP - PSUSA/00010552/201812

Applicant(s): Advanced Accelerator Applications (SomaKit TOC), various

PRAC Rapporteur: Ronan Grimes

Scope: Evaluation of a PSUSA procedure

16.2.3. Nitric oxide - INOMAX (CAP); NAP - PSUSA/00002172/201812

Applicant(s): Linde Healthcare AB (INOmax), various

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

16.2.4. Raloxifene - EVISTA (CAP); OPTRUMA (CAP); RALOXIFENE TEVA (CAP), NAP - PSUSA/00002603/201812

Applicant(s): Daiichi Sankyo Europe GmbH (Evista), Eli Lilly Nederland B.V. (Optruma), Teva B.V. (Raloxifene Teva), various

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

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

16.3.1. Acetylsalicylic acid, bisoprolol (NAP) - PSUSA/00010287/201811

Applicant(s): various

PRAC Lead: Tatiana Magalova

Scope: Evaluation of a PSUSA procedure

16.3.2. Amino acid combinations, glucose, triglyceride combinations[71], with or without electrolytes, mineral compounds[72] [73] (NAP) - PSUSA/00010190/201812

Applicant(s): various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.3.3. Anti-T lymphocyte immunoglobulin (horse) (NAP) - PSUSA/00010433/201811

Applicant(s): various

PRAC Lead: Zane Neikena

Scope: Evaluation of a PSUSA procedure

[71] E.g. olive oil, soya bean oil, fish oil
[72] Intravenous (I.V.) application only
[73] Nationally authorised product Numeta only

16.3.4. Atomoxetine (NAP) - PSUSA/00000262/201811

Applicant(s): various

PRAC Lead: Eva Segovia

Scope: Evaluation of a PSUSA procedure

16.3.5. Cefotaxime (NAP) - PSUSA/00000599/201812

Applicant(s): various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.3.6. Clevidipine (NAP) - PSUSA/00010288/201811

Applicant(s): various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.3.7. Danaparoid (NAP) - PSUSA/00000923/201812

Applicant(s): various

PRAC Lead: Ronan Grimes

Scope: Evaluation of a PSUSA procedure

16.3.8. Hydromorphone (NAP) - PSUSA/00001686/201811

Applicant(s): various

PRAC Lead: Gabriela Jazbec

Scope: Evaluation of a PSUSA procedure

16.3.9. Hydroxycarbamide[74] (NAP) - PSUSA/00009182/201812

Applicant(s): various

PRAC Lead: Nikica Mirosevic Skvrce

Scope: Evaluation of a PSUSA procedure

16.3.10. Levonorgestrel, ethinylestradiol; ethinylestradiol[75] (NAP) - PSUSA/00010442/201901

Applicant(s): various

PRAC Lead: Adrien Inoubli

[74] Non-centrally authorised product(s) only
[75] Combination pack

Scope: Evaluation of a PSUSA procedure

16.3.11. Naltrexone (NAP) - PSUSA/00002117/201811

Applicant(s): various

PRAC Lead: Ronan Grimes

Scope: Evaluation of a PSUSA procedure

16.3.12. Sertindole (NAP) - PSUSA/00002695/201901

Applicant(s): various

PRAC Lead: Julia Pallos

Scope: Evaluation of a PSUSA procedure

16.3.13. Terazosin (NAP) - PSUSA/00002895/201811

Applicant(s): various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.3.14. Yellow fever vaccine (live) (NAP) - PSUSA/00003135/201812

Applicant(s): various

PRAC Lead: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.4. Follow-up to PSUR/PSUSA procedures

16.4.1. Capecitabine - XELODA (CAP) - EMEA/H/C/000316/LEG 034

Applicant: Roche Registration GmbH

PRAC Rapporteur: Martin Huber

Scope: Review of all cases of hyperammonaemia and hyperammonaemic encephalopathy as requested in the conclusions of PSUSA/00000531/201804 adopted in January 2019

16.4.2. Cobimetinib - COTELLIC (CAP) - EMEA/H/C/003960/LEG 005

Applicant: Roche Registration GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Review of the risk of colitis as requested in the conclusions of PSUSA/00010450/201808 adopted in March 2019

16.4.3. Idebenone - RAXONE (CAP) - EMEA/H/C/003834/LEG 013

Applicant: Santhera Pharmaceuticals (Deutschland) GmbH

PRAC Rapporteur: Amelia Cupelli

Scope: Detailed review on events of alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, blood lactate dehydrogenase increased, gamma-glutamyl-transferase increased, blood bilirubin increased and hepatitis observed in clinical studies and post-authorisation safety studies. The total number of exposed patients in the respective studies and pooled data should also be provided; as well as a proposal for relevant frequency for 'hepatic disorders' as an undesirable effect, as requested in the conclusions of PSUSA/00010412/201809 adopted in April 2019

