26 November 2020
EMA/PRAC/672654/2020
Human Medicines Division

Pharmacovigilance Risk Assessment Committee (PRAC)

Minutes of the meeting on 06 – 09 July 2020

Chair: Sabine Straus – Vice-Chair: Martin Huber

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).

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

1. Introduction

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

The Chairperson opened the 06-09 July 2020 meeting by welcoming all participants. Due to the current coronavirus (COVID-19) outbreak, and the associated EMA Business Continuity Plan (BCP), the meeting was held remotely.

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 (Annex II – List of participants). No new or additional conflicts were declared.

Discussions, deliberations and voting took place in full respect of the restricted involvement of Committee members and experts in line with the relevant provisions of revision 2 of the Rules of Procedure (EMA/PRAC/567515/2012 Rev.2). All decisions taken at this meeting held under the conditions of an emergency situation, the Agency's BCP and in compliance with internal guidelines were made in the presence of a quorum of members (i.e. 18 or more members were present in the room). All decisions, recommendations and advice were agreed unanimously, unless otherwise specified.

The PRAC Chair welcomed Tiphaine Vaillant, as the new alternate for France, replacing Adrien Inoubli who took over the role of member for France.

Finally, the PRAC welcomed the German presidency of the Council of the EU.

1.2. Agenda of the meeting on 06 – 09 July 2020

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 08 - 11 June 2020

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 08 - 11 June 2020 were published on the EMA website on 01 December 2020 (EMA/PRAC/645617/2020).

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

2.1. Newly triggered procedures

None

2.2. Ongoing procedures

None

2.3. Procedures for finalisation

None

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

3.1. Newly triggered procedures

None

3.2. Ongoing procedures

3.2.1. Ifosfamide[1] (NAP) - EMEA/H/A-31/1495

Applicant(s): various

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

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

Background

A referral procedure under Article 31 of Directive 2001/83/EC is ongoing for the review of ifosfamide solution and concentrate for solution following epidemiological studies suggesting an increased risk of ifosfamide-induced encephalopathy with ifosfamide EG (ifosfamide) solution for infusion compared with ifosfamide powder. For further background, see PRAC minutes March 2020.

Summary of recommendation(s)/conclusions

- The PRAC discussed the assessment reports issued 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/111338/2020 rev1).
- The PRAC adopted a list of questions to study authors *Hillaire-Buys et al*[2].
- The PRAC adopted a separate list of questions to study authors *Hillaire-Buys, Zenut et al*[3].

[1] Solution, concentrate for solution
[2] Hillaire-Buys D, et al. Liquid formulation of ifosfamide increased risk of encephalopathy: A case-control study in a pediatric population. Therapie. 2019 Oct 28:S0040-5957(19)30153-2
[3] Hillaire-Buys, Zenut et al. Enquête officielle ifosfamide et effets neurologiques centraux (official investigation of ifosfamide and central neurological effects) Holoxan laboratoire Baxter, Ifosfamide EG EuroGenerics Laboratory, September 2015

3.2.2. Ulipristal acetate[4] – ESMYA (CAP); NAP - EMEA/H/A-31/1496

Applicant(s): Gedeon Richter Plc.; various

PRAC Rapporteur: Annika Folin; 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 the review of medicinal products containing ulipristal acetate 5 mg after a new case of serious liver injury leading to liver transplantation following exposure to Esmya (ulipristal acetate) was reported despite the implementation of risk minimisation measures (RMMs) in 2018 in line with the conclusions of a previous referral procedure under Article 20 of Regulation (EC) No 726/2004 on Esmya (ulipristal acetate). In March 2020, the PRAC recommended the provisional suspension of the marketing authorisations of ulipristal acetate 5 mg-containing products, until the review is finalised. For further background, see PRAC minutes March 2020 and PRAC minutes June 2020.

Summary of recommendation(s)/conclusions

- The PRAC received feedback from the ad-hoc expert group (AHEG) meeting held on 02 July 2020.

3.3. Procedures for finalisation

None

3.4. Re-examination procedures[5]

None

3.5. Others

None

4. Signals assessment and prioritisation[6]

4.1. New signals detected from EU spontaneous reporting systems

See Annex I 14.1.

[4] 5 mg
[5] Re-examination of PRAC recommendation under Article 32 of Directive 2001/83/EC
[6] Each signal refers to a substance or therapeutic class. The route of marketing authorisation is indicated in brackets (CAP for Centrally Authorised Products; NAP for Nationally Authorised Products including products authorised via Mutual Recognition Procedures and Decentralised Procedure). Product names are listed for reference Centrally Authorised Products (CAP) only. PRAC recommendations will specify the products concerned in case of any regulatory action required

4.2. New signals detected from other sources

None

4.3. Signals follow-up and prioritisation

4.3.1. Adalimumab - AMGEVITA (CAP); AMSPARITY (CAP), HALIMATOZ (CAP); HEFIYA (CAP); HULIO (CAP); HUMIRA (CAP) - EMEA/H/C/000481/SDA/118; HYRIMOZ (CAP); IDACIO (CAP); IMRALDI (CAP)

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

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of abnormal weight gain

EPITT 19520 – Follow-up to February 2020

Background

For background information, see PRAC minutes February 2020.

Discussion

Having considered the available evidence, including the data submitted by the MAH for Humira (adalimumab), the PRAC agreed that further information was required before drawing a final recommendation. Therefore, the PRAC agreed to request responses from the MAH to a further list of questions (LoQ).

Summary of recommendation(s)

- The MAH for Humira (adalimumab) should submit to EMA, within 60 days, responses to a LoQ agreed by the PRAC.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

Post-meeting note: Upon MAH's request, the PRAC agreed to extend the timelines for the submission of MAH's responses by 90 days.