16.4.4. Natalizumab - TYSABRI (CAP) - EMEA/H/C/000603/LEG 069

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Detailed analyses of skin melanoma and malignant melanoma as requested in the conclusions of PSUSA/00002127/201808 adopted in February 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)[76]

17.1.1. Damoctocog alfa pegol - JIVI (CAP) - EMEA/H/C/PSP/S/0070.1

Applicant: Bayer AG

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to PSP/S/0070 [protocol for an observational study to assess the effectiveness and long term safety of prophylaxis with damoctocog alfa pegol in real-world settings through the collection of total bleeding events and analysis of the annualised bleeding rate (ABR) in the different prophylaxis regimens (following approved local label or any other regimen prescribed by the physician as part of normal clinical practice) in patients with haemophilia A as per the request for supplementary information (RSI) adopted in February 2019

17.1.2. Levofloxacin - QUINSAIR (CAP) - EMEA/H/C/PSA/S/0039

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Amendment to a protocol initially endorsed by PRAC in April 2017 (EMEA/H/C/PSP/S/0049.2) for a post-marketing, observational safety study in patients with

[76] In accordance with Article 107n of Directive 2001/83/EC

cystic fibrosis to evaluate the long-term safety of Quinsair (levofloxacin) over a five-year period (2017 to 2021) compared to other inhaled approved antibiotic therapies in cystic fibrosis (CF) patients who are enrolled in the United Kingdom (UK) CF registry. The primary objective is extended to evaluate the safety profile of Quinsair (levofloxacin) over a three-year period (2019 to 2021) compared to other inhaled approved antibiotic therapies in CF patients who are enrolled in the German CF registry

17.1.3. Radium (Ra^{223}) dichloride - XOFIGO (CAP) - EMEA/H/C/PSP/S/0076.1

Applicant: Bayer AG

PRAC Rapporteur: Rugile Pilviniene

Scope: MAH's response to PSP/S/0076 [protocol for a PASS to estimate the incidence rate of symptomatic bone fractures among users of Xofigo (radium-223) in routine clinical practice] as per the request for supplementary information (RSI) adopted in March 2019

17.1.4. Rurioctocog alfa pegol - ADYNOVI (CAP) - EMEA/H/C/PSP/S/0077.1

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to PSP/S/0077 [protocol for a study evaluating the long-term safety of Adynovi (rurioctocog alfa pegol) in adults and adolescents ≥12 years of age with haemophilia A] as per the request for supplementary information (RSI) adopted in March 2019

17.1.5. Teduglutide - REVESTIVE (CAP) - EMEA/H/C/PSA/S/0040

Applicant: Shire Pharmaceuticals Ireland Limited

PRAC Rapporteur: Anette Kirstine Stark

Scope: Amendment to a protocol previously agreed in July 2013 for study TED-R-13-002: an international short bowel syndrome registry: a prospective, long-term observational cohort study of patients with short bowel syndrome

17.1.6. Umeclidinium bromide – INCRUSE ELLIPTA (CAP), ROLUFTA ELLIPTA (CAP); umeclidinium bromide, vilanterol – ANORO ELLIPTA (CAP), LAVENTAIR ELLIPTA (CAP) - EMEA/H/C/PSA/S/0032.2

Applicant(s): GlaxoSmithKline (Ireland) Limited (Incruse Ellipta, Anoro Ellipta, Laventair Ellipta), GlaxoSmithKline Trading Services Limited (Rolufta Ellipta)

PRAC Rapporteur: Amelia Cupelli

Scope: MAH's response to PSA/S/0032.1 [amendment to a protocol initially 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

17.1.7. Valproate (NAP) - EMEA/H/N/PSP/J/0072.1

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

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: MAH's response to PSP/J/0072 [protocol for a retrospective observational study to investigate the association between paternal exposure to valproate and the risk of congenital anomalies and neurodevelopmental disorders including autism in offspring, 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

17.1.8. Valproate (NAP) - EMEA/H/N/PSP/J/0073.1

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

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: MAH's response to PSP/J/0073 [protocol for a survey among healthcare professionals (HCP) to assess the knowledge of HCP and behaviour with regard to the pregnancy prevention programme (PPP), the receipt/use of direct healthcare professional communication (DHPC) and educational materials as well as for a survey among patients to assess the knowledge of patients with regards to PPP and receipt/use of educational materials, 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