4.3.2. Lisdexamfetamine (NAP)

Applicant(s): various

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of QT prolongation and cardiac arrhythmia

EPITT 19533 – Follow-up to February 2020

Background

For background information, see PRAC minutes February 2020.

Discussion

Having considered the available evidence and the assessment of the data submitted by the MAH Shire Pharmaceuticals for lisdexamfetamine-containing product(s), the PRAC agreed that there is sufficient evidence for a causal association between lisdexamfetamine and QT prolongation. Therefore, the PRAC agreed that the product information for lisdexamfetamine should be updated.

Summary of recommendation(s)

- The MAHs for lisdexamfetamine-containing products should submit to the relevant National Competent Authorities (NCAs) of the Member States, within 60 days, a variation to amend[7] the product information.
- The MAHs of lisdexamfetamine-containing products should additionally monitor and present reviews of the risk of arrhythmias, cardiac arrest and sudden death in the next PSUR[8].

For the full PRAC recommendation, see EMA/PRAC/367621/2020 published on 03/08/2020 on the EMA website.

4.3.3. Lopinavir, ritonavir – ALUVIA (Art 58[9]) - EMEA/H/W/000764/SDA/033, KALETRA (CAP) - EMEA/H/C/000368/SDA/123, LOPINAVIR/RITONAVIR MYLAN (CAP); NAP

Applicant(s): AbbVie Deutschland GmbH & Co. KG (Aluvia, Kaletra), Mylan S.A.S (Lopinavir, Ritonavir Mylan), various

PRAC Rapporteur: Adrien Inoubli

Scope: Signal of adrenal dysfunction in infants

EPITT 19527 – Follow-up to March 2020

Background

For background information, see PRAC minutes March 2020.

Discussion

Having considered the evidence from the literature, the cumulative review provided by the MAH for Kaletra (lopinavir/ritonavir) and the responses from the *Kariyawasam et al.*[10] study authors, the PRAC agreed that there is insufficient evidence at present that the potential adrenal dysfunction observed in some infants receiving lopinavir/ritonavir from birth is associated with any clinical impact. The PRAC agreed that no further regulatory action is warranted at this stage.

Summary of recommendation(s)

- The MAHs for lopinavir/ritonavir-containing products should continue to monitor cases of adrenal dysfunction as part of routine safety surveillance.

[7] Update of SmPC sections 4.4 and 4.8. The package leaflet is to be updated accordingly
[8] Data lock point (DLP): 22/02/2021
[9] Article 58 of Regulation (EC) No 726/2004 allows the Committee for Medicinal Products for Human Use (CHMP) to give opinions, in co-operation with the World Health Organisation (WHO) on medicinal products for human use that are intended exclusively for markets outside of the European Union (EU)
[10] Kariyawasam D et al. Lopinavir-Ritonavir Impairs Adrenal Function in Infants. Clin Infect Dis. 2019 Oct 21. pii: ciz888. doi: 10.1093/cid/ciz888

4.3.4. Teriparatide - FORSTEO (CAP) - EMEA/H/C/000425/SDA/052, MOVYMIA (CAP) - EMEA/H/C/004368/SDA/002; TERROSA (CAP) - EMEA/H/C/003916/SDA/002; NAP

Applicant(s): Eli Lilly Nederland B.V. (Forsteo), Gedeon Richter Plc. (Terrosa), Stada Arzneimittel AG (Movymia), various

PRAC Rapporteur: Adrien Inoubli

Scope: Signal of myeloma

EPITT 19511 – Follow-up to February 2020

Background

For background information, see PRAC minutes February 2020.

Discussion

Having considered the available evidence and the assessment of the data submitted by the MAHs of Forsteo, Movymia and Terrosa (teriparatide), the PRAC agreed that at this stage, there is still insufficient evidence to conclude that teriparatide therapy induces monoclonal gammopathy of undetermined significance (MGUS) or multiple myeloma (MM). Therefore, the PRAC agreed to request additional information from the MAHs.

Summary of recommendation(s)

- The MAH for Forsteo (teriparatide) should provide to EMA, within 30 days, a review of cases of MGUS and MM with time to onset below one year and cases with concomitant use of glucocorticoids.
- The MAHs for Forsteo, Movymia and Terrosa (teriparatide) should submit to EMA, within 30 days, a review of cases of MGUS and MM in association with treatment with parathyroid hormone.

4.3.5. Tumour necrosis factor (TNF) inhibitors: adalimumab - AMGEVITA (CAP), AMSPARITY (CAP), HALIMATOZ (CAP), HEFIYA (CAP), HULIO (CAP), HUMIRA (CAP) - EMEA/H/C/000481/SDA/120, HYRIMOZ (CAP), IDACIO (CAP), IMRALDI (CAP); certolizumab pegol - CIMZIA (CAP) - EMEA/H/C/001037/SDA/039; etanercept - BENEPALI (CAP), ENBREL (CAP) - EMEA/H/C/000262/SDA/173, ERELZI (CAP); golimumab - SIMPONI (CAP) - EMEA/H/C/000992/SDA/036; infliximab - FLIXABI (CAP), INFLECTRA (CAP), REMICADE (CAP) - EMEA/H/C/000240/SDA/158, REMSIMA (CAP), ZESSLY (CAP)

Applicant(s): AbbVie Deutschland GmbH Co. KG (Humira), Amgen Europe B.V. (Amgevita), Celltrion Healthcare Hungary Kft. (Remsima), Fresenius Kabi Deutschland GmbH (Idacio), Mylan S.A.S. (Hulio), Janssen Biologics B.V. (Simponi, Remicade), Pfizer Europe MA EEIG (Amsparity, Enbrel, Inflectra), Samsung Bioepis NL B.V. (Benepali, Flixabi, Imraldi), Sandoz GmbH (Erelzi, Halimatoz, Hefiya, Hyrimoz, Zessly), UCB Pharma S.A. (Cimzia)

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of Kaposi's sarcoma

EPITT 19480 – Follow-up to April 2020

Background

For background information, see PRAC minutes April 2020.