17.1.9. Valproate (NAP) - EMEA/H/N/PSP/J/0075.1

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

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: MAH's response to PSP/J/0075 [protocol for a drug utilisation study (DUS) to assess the effectiveness of the new risk minimisation measures (RMMs) and to further characterise the prescribing patterns for valproate 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

17.1.10. Voretigene neparvovec - LUXTURNA (CAP) - EMEA/H/C/PSP/S/0078.1

Applicant: Novartis Europharm Limited, ATMP[77]

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: MAH's response to PSP/S/0078 [protocol for a post-authorisation observational study to collect long-term safety information (i.e., for 5 years after treatment) associated with voretigene neparvovec (vector and/or transgene), its subretinal injection procedure, the concomitant use of corticosteroids, or a combination of these procedures and products]

[77] Advanced therapy medicinal product

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

17.2. Protocols of PASS non-imposed in the marketing authorisation(s)[78]

17.2.1. Benralizumab - FASENRA (CAP) - EMEA/H/C/004433/MEA 004.2

Applicant: AstraZeneca AB

PRAC Rapporteur: David Olsen

Scope: MAH's response to MEA 004.1 [protocol for study D3250R00042: a descriptive study of the incidence of malignancy in patients with severe asthma overall and among those receiving benralizumab and other therapies in real-world settings] as per the request for supplementary information (RSI) adopted in February 2019

17.2.2. Cangrelor - KENGREXAL (CAP) - EMEA/H/C/003773/MEA 002

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Amelia Cupelli

Scope: Protocol for study DFIDM-1801 (ARCANGELO (itAlian pRospective study on CANGrELOr)): a multicentre prospective observational study of acute coronary syndrome patients undergoing percutaneous coronary intervention (PCI) who receive cangrelor and transition to either clopidogrel, prasugrel or ticagrelor

17.2.3. Ciclosporin - VERKAZIA (CAP) - EMEA/H/C/004411/MEA 001.1

Applicant: Santen Oy

PRAC Rapporteur: Jan Neuhauser

Scope: MAH's response to MEA 001 [protocol and feasibility study for a case-control study linked to existing cancer registries to understand the data sources and analytic methods available to quantify the risk of periocular skin cancer, conjunctival or corneal neoplasia in children treated with Verkazia (ciclosporin)] as per the request for supplementary information (RSI) adopted in February 2019

17.2.4. Erenumab - AIMOVIG (CAP) - EMEA/H/C/004447/MEA 001

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Kirsti Villikka

Scope: Protocol for study CAMG334A2023: a non-interventional study to examine patient characteristics and drug utilisation patterns in migraine patients treated with prophylactic drugs in the Nordic registries [final clinical study report (CSR) expected end of data collection + 1 year] (from the initial opinion/MA)

[78] 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

17.2.5. Estrogens conjugated, bazedoxifene - DUAVIVE (CAP) - EMEA/H/C/002314/MEA 002.12

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Martin Huber

Scope: Substantial amendment to a protocol previously agreed in May 2015 for ongoing US study B2311060 (listed as a category 3 study in the RMP): a study to estimate the incidence and to compare the risks of endometrial hyperplasia and endometrial cancer in postmenopausal women initiating either Duavive (estrogens conjugated/bazedoxifene) or estrogen + progestin (E+P) combination hormone replacement therapy (HRT)

17.2.6. Lenvatinib - LENVIMA (CAP) - EMEA/H/C/003727/MEA 014.1

Applicant: Eisai GmbH

PRAC Rapporteur: Annika Folin

Scope: MAH's response to MEA 014 [protocol for study E7080-G000-508: an observational study to characterise hepatic related toxicity and overall safety profile in real-life conditions in the EU (Western population) in hepatocellular carcinoma (HCC) patients, including patients with Child-Pugh B] as per the request for supplementary information (RSI) adopted in January 2019

17.2.7. Mogamulizumab - POTELIGEO (CAP) - EMEA/H/C/004232/MEA 001

Applicant: Kyowa Kirin Holdings B.V.

PRAC Rapporteur: Anette Kirstine Stark

Scope: Protocol for a PASS to characterise the safety of allogeneic haematopoietic stem cell transplantation (HSCT) in patients with cutaneous T-cell lymphoma (CTCL) treated with mogamulizumab [final clinical study report expected in July 2024] (from the initial opinion/MA)

17.2.8. Patisiran - ONPATTRO (CAP) - EMEA/H/C/004699/MEA 002.1

Applicant: Alnylam Netherlands B.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: MAH's response to MEA 002 [Protocol for study ALN-TTR02-0009: a prospective observational study to monitor and assess the safety of Onpattro (patisiran) in a real-world cohort of hereditary transthyretin amyloidosis (hATTR) patients] as per the request for supplementary information (RSI) adopted in February 2019