Discussion

Having considered the cumulative reviews submitted by the MAHs for Cimzia (certolizumab pegol), Enbrel (etanercept), Humira (adalimumab) and Remicade (infliximab) as reference tumour necrosis factor alfa (TNFα)-inhibitor products, the PRAC concluded that there is sufficient evidence for an association between TNFα-inhibitors and Kaposi's sarcoma and that the product information of adalimumab-, certolizumab-, etanercept-, golimumab- and infliximab-containing products should be updated accordingly.

Summary of recommendation(s)

- The MAHs of adalimumab-, certolizumab-, etanercept-, golimumab- and infliximab-containing products should submit to the EMA, within 60 days, a variation to amend[11] the product information.

For the full PRAC recommendation, see EMA/PRAC/367621/2020 published on 03/08/2020 on the EMA website.

4.4. Variation procedure(s) resulting from signal evaluation

None

5. Risk management plans (RMPs)

5.1. Medicines in the pre-authorisation phase

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

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

5.1.1. Cabotegravir - EMEA/H/C/004976

Scope: Treatment of human imunodeficiency virus type 1 (HIV-1)

5.1.2. Influenza quadrivalent vaccine (rDNA[12]) - EMEA/H/C/005159

Scope: Prevention of influenza disease

5.1.3. Lonafarnib - EMEA/H/C/005271, Orphan

Applicant: EigerBio Europe Limited

Scope (accelerated assessment): Treatment of Hutchinson-Gilford progeria syndrome and progeroid laminopathies

[11] Update of SmPC section 4.8. The package leaflet is to be updated accordingly
[12] Ribosomal deoxyribonucleic acid

5.1.4. Lumasiran - EMEA/H/C/005040, Orphan

Applicant: Alnylam Netherlands B.V.

Scope (accelerated assessment): Treatment of primary hyperoxaluria type 1 (PH1)

5.1.5. Meningococcal group A, C, W-135 and Y conjugate vaccine - EMEA/H/C/005084

Scope: Immunisation against Neisseria meningitidis serogroups A, C, W-135 and Y

5.1.6. Rilpivirine - EMEA/H/C/005060

Scope: Treatment of human immunodeficiency virus type 1 (HIV-1)

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

See also Annex I 15.2.

5.2.1. Dapagliflozin - EDISTRIDE (CAP) - EMEA/H/C/004161/WS1844/0039; FORXIGA (CAP) - EMEA/H/C/002322/WS1844/0057

Applicant: AstraZeneca AB

PRAC Rapporteur: Annika Folin

Scope: Re-categorisation of study D169C00011: a retrospective cohort study on the risk of diabetic ketoacidosis (DKA) to determine the effectiveness of additional risk minimisation measures (aRMMs) in place for DKA by assessing the impact of the risk minimisation measures (RMMs) on the risk of DKA in type 1 diabetes mellitus (T1DM) patients who are treated with dapagliflozin in Europe, from a category 1 to a category 3 study in the RMP (version 20). Annex II-D on 'Conditions or restrictions with regard to the safe and effective use of the medicinal product' is updated accordingly

Background

Dapagliflozin is a sodium-glucose co-transporter-2 (SGLT2) inhibitor indicated as Edistride and Forxiga, in adults for the treatment of insufficiently controlled type 2 diabetes mellitus (T2DM) as an adjunct to diet and exercise, either as monotherapy when metformin is considered inappropriate due to intolerance or in addition to other medicinal products for the treatment of T2DM. It is also indicated in adults for the treatment of insufficiently controlled type 1 diabetes mellitus (T1DM) as an adjunct to insulin in patients with body mass index (BMI) $\geq$ 27 kg/m^2, when insulin alone does not provide adequate glycaemic control despite optimal insulin therapy.

The PRAC is evaluating a worksharing variation for Edistride and Forxiga, centrally authorised products containing dapagliflozin, evaluating a request to re-categorise study D169C00011: a retrospective cohort study on the risk of diabetic ketoacidosis (DKA) to determine the effectiveness of additional risk minimisation measures (aRMMs) in place for DKA by assessing the impact of the risk minimisation measures (RMMs) on the risk of DKA in type 1 diabetes mellitus (T1DM) patients who are treated with dapagliflozin in Europe, from a category 1 to a category 3 study in the RMP. The PRAC is responsible for providing advice to the CHMP on the requested updates to the RMP to support this variation.

Summary of advice

- The RMP for Edistride and Forxiga (dapagliflozin) in the context of the variation procedure under evaluation by the CHMP could be considered acceptable provided that an update to RMP version 20 is submitted.
- Taking into account that study D169C00011 is listed as a category 1 study, key to the benefit risk balance of dapagliflozin 5mg in the T1DM indication, and considering the limited new data on DKA available from the post-marketing experience with dapagliflozin 5mg in T1DM patients in the EU, the PRAC agreed that a PASS re-categorisation was not justified at this stage. The MAH should provide further justification including provision of data to support a request for a study reclassification.

5.2.2. Ipilimumab - YERVOY (CAP) - EMEA/H/C/002213/II/0080

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Menno van der Elst

Scope: Submission of an updated RMP (version 28.0) in order to propose the discontinuation of the healthcare professional adverse reaction management guide as an additional risk minimisation measure (aRMM). Annex II-D on 'Conditions or restrictions with regard to the safe and effective use of the medicinal product' is updated accordingly. The MAH took the opportunity to bring in line the product information with the latest quality review of documents (QRD) template (version 10.1) and in line with the latest Annex to the European Commission (EC) guideline on 'excipients in the labelling and package leaflet of medicinal products for human use' on sodium content

Background

Ipilimumab is a cytotoxic T-lymphocyte antigen-4 (CTLA-4) immune checkpoint inhibitor (ICI) indicated, as Yervoy, for the treatment of advanced (unresectable or metastatic) melanoma in adults, and adolescents 12 years of age and older. It is also indicated in combination with nivolumab for the treatment of advanced (unresectable or metastatic) melanoma in adults. In addition, it is indicated in combination with nivolumab for the first-line treatment of adult patients with intermediate/poor-risk advanced renal cell carcinoma (RCC).

The PRAC is evaluating a type II variation for Yervoy, a centrally authorised product containing ipilimumab, proposing the discontinuation of the healthcare professional (HCP) adverse reaction management guide as an additional risk minimisation measure (aRMM). 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 (version 28.0) for Yervoy (ipilimumab) in the context of the variation procedure under evaluation is considered acceptable.
- The PRAC supported the removal of the existing educational material for HCP on 'immune-related adverse events (irAEs)' as these risk and risk minimisations are well integrated in clinical practice and adequately mitigated by routine risk minimisation measures (RMMs) and clinical guidelines. In addition, this in line with other immune checkpoint inhibitors (ICI)-medicinal products. For patients, the maintenance of the patient educational materials is warranted. In addition, the PRAC agreed with the deletion of the targeted questionnaires for gastrointestinal (GI)-, hepatic-, neurologic-

and skin irAEs, as these adverse drug reactions (ADRs) have been well characterised in the past years. Finally, 'embryofoetal toxicity' should be followed in PSURs as an important potential risk.

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

See also Annex I 15.3.

5.3.1. Dabigatran etexilate - PRADAXA (CAP) - EMEA/H/C/000829/X/0122/G

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Anette Kirstine Stark

Scope: Grouped applications consisting of: 1) extension application to add two new pharmaceutical forms coated granules (20 mg, 30 mg, 40 mg, 50 mg, 110 mg, 150 mg) and powder and solvent for oral solution (6.25 mg/mL)); 2) extension of indication to include treatment of venous thromboembolic events (VTE) and prevention of recurrent VTE in paediatric patients from birth to less than 18 years of age for Pradaxa (dabigatran etexilate) 75 mg, 110 mg, 150 mg capsules based on paediatric trials, namely study 1160.106: an open-label, randomized, parallel-group, active-controlled, multi-centre non-inferiority study of dabigatran etexilate versus standard of care for venous thromboembolism treatment in children from birth to less than 18 years of age, and study 1160.108: an open label, single arm safety prospective cohort study of dabigatran etexilate for secondary prevention of venous thromboembolism in children from 0 to less than 18 years. As a consequence, sections 4.1, 4.2, 4.3, 4.4, 4.5, 4.7, 4.8, 4.9, 5.1, 5.2 and 5.3 of the SmPC are updated. The package leaflet and labelling are updated in accordance. The RMP (version 37.0) is updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet

Background

Dabigatran etexilate is a reversible direct thrombin inhibitor indicated, as Pradaxa, for the primary prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery. It is also indicated for the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF) with one or more risk factors. In addition, it is indicated for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.

The CHMP is evaluating grouped application for Pradaxa, a centrally authorised product containing dabigatran etexilate, consisting of an extension application to add two new pharmaceutical forms, coated granules and powder and solvent for oral solution, and an extension of indication to include 'treatment of venous thromboembolic events (VTE) and prevention of recurrent VTE in paediatric patients from birth to less than 18 years of age' for Pradaxa (dabigatran etexilate) 75 mg, 110 mg, 150 mg capsules based on paediatric trials. 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 February 2020.

Summary of advice

- The RMP for Pradaxa (dabigatran etexilate) in the context of the variation procedure under evaluation by the CHMP could be considered acceptable provided that an update to RMP version 38.0 is submitted.
- The applicant should remove 'patients with antiphospholipid antibody syndrome' as missing information from the list of safety concerns. In addition, the proposed post-authorisation pharmacovigilance plan should be amended to include measures to assess the effectiveness of the training video for healthcare professionals (HCPs) and caregivers to ensure the correct reconstitution and handling of the oral solution dose form in in order to address the risk of medication error. The content and format should be agreed on a national level. Finally, the proposed risk minimisation measures are not sufficient to minimise the risks of the medicinal product at present. The training video relating to the risk of medication error with the oral solution should be made mandatory.

6. Periodic safety update reports (PSURs)

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

See also Annex I 16.1.

6.1.1. Aflibercept[13] - EYLEA (CAP) - PSUSA/00010020/201911

Applicant: Bayer AG

PRAC Rapporteur: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

Background

Aflibercept is an engineered angiogenic protein indicated, as Eylea, for the treatment of neovascular (wet) age-related macular degeneration (AMD). It is also indicated for visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO), visual impairment due to diabetic macular oedema (DME), and visual impairment due to myopic choroidal neovascularisation (myopic CNV).

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Eylea, a centrally authorised medicine containing aflibercept 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 Eylea (aflibercept) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include retinal haemorrhage as an undesirable effect with a frequency 'very common'. Therefore, the current terms of the marketing authorisation(s) should be varied[14].