17.2.9. Ropeginterferon alfa-2b - BESREMI (CAP) - EMEA/H/C/004128/MEA 001

Applicant: AOP Orphan Pharmaceuticals AG

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Protocol for EUPAS29462 study: a prospective, multicentre, non-interventional observational PASS to further investigate the safety and tolerability of ropeginterferon alfa-2b in polycythaemia vera patients with a special focus on hepatotoxicity to evaluate the

effectiveness of risk minimisation measures and to evaluate cardiovascular safety during titration phase [final study report expected in Q3 2023] (from initial opinion/MA)

17.2.10. Sarilumab - KEVZARA (CAP) - EMEA/H/C/004254/MEA 002.3

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Eva Segovia

Scope: MAH's response to MEA 002.2 [PASS protocol for a safety surveillance programme using existing EU rheumatoid arthritis (RA) registries conducted in four countries: Germany (German Register for Rheumatoid Arthritis Observation of Biologic Therapy (RABBIT) (OBS15180)), Spain (Spanish Registry for Adverse Events for Biological Therapy in Rheumatic Diseases (BIOBASASER) (6R88-RA-1720)), Sweden (Register for Antirheumatic Therapies in Sweden (ARTIS) (OBS15220)) and UK (British Society for Rheumatology Biologicals Register (BSRBR) (6R88-RA-1634))] as per the request for supplementary information (RSI) adopted in March 2019

17.2.11. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/MEA 008.2

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: MAH's response to MEA 008.1 [protocol for study A3921312 (listed as a category 3 study in the RMP): a prospective non-interventional comparative active surveillance PASS of serious infection, malignancy, cardiovascular and other adverse event rates among patients treated with Xeljanz (tofacitinib) for moderately to severely active rheumatoid arthritis (RA) within the British Society for Rheumatology Biologics Register-Rheumatoid Arthritis (BSRBR-RA)] as per the request for supplementary information (RSI) adopted in February 2019

17.2.12. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/MEA 009.2

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: MAH's response to MEA 009.1 [protocol for study A3921314 (listed as a category 3 study in the RMP): a prospective non-interventional comparative active surveillance PASS of serious infection, malignancy, cardiovascular and other adverse event rates among patients treated with Xeljanz (tofacitinib) for moderately to severely active rheumatoid arthritis (RA) within the Swedish (ARTIS) register] as per the request for supplementary information (RSI) adopted in February 2019

17.2.13. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/MEA 010.2

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: MAH's response to MEA 010.1 [protocol for study A3921316 (listed as a category 3 study in the RMP): a prospective non-interventional comparative active surveillance PASS of serious infection, malignancy, cardiovascular and other adverse event rates among patients

treated with Xeljanz (tofacitinib) for moderately to severely active rheumatoid arthritis (RA) within the Spanish registry of adverse events of biological therapies and biosimilars in rheumatoid diseases (BIOBADASER)] as per the request for supplementary information (RSI) adopted in February 2019

17.2.14. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/MEA 011.2

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: MAH's response to MEA 011.1 [Protocol for study A3921317 (listed as a category 3 study in the RMP): a prospective non-interventional comparative active surveillance PASS of serious infection, malignancy, cardiovascular and other adverse event rates among patients treated with Xeljanz (tofacitinib) for moderately to severely active rheumatoid arthritis (RA) within the German registry Rheumatoide Arthritis: Beobachtung der Biologika-Therapie (RABBIT)] as per the request for supplementary information (RSI) adopted in February 2019

17.3. Results of PASS imposed in the marketing authorisation(s)[79]

None

17.4. Results of PASS non-imposed in the marketing authorisation(s)[80]

17.4.1. Abatacept - ORENCIA (CAP) - EMEA/H/C/000701/II/0124/G

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Kimmo Jaakkola

Scope: Grouped variations consisting of: 1) submission of the final reports from studies (listed as category 3 studies in the RMP), namely, study IM101125: a nationwide post-marketing study on the safety of abatacept treatment in Sweden Using the 'Antirheumatic Therapies in Sweden (ARTIS)' register, study IM101127: a long-term observation of treatment with biologics in rheumatoid arthritis (Rheumatoide Arthritis: Beobachtung der Biologika-Therapie (RABBIT)), study IM101211: a multinational surveillance of abatacept-treated patients during disease registries, study IM101213: a post-marketing observational study assessing the long-term safety of abatacept using a population-based cohort of rheumatoid arthritis patients in the province of British Columbia, Canada, as well as the interim report from study IM101121: Abatacept Pregnancy Exposure Registry 'Organization of Teratology Information Specialists (OTIS)' autoimmune diseases in pregnancy project as an extension study. These are biologic registries and pharmacoepidemiology studies to assess the risk associated with the use of abatacept during post-marketing in geographically diverse populations and subgroups; 2) submission of the final study report from study IM101488: a retrospective cohort study assessing the long-term safety of abatacept; 3) The deadline for submission of the final study report from study IM101121 (pregnancy registry) is proposed to be extended. The RMP (version 26) is updated accordingly and also include the addition of two epidemiological studies as category 3