[13] Ophthalmological indication(s) only
[14] 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

- In the next PSUR, the MAH should provide a detailed review regarding cases of excretion of aflibercept in breast milk and a possible influence on vascular endothelial growth factor (VEGF) in mother's milk and, in accordance with the current literature review on breastfeeding by *Juncal et al*.[15]. The MAH should propose to update the product information as appropriate. The MAH should continue to provide information on cases of retinal artery occlusion with focus on cases of intraocular inflammation and/or transient intraocular pressure increase, as well as on the available literature.

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.

6.1.2. Dimethyl fumarate[16] - SKILARENCE (CAP) - PSUSA/00010647/201912

Applicant: Almirall S.A

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

Background

Dimethyl fumarate is an immunomodulator indicated, as Skilarence, for the treatment of moderate to severe plaque psoriasis in adults in need of systemic medicinal therapy.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Skilarence (dimethyl fumarate) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include herpes zoster as an undesirable effect with the frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[17].
- In the next PSUR, the MAH should provide details on cases of Fanconi syndrome. The MAH should also provide information on serious cases of eosinophilia and information.

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 two-yearly and the list of Union reference dates (EURD list) will be updated accordingly.

[15] Juncal VR, Paracha Q, Bamakrid M, Francisconi CLM, Farah J, Kherani A, et al. Ranibizumab and aflibercept levels in breast milk after intravitreal injection. Ophthalmology. 2019
[16] Indicated for the treatment of psoriasis
[17] 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

6.1.3. Levodopa - INBRIJA (CAP) - PSUSA/00107800/201912

Applicant: Acorda Therapeutics Ireland Limited

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Evaluation of a PSUSA procedure

Background

Levodopa is a dopamine precursor indicated, as Inbrija, for the intermittent treatment of episodic motor fluctuations (OFF episodes) in adult patients with Parkinson's disease (PD) treated with a levodopa/dopa-decarboxylase inhibitor.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Inbrija, a centrally authorised medicine containing levodopa 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 Inbrija (levodopa) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include sensation of choking as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[18].
- In the next PSUR, the MAH should continue to monitor cases of dyspnoea/wheezing/asthma (i.e. potentially bronchospasm related events) and provide an assessment of the causality mechanism with a proposal for updating the risk minimisation measures, as appropriate. The MAH should also provide information regarding cases of upper respiratory tract infections and further discuss the risk of respiratory infection. In addition, the MAH should provide a detailed analysis of cases of medication errors and provide a discussion of a plausible mechanism with a proposal for risk minimisation measures, 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.

6.1.4. Liraglutide - SAXENDA (CAP); VICTOZA (CAP) - PSUSA/00001892/201912

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) receptor agonist indicated, as Victoza, for the treatment of adults, adolescents and children aged 10 years and above with insufficiently controlled type 2 diabetes mellitus (T2DM) as an adjunct to diet and exercise, subject to specific conditions. It is also indicated, as Saxenda, as an adjunct to a reduced-calorie diet

[18] 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

and increased physical activity for weight management in adult patients with specific body mass index (BMI) parameters.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of Saxenda and Victoza, centrally authorised medicines containing liraglutide 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 Saxenda and Victoza (liraglutide) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include information that hypoglycaemia has occurred in cases of overdose. In addition, the product information for Victoza (liraglutide) should be updated to add information on traceability of biological medicinal product(s). Therefore, the current terms of the marketing authorisation(s) should be varied[19].

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.

6.1.5. Olaparib - LYNPARZA (CAP) - PSUSA/00010322/201912

Applicant: AstraZeneca AB

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

Background

Olaparib is an inhibitor of human poly (ADP-ribose) polymerase enzymes indicated for the treatment of ovarian, fallopian tube, or primary peritoneal cancer and breast cancer, under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Lynparza, a centrally authorised medicine containing olaparib 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 Lynparza (olaparib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include erythema nodosum and angioedema as undesirable effects with a frequency 'rare' and 'uncommon' respectively. Therefore, the current terms of the marketing authorisation(s) should be varied[20].

[19] Update of SmPC section 4.9. In addition, update of SmPC section 4.4 for Victoza (liraglutide). The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion
[20] 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

- In the next PSUR, the MAH should provide a safety review of serious cases of ileus and propose a plausible mechanism with a proposal for risk minimisation measures, 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. Secukinumab - COSENTYX (CAP) - PSUSA/00010341/201912

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

Background

Secukinumab is a fully human immunoglobulin G1 (IgG1)/κ monoclonal antibody indicated, as Cosentyx, for the treatment of plaque psoriasis, psoriatic arthritis and axial spondyloarthritis (axSpA), under certain conditions.

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 fatigue, nausea and headache as undesirable effects with a frequency 'common'. Therefore, the current terms of the marketing authorisation(s) should be varied[21].
- In the next PSUR, the MAH should provide a detailed cumulative review of cases of serious cutaneous infections with a proposal for updating the product information, as appropriate. The MAH should also closely monitor cases of Guillain-Barre syndrome (GBS) and provide a summary of the available information.

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.

6.1.7. Semaglutide - OZEMPIC (CAP) - PSUSA/00010671/201911

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

Background

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

Semaglutide is a glucagon-like peptide-1 (GLP-1) receptor agonist indicated, as Ozempic, 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, 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 Ozempic, a centrally authorised medicine containing semaglutide 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 Ozempic (semaglutide) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include hypersensitivity, covering undesirable effects related to hypersensitivity, rash and urticaria, with a frequency 'uncommon'. In addition, the product information should be updated to add information on traceability of biological medicinal product(s). Therefore, the current terms of the marketing authorisation(s) should be varied[22].
- In the next PSUR, the MAH should provide a cumulative review of cases of angioedema and provide a discussion on a plausible mechanism with a proposal for updating 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.

6.1.8. Ustekinumab - STELARA (CAP) - PSUSA/00003085/201912

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

Background

Ustekinumab is a fully human immunoglobulin IgG1/κ monoclonal antibody indicated, as Stelara, for the treatment of plaque psoriasis, paediatric plaque psoriasis, psoriatic arthritis (PsA), Crohn's disease and ulcerative colitis, under certain conditions.

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.
- The current terms of the marketing authorisation(s) should be maintained.

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

- In the next PSUR, the MAH should provide cumulative reviews of cases of suicidal ideation and behaviour, acute generalised exanthematous pustulosis (AGEP), bullous pemphigoid, sarcoidosis and sarcoid-like reactions. The MAH should also provide an updated discussion of the cumulative review on influenza.
- The MAH should submit to EMA, within 60 days, a cumulative review of cases of major adverse cardiovascular events (MACE), including fatal cases.

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. Clofarabine - EVOLTRA (CAP); IVOZALL (CAP); NAP - PSUSA/00000805/201912

Applicants: Genzyme Europe BV (Evoltra), Orphelia Pharma SAS (Ivozall), various

PRAC Rapporteur: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

Background

Clofarabine is a purine nucleoside anti-metabolite indicated for the treatment of acute lymphoblastic leukaemia (ALL) in paediatric patients who have relapsed or are refractory after receiving at least two prior regimens and where there is no other treatment option anticipated to result in a durable response.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of Evoltra and Ivozall, centrally authorised medicines containing clofarabine, and nationally authorised medicine(s) containing clofarabine 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 clofarabine-containing medicinal product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include the need for a filtration step before administration. Therefore, the current terms of the marketing authorisations should be varied[23].

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.

[23] Update of SmPC section 4.2 and of Annex III-A on labelling on 'Method and route(s) of administration' of 'Particulars to appear on the outer packaging outer carton'. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

6.2.2. Clopidogrel - CLOPIDOGREL ZENTIVA (CAP), ISCOVER (CAP), PLAVIX (CAP); clopidogrel, acetylsalicylic acid - DUOPLAVIN (CAP); NAP - PSUSA/00000820/201911

Applicants: Sanofi-aventis groupe (DuoPlavin, Iscover, Plavix), Zentiva k.s. (Clopidogrel Zentiva), various

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Evaluation of a PSUSA procedure

Background

Clopidogrel is a prodrug of an inhibitor of platelet aggregation and acetylsalicylic acid (ASA) is a cyclooxygenase-1 (COX-1) inhibitor. Clopidogrel is indicated for the secondary prevention of atherothrombotic events and in association with acetylsalicylic acid in patients with acute coronary syndrome. In combination, clopidogrel/acetylsalicylic acid is also indicated for the prevention of atherothrombotic and thromboembolic events and for the prevention of atherothrombotic and thromboembolic events in atrial fibrillation under certain conditions.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of Clopidogrel Zentiva, Iscover, Plavix and DuoPlavin, centrally authorised medicines containing clopidogrel, and nationally authorised medicine(s) containing clopidogrel and clopidogrel/acetylsalicylic acid 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 clopidogrel-containing medicinal product(s) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisations should be maintained.
- In the next PSUR, the MAHs should provide an assessment of medication errors associated to clopidogrel or clopidogrel/acetylsalicylic acid with other medicinal products that interfere with haemostasis. In addition, the MAHs should provide information on off-label use of the triple antiplatelet therapy (aspirin + clopidogrel + dipyridamole) for secondary stroke prevention with a proposal for updating 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. Docetaxel - DOCETAXEL ZENTIVA (CAP); TAXOTERE (CAP); NAP - PSUSA/00001152/201911

Applicants: Sanofi Mature IP (Taxotere), Zentiva, k.s. (Docetaxel Zentiva), various

PRAC Rapporteur: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

Background

Docetaxel is an antineoplastic agent indicated for the treatment of breast cancer, non-small cell lung cancer, prostate cancer, gastric adenocarcinoma and head and neck cancer, under certain conditions.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of Docetaxel Zentiva and Taxotere, centrally authorised medicines containing docetaxel, and nationally authorised medicine(s) containing docetaxel 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 docetaxel-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 cumulative reviews of cases of capillary leak syndrome and of cases of psoriasis. The MAHs should also provide a discussion on the use of reduced-dose premedication regimens with dexamethasone, based on data from clinical trials and literature. All MAHs should review the literature data regarding cross resistance between taxanes and androgen biosynthesis inhibitors.
- The MAH Sanofi Mature IP should submit to EMA, within 180 days, a detailed review on potential risk for decreased efficacy of docetaxel when used along with selective cyclooxygenase-2 (COX-2) inhibitors with a proposal for updating risk minimisation measures, 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.

6.2.4. Lenalidomide - LENALIDOMIDE ACCORD (CAP); REVLIMID (CAP); NAP - PSUSA/00001838/201912

Applicants: Accord Healthcare S.L.U. (Lenalidomide Accord), Celgene Europe BV (Revlimid), various