[79] In accordance with Article 107p-q of Directive 2001/83/EC
[80] 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

studies in the RMP, namely: study IM101803: a nationwide post-marketing study on the safety of abatacept treatment in Denmark using the DANBIO[81] register and IM101W52: a nationwide post-marketing study on the safety of abatacept treatment in Sweden using the ARTIS register. In addition, the RMP is updated to remove the following missing information: combination therapy, including biologic therapy, and elderly patients

17.4.2. Exenatide - BYDUREON (CAP) - EMEA/H/C/002020/II/0059

Applicant: AstraZeneca AB

PRAC Rapporteur: Annika Folin

Scope: Submission of the final clinical study report (CSR) for study H80-MC-B016: a modified prescription-event monitoring programme (modified PEM) to be conducted in the UK enrolling patients with type 2 diabetes mellitus (T2DM) to quantify the incidence of acute pancreatitis in the first 12 months after initiating treatment with prescription exenatide once weekly. The RMP (version 33) is updated accordingly (in fulfilment of post-authorisation measures (PAM) MEA 010.5)

17.4.3. Pegvisomant - SOMAVERT (CAP) - EMEA/H/C/000409/II/0089

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Adrien Inoubli

Scope: Submission of the final clinical study report (CSR) from study A6291010 (ACROSTUDY) (listed as a category 3 study in the RMP): an open-label, global, non-interventional PASS performed to monitor the long-term safety and outcomes of pegvisomant treatment in clinical practice (in fulfilment of post approval measure (PAM) MEA 059)

17.4.4. Rivastigmine - EXELON (CAP) - EMEA/H/C/000169/WS1557/0120; PROMETAX (CAP) - EMEA/H/C/000255/WS1557/0121

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ghania Chamouni

Scope: Submission of the final report for study CENA713D2409: a drug utilisation study (DUS) aimed to assess the extent of inappropriate use of Exelon/Prometax (rivastigmine) (fulfilment of post-authorisation measures (PAM) Exelon MEA 034 and Prometax MEA 035)

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

17.5.1. Alirocumab - PRALUENT (CAP) - EMEA/H/C/003882/MEA 017.4

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: MAH's responses to MEA 017.3 [second interim report for study ALIROC07997: a

[81] A nationwide registry of biological therapies in Denmark

PASS using healthcare databases, in order to monitor the safety of Praluent (alirocumab) in patients affected with the human immunodeficiency virus (HIV)] as per the request for supplementary information (RSI) adopted in March 2019

17.5.2. Apremilast - OTEZLA (CAP) - EMEA/H/C/003746/MEA 005.5

Applicant: Celgene Europe BV

PRAC Rapporteur: Eva Segovia

Scope: Three-year report for apremilast psoriasis registry in the EU, long-term benefits and safety of systemic psoriasis therapy: German registry on the treatment of psoriasis with biologics and systemic therapeutics (PsoBest) (from initial MA/opinion)

17.5.3. Ataluren - TRANSLARNA (CAP) - EMEA/H/C/002720/MEA 002.5

Applicant: PTC Therapeutics International Limited

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Four-year interim report for study PTC124-GD-025o-DMD (listed as a category 3 study in the RMP): a post-approval registry observational study exploring the long-term of ataluren safety and effectiveness in usual care setting [final clinical study report (CSR) expected in April 2023]

17.5.4. Elosulfase alfa - VIMIZIM (CAP) - EMEA/H/C/002779/ANX 005.4

Applicant: BioMarin International Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Fifth annual report (reporting period: 14 February 2018 to 13 February 2019) for the multicentre, multinational, observational Morquio A registry study (MARS): a voluntary observational registry study to characterise and describe the mucopolysaccharidosis IV type A (MPS IVA) population and to evaluate the long-term effectiveness and safety of Vimizim (elosulfase alfa) [final clinical study report (CSR) expected by March 2025]

17.5.5. Estrogens conjugated, bazedoxifene - DUAVIVE (CAP) - EMEA/H/C/002314/MEA 003.6

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Martin Huber

Scope: MAH's response to MEA 003.5 [first interim report for a drug utilisation study (DUS) on conjugated oestrogens/bazedoxifene (CE/BZA) in the European Union (EU) to describe baseline characteristics and utilisation patterns of EU patients initiating Duavive (CE/BZA) or oestrogen + progestin (E+P) combination hormone replacement therapy (HRT)]

17.5.6. Infliximab - FLIXABI (CAP) - EMEA/H/C/004020/MEA 002.1

Applicant: Samsung Bioepis NL B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Annual interim report for an established nationwide prospective study (listed as a

category 3 study in the RMP) from the use of biological agents to treat patients with rheumatological disorders in routine clinical practice using the British Society of Rheumatology Biologics Register for Rheumatoid Arthritis (BSRBR): an established nationwide register [final clinical study report expected in 2027]

17.5.7. Infliximab - FLIXABI (CAP) - EMEA/H/C/004020/MEA 005.1

Applicant: Samsung Bioepis NL B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Annual interim report for a study (listed as a category 3 study in the RMP): a prospective, observational cohort study whose objectives are to evaluate the long-term effectiveness, safety, and costs associated with tumour necrosis factor-inhibitor therapies in the treatment of rheumatoid arthritis (RA) and to compare this to a cohort of RA patients who are treated with non-biologic disease-modifying antirheumatic drugs (DMARDs) using the German Register for Rheumatoid Arthritis Observation of Biologic Therapy (RABBIT) [final clinical study report planned expected in 2027]

17.5.8. Infliximab - FLIXABI (CAP) - EMEA/H/C/004020/MEA 006.1

Applicant: Samsung Bioepis NL B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Annual interim report for a study (listed as a category 3 in the RMP) conducted in the Spanish register of adverse events of biological therapies in rheumatic diseases (BIOBADASER) to identify relevant adverse events occurring during treatment of rheumatic diseases with biological therapies, to estimate the frequency of their occurrence; to identify unexpected adverse events; to identify relevant adverse events that occur following the suspension of the treatment, to estimate the relative risk of occurrence of adverse events with biological therapies in patients with rheumatoid arthritis (RA) compared to those not exposed to these treatments; to identify risk factors for suffering adverse reactions with these treatments; to evaluate, under non-experimental conditions, the treatment duration before the biological medications had been suspended in patients with rheumatic diseases, as well as the reasons for the interruption of the treatment [final clinical study report planned expected in 2027]

17.5.9. Lumacaftor, ivacaftor - ORKAMBI (CAP) - EMEA/H/C/003954/ANX 003.3

Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Second annual report for study VX14 809 108: an observational study to evaluate the utilisation patterns and long-term effects of lumacaftor/ivacaftor therapy in patients with cystic fibrosis (CF) [final report expected: December 2021]

17.5.10. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/MEA 023.11

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Rhea Fitzgerald

Scope: Ninth annual interim report for study CNTO1275PSO4005 (Nordic database initiative): a prospective cohort registry, five-year observational study of adverse events (AEs) observed in patients exposed to ustekinumab

17.5.11. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/MEA 024.12

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Rhea Fitzgerald

Scope: Ninth annual interim report for study CNTO1275PSO4007 (Nordic pregnancy research initiative) (C0743T): exposure to ustekinumab during pregnancy in patients with psoriasis: a review and analysis of birth outcomes from the Swedish, Danish, and Finnish medical birth registers

17.5.12. Fingolimod - GILENYA (CAP) - EMEA/H/C/002202/MEA 038.1

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ghania Chamouni

Scope: MAH's response to MEA 038 [amendment to the previously agreed protocol for study D2311: a phase 3, double-blind, double dummy, randomised, multicentre, active controlled study evaluating efficacy and safety of fingolimod once daily versus interferon β-1a once weekly in paediatric patients with multiple sclerosis (MS) aged 10 to <18 years old (from X/44/G)] as per the request for supplementary information (RSI) adopted in April 2019

17.5.13. Venetoclax - VENCLYXTO (CAP) - EMEA/H/C/004106/MEA 006

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Eva Jirsová

Scope: Interim study report for study M12-175: a phase 1 study evaluating the safety and pharmacokinetics of venetoclax (ABT-199) in subjects with relapsed or refractory chronic lymphocytic leukaemia and non-Hodgkin lymphoma

17.6. New Scientific Advice

None

17.7. Ongoing Scientific Advice

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

17.8. 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. Chenodeoxycholic acid - CHENODEOXYCHOLIC ACID LEADIANT (CAP) - EMEA/H/C/004061/S/0010 (without RMP)