PRAC Rapporteur: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

Background

Lenalidomide is an anti-neoplastic, anti-angiogenic, pro-erythropoietic, and immunomodulatory agent indicated for the treatment of multiple myeloma, myelodysplastic syndromes, mantle cell lymphoma and follicular lymphoma, under certain conditions.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of Lenalidomide Accord and Revlimid, centrally authorised medicines containing lenalidomide, and nationally authorised medicine(s) containing lenalidomide 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 lenalidomide-containing medicinal product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include pulmonary hypertension as an undesirable effect with a frequency 'not common' for all grades and 'rare' for grades 3-4. In addition, a warning on the risk of pulmonary hypertension should be added. For Lenalidomide Accord (lenalidomide), the PRAC recommended the removal of the additional monitoring status and consequently the removal of the black triangle and additional monitoring statements from the product information. Therefore, the current terms of the marketing authorisations should be varied[24].
- In the next PSUR, the MAHs should provide a detailed cumulative review of cases of Epstein-Barr virus (EBV) and EBV associated lymphoproliferative disorders with a proposal to update the product information, as appropriate. In addition, the MAHs should provide cumulative reviews of cases of B-cell acute lymphoblastic leukaemia (B-ALL) and of cases of gynaecomastia with a proposal to update the product information, as appropriate. The MAHs should also provide detailed discussions on medication errors and on off-label use. The MAHs should monitor cases of hepatitis E and discuss them under the identified risk of serious infections, as well as discuss cases with a fatal outcome.
- The MAH Celgene should submit to EMA, within 30 days, a detailed cumulative review of cases of B-cell acute lymphoblastic leukaemia, together with a proposal for updating 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.

6.2.5. Lutetium (^{177}Lu) chloride - ENDOLUCINBETA (CAP); LUMARK (CAP); NAP - PSUSA/00010391/201912

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

PRAC Rapporteur: Ronan Grimes

Scope: Evaluation of a PSUSA procedure

Background

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

Based on the assessment of the PSUR(s), 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 authorisation(s).

Summary of recommendation(s) and conclusions

[24] 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

- Based on the review of the data on safety and efficacy, the benefit-risk balance of lutetium (^{177}Lu) chloride-containing medicinal product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend existing warnings on renal irradiation and on myelosuppression. In addition, pancytopenia, neutropenia and dry mouth should be added as undesirable effects with a frequency 'not known', 'common' and 'not known' respectively. Therefore, the current terms of the marketing authorisations should be varied[25].
- In the next PSUR, the MAHs should discuss any new information on veno-occlusive liver disease and radiation induced hepatotoxicity.

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. Bacillus clausii multi-antibioresistant spores (NAP) - PSUSA/00000284/201911

Applicant(s): various

PRAC Lead: Ilaria Baldelli

Scope: Evaluation of a PSUSA procedure

Background

Bacillus clausii multi-antibioresistant spores are antidiarrheal microorganisms indicated for the treatment and prophylaxis of intestinal dysmicrobism and subsequent endogenous dysvitaminosis and as therapy for aiding the recovery of the intestinal microbial flora, altered during the treatment with antibiotics or chemotherapeutic agents. In addition, they are indicated for treatment of acute and chronic gastrointestinal disorders in breastfeeding infants, attributable to intoxication or intestinal dysmicrobism and dysvitaminosis. They are also indicated for treatment of diarrhoea and vitamin deficiency.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing Bacillus clausii multi-antibioresistant spores 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 Bacillus clausii multi-antibioresistant spores-containing medicinal product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a warning on bacteraemia/sepsis in patients with a compromised immune system or those severely ill,

[25] 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

and in preterm infants. In addition, a cross reference on septicaemia and sepsis (in immunocompromised or severely ill patients should be added to the existing undesirable effect section of the product information. Therefore, the current terms of the marketing authorisation(s) should be varied[26].

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. Flurbiprofen (NAP) - PSUSA/00001450/201911

Applicant(s): various

PRAC Lead: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

Background

Flurbiprofen is a propionic acid derivative indicated for the treatment of rheumatoid disease, osteoarthritis, ankylosing spondylitis, musculoskeletal disorders and trauma. It is also indicated for its analgesic effect in the relief of mild to moderate pain. Formulations used via oromucosal route of administration (mouthwashes, oral sprays and lozenges) are indicated for topical management of painful and/or inflammatory conditions of the oropharynx. Ophthalmic formulations are indicated for the treatment of inflammation of the anterior segment of the eye after cataract surgery and laser trabeculoplasty, as well as for the inhibition of intraoperative miosis, and as an analgesic in relieving ocular pain associated with surgery.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing flurbiprofen 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 flurbiprofen-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 MAH should continue to monitor cases of acute generalised exanthematous pustulosis (AGEP) and cases of acute localised exanthematous pustulosis (ALEP). The MAHs of flurbiprofen-containing medicinal products for systemic use should provide a cumulative review of cases of undesirable effects related to the administration in CYP2C9[27] intermediate or poor metabolisers, with a discussion of the available cases and of the literature. The MAHs of flurbiprofen-containing medicinal products as ophthalmic solutions should provide a cumulative review of cases of corneal complications with a proposal for updating the product information, as appropriate.

[26] Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position
[27] Cytochrome P450 2C9

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[28] (NAP) - PSUSA/00010236/202001

Applicant(s): various

PRAC Lead: Zane Neikena

Scope: Evaluation of a PSUSA procedure

Background

Iron[29] as a parental preparation is an anti-anaemic indicated for the treatment of iron deficiency (ID) if the diagnosis is confirmed by laboratory tests when oral iron preparations are ineffective or cannot be used due to intolerance. Some preparations are indicated for rapid iron supply where oral iron preparations are ineffective.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing iron for parental preparation(s) 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) for parental preparation(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information of ferric carboxymaltose should be updated to include hypophosphataemic osteomalacia as a warning and as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[30].
- In the next PSUR, all MAHs should include foetal bradycardia as an important identified risk in order to further characterise this risk as part of the safety concerns. The MAHs for intravenous iron preparations should provide a discussion on how to reflect the foetal monitoring in the product information, as appropriate. The MAHs for iron sucrose should continue to address overdose as important potential risk with a proposal for updating any risk minimisation measures, as appropriate. The MAH Vifor for ferric carboxymaltose should provide a separate comprehensive causality analysis of fatal cases and of cases of foetal death. The MAH Vifor for ferric carboxymaltose should also provide a detailed cumulative review of cases of hypophosphataemic osteomalacia. The MAH Vifor for iron sucrose and ferric carboxymaltose should provide a cumulative review of cases of medication errors with a proposal for updating the product information, as appropriate.