Applicant: Leadiant GmbH

PRAC Rapporteur: Adam Przybylkowski

Scope: Annual reassessment of the marketing authorisation

18.1.2. Idursulfase - ELAPRASE (CAP) - EMEA/H/C/000700/S/0080 (without RMP)

Applicant: Shire Human Genetic Therapies AB

PRAC Rapporteur: Menno van der Elst

Scope: Annual reassessment of the marketing authorisation

18.2. Conditional renewals of the marketing authorisation

18.2.1. Brentuximab vedotin - ADCETRIS (CAP) - EMEA/H/C/002455/R/0067 (without RMP)

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Menno van der Elst

Scope: Conditional renewal of the marketing authorisation

18.2.2. Ixazomib - NINLARO (CAP) - EMEA/H/C/003844/R/0017 (without RMP)

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Annika Folin

Scope: Conditional renewal of the marketing authorisation

18.3. Renewals of the marketing authorisation

18.3.1. Afamelanotide - SCENESSE (CAP) - EMEA/H/C/002548/R/0026 (without RMP)

Applicant: Clinuvel Europe Limited

PRAC Rapporteur: Martin Huber

Scope: 5-year renewal of the marketing authorisation

18.3.2. Dalbavancin - XYDALBA (CAP) - EMEA/H/C/002840/R/0028 (without RMP)

Applicant: Allergan Pharmaceuticals International Limited

PRAC Rapporteur: Rugile Pilviniene

Scope: 5-year renewal of the marketing authorisation

18.3.3. Dasabuvir - EXVIERA (CAP) - EMEA/H/C/003837/R/0045 (without RMP)

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Maria del Pilar Rayon

Scope: 5-year renewal of the marketing authorisation

18.3.4. Dronedarone - MULTAQ (CAP) - EMEA/H/C/001043/R/0042 (with RMP)

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Menno van der Elst

Scope: 5-year renewal of the marketing authorisation

18.3.5. Eliglustat - CERDELGA (CAP) - EMEA/H/C/003724/R/0022 (without RMP)

Applicant: Genzyme Europe BV

PRAC Rapporteur: Eva Segovia

Scope: 5-year renewal of the marketing authorisation

18.3.6. Lapatinib - TYVERB (CAP) - EMEA/H/C/000795/R/0060 (without RMP)

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Annika Folin

Scope: 5-year renewal of the marketing authorisation

18.3.7. Naloxegol - MOVENTIG (CAP) - EMEA/H/C/002810/R/0028 (without RMP)

Applicant: Kyowa Kirin Holdings B.V.

PRAC Rapporteur: Ronan Grimes

Scope: 5-year renewal of the marketing authorisation

18.3.8. Nintedanib - OFEV (CAP) - EMEA/H/C/003821/R/0025 (without RMP)

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: 5-year renewal of the marketing authorisation

18.3.9. Olaparib - LYNPARZA (CAP) - EMEA/H/C/003726/R/0029 (without RMP)

Applicant: AstraZeneca AB

PRAC Rapporteur: Amelia Cupelli

Scope: 5-year renewal of the marketing authorisation

18.3.10. Ombitasvir, paritaprevir, ritonavir - VIEKIRAX (CAP) - EMEA/H/C/003839/R/0054 (without RMP)

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Maria del Pilar Rayon

Scope: 5-year renewal of the marketing authorisation

18.3.11. Panitumumab - VECTIBIX (CAP) - EMEA/H/C/000741/R/0094 (without RMP)

Applicant: Amgen Europe B.V.

PRAC Rapporteur: David Olsen

Scope: 5-year renewal of the marketing authorisation

18.3.12. Ramucirumab - CYRAMZA (CAP) - EMEA/H/C/002829/R/0031 (without RMP)

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: 5-year renewal of the marketing authorisation

18.3.13. Rasagiline - RASAGILINE RATIOPHARM (CAP) - EMEA/H/C/003957/R/0014 (without RMP)

Applicant: Teva B.V.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: 5-year renewal of the marketing authorisation

18.3.14. Safinamide - XADAGO (CAP) - EMEA/H/C/002396/R/0032 (without RMP)

Applicant: Zambon S.p.A.

PRAC Rapporteur: Rhea Fitzgerald

Scope: 5-year renewal of the marketing authorisation

18.3.15. Sevelamer carbonate - SEVELAMER CARBONATE WINTHROP (CAP) - EMEA/H/C/003971/R/0022 (without RMP)

Applicant: Genzyme Europe BV

PRAC Rapporteur: Laurence de Fays

Scope: 5-year renewal of the marketing authorisation

18.3.16. Tilmanocept - LYMPHOSEEK (CAP) - EMEA/H/C/002085/R/0016 (with RMP)

Applicant: Norgine B.V.