The PRAC agreed that the current entry in the EURD list 'iron (parenteral preparation(s) except iron dextran)' should be split into separate entries for each iron containing parenteral preparation as: iron sucrose, iron isomaltoside, ferric carboxymaltose and sodium ferric gluconate with the same data lock point (DLP) and retain the same yearly PSUR submission

[28] Parenteral preparation(s) only, except iron dextran
[29] as iron sucrose, ferric carboxymaltose, iron isomaltoside and sodium ferric gluconate
[30] 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 CMDh for adoption of a position

frequency. 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. The EURD list should be updated accordingly.

6.3.4. Iron dextran (NAP) - PSUSA/00010696/202001

Applicant(s): various

PRAC Lead: Zane Neikena

Scope: Evaluation of a PSUSA procedure

Background

Iron dextran is an anti-anaemic parenteral preparation indicated for the treatment of all cases of iron deficiency when oral iron preparations are ineffective or cannot be used, where there is a clinical need for a rapid iron supply. In addition, it is indicated for inflammatory bowel disease.

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.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAHs should include foetal bradycardia as an important identified risk in order to further characterise this risk in the safety concerns for iron dextran-containing medicinal products. The MAHs for intravenous iron dextran preparations should provide a discussion on how to reflect foetal monitoring in 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.

6.3.5. Pancuronium (NAP) - PSUSA/00002275/201912

Applicant(s): various

PRAC Lead: Ronan Grimes

Scope: Evaluation of a PSUSA procedure

Background

Pancuronium is a non-depolarising, long-acting neuromuscular blocking agent indicated as a muscle relaxant during general anaesthesia. It is also indicated for mechanical ventilation, intractable status asthmaticus and tetanus.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing pancuronium 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 pancuronium-containing medicinal product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include warnings on post-operative pulmonary complications and myopathy. In addition, myopathy should be added as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[31].
- In the next PSUR, the MAHs should provide a cumulative review of cases of hearing loss.

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

6.4.1. Levetiracetam - KEPPRA (CAP) - EMEA/H/C/000277/LEG 088.2

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Laurence de Fays

Scope: MAH's response to LEG 088 [cumulative review of cases of cardiac arrhythmia and cases of torsades de pointes/QT prolongation as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00001846/201811) adopted in July 2019] as per the request for supplementary information (RSI) adopted in May 2020

Background

Levetiracetam is a pyrrolidone derivative indicated, as Keppra, 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, it 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.

Following the evaluation of the most recently submitted PSUR(s) for the above mentioned medicine(s), the PRAC requested the MAH for Keppra (levetiracetam) to submit further data on cases of cardiac arrhythmia and cases of torsades de pointes/QT prolongation. For further background, see PRAC minutes July 2019, PRAC minutes February 2020 and PRAC minutes May 2020. The responses were assessed by the Rapporteur for further PRAC advice.

Summary of advice/conclusion(s)

[31] 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 CMDh for adoption of a position

- Based on the available data and the Rapporteur's assessment, the PRAC agreed that the product information should be updated to include a warning on electrocardiogram QT interval prolongation and to add electrocardiogram QT prolonged as an undesirable effect with a frequency 'rare'.
- The MAH should submit to EMA, within 60 days, a variation to update[32] the product information accordingly.

6.4.2. Linaclotide - CONSTELLA (CAP) - EMEA/H/C/002490/LEG 015

Applicant: Allergan Pharmaceuticals International Limited

PRAC Rapporteur: Martin Huber

Scope: Details on study Truven MarketScan[33] and cumulative review of cases of intestinal perforation as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00010025/201908) adopted in March 2020

Background

Linaclotide is a guanylate cyclase-C receptor agonist (GCCA), indicated as Constella, for the symptomatic treatment of moderate to severe irritable bowel syndrome with constipation (IBS-C) in adults.

Following the evaluation of the most recently submitted PSUR(s) for the above mentioned medicine(s), the PRAC requested the MAH to submit further data on cases of intestinal perforation. For background, see PRAC minutes March 2020. The responses were assessed by the Rapporteur for further PRAC advice.

Summary of advice/conclusion(s)

- Based on the available data and the Rapporteur's assessment, the PRAC agreed that the product information should be updated to include a warning on the occurrence of intestinal perforation and to add gastrointestinal perforation as an undesirable effect[34].
- The MAH should submit to EMA, within 60 days, a variation to update[35] the product information accordingly.

6.5. Variation procedure(s) resulting from PSUSA evaluation

None

6.6. Expedited summary safety reviews[36]

6.6.1. Remdesivir – VEKLURY (compassionate use[37]) - EMEA/H/K/5622/CU/PSM 002

Applicant: Gilead Sciences Ireland UC

[32] Update of SmPC sections 4.4 and 4.8. The package leaflet is to be updated accordingly
[33] Truven MarketScan claims database used to assess the potential association between linaclotide and gastrointestinal (GI) perforation
[34] The frequency should be calculated according to the guideline on summary of product characteristics
[35] Update of SmPC sections 4.4 and 4.8. The package leaflet is to be updated accordingly
[36] Requirement to the compassionate use opinion to submit expedited summary safety reports for review accompanied by a summary of remdesivir distribution, In addition to the 6-monthly or annual PSURs falling within the pandemic period
[37] CHMP opinion on the compassionate use in accordance with Article 83(3) of