PRAC Rapporteur: Rugile Pilviniene

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 08-11 July 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
Maria Popova-Kiradjieva	Member	Bulgaria	No interests declared	Full involvement
Željana Margan Koletić	Alternate	Croatia	No interests declared	Full involvement
Panagiotis Psaras	Alternate	Cyprus	No interests declared	Full involvement
Eva Jirsovà	Member	Czech Republic	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
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:	17.1.2. Levofloxacin - QUINSAIR (CAP)
Adrien Inoubli	Alternate	France	No interests declared	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Martin Huber	Member (Vice-Chair)	Germany	No interests declared	Full involvement
Brigitte Keller-Stanislawski	Alternate	Germany	No interests declared	Full involvement
Julia Pallos	Member	Hungary	No interests declared	Full involvement
Guðrún Stefánsdóttir	Member	Iceland	No participation in discussion, final deliberations and voting on:	4.3.2. Mesalazine (NAP)
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
Marcel Bruch	Member	Luxembourg	No interests declared	Full involvement
Benjamin Micallef	Alternate	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:	3.1.1. Cyproterone acetate (NAP) 3.2.2. Estradiol (NAP) 4.3.5. Vascular endothelial growth factor (VEGF) inhibitors 17.1.1. Damoctocog alfa pegol - JIVI (CAP) 17.1.3. Radium (Ra223) dichloride - XOFIGO (CAP)
Karen Pernille Harg	Alternate	Norway	No interests declared	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Adam Przybylkowski	Member	Poland	No interests declared	Full involvement
Ana Diniz Martins	Member	Portugal	No interests declared	Full involvement
Roxana Stefania Stroe	Member	Romania	No interests declared	Full involvement
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
Julie Williams	Member	United Kingdom	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
Antoine Pariente	Member	Independent scientific expert	No restrictions applicable to this meeting	Full involvement
Livia Puljak	Member	Independent scientific expert	No interests declared	Full involvement
Stefan Weiler	Member	Independent scientific expert	No restrictions applicable to this meeting	Full involvement
Raymond Anderson	Member	Healthcare Professionals' Representative	No interests declared	Full involvement
Roberto Frontini	Alternate	Healthcare Professionals' Representative	No interests declared	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
Sophie Kiridis	Expert - via telephone*	Belgium	No interests declared	Full involvement
Fabrice Moore	Expert - via telephone*	Belgium	No interests declared	Full involvement
Flora Musuamba Tshinanu	Expert - in person*	Belgium	No interests declared	Full involvement
Veerle Verlinden	Expert - in person*	Belgium	No interests declared	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Ane Blicher Schelde	Expert - in person*	Denmark	No interests declared	Full involvement
Anita Vibsig Neutzsky-Wulff	Expert - in person*	Denmark	No interests declared	Full involvement
Maija Kaukonen	Expert - via telephone*	Finland	No interests declared	Full involvement
Delphine Allue	Expert - in person*	France	No interests declared	Full involvement
Pauline Dayani	Expert - in person*	France	No interests declared	Full involvement
Emilie Patras de Campaigno	Expert - in person*	France	No interests declared	Full involvement
Emmanuelle Ripoche	Expert - in person*	France	No interests declared	Full involvement
Muriel Uzzan	Expert - in person*	France	No interests declared	Full involvement
Christine Diesinger	Expert - via telephone*	Germany	No interests declared	Full involvement
Claudia Kayser	Expert - via telephone*	Germany	No interests declared	Full involvement
Kerstin Löschcke	Expert - in person*	Germany	No interests declared	Full involvement
Karin Seifert	Expert - in person*	Germany	No restrictions applicable to this meeting	Full involvement
Kate Browne	Expert - via telephone*	Ireland	No interests declared	Full involvement
Ruchika Sharma	Expert - via telephone*	Ireland	No interests declared	Full involvement
Gunta Pauksena	Expert - in person*	Latvia	No interests declared	Full involvement
Quirine Fillekes	Expert - in person*	Netherlands	No interests declared	Full involvement
Anja van Haren	Expert - in person*	Netherlands	No interests declared	Full involvement
Anouk Neuteboom	Expert - in person*	Netherlands	No interests declared	Full involvement
Nicole Visser	Expert - in person*	Netherlands	No interests declared	Full involvement
Lies van Vlijmen	Expert - in person*	Netherlands	No interests declared	Full involvement
Sílvia Duarte	Expert - in person*	Portugal	No interests declared	Full involvement
Consuelo Mejias Pavon	Expert - via telephone*	Spain	No interests declared	Full involvement
Charlotte Backman	Expert - in person*	Sweden	No interests declared	Full involvement
Karin Nylén	Expert - via telephone*	Sweden	No interests declared	Full involvement
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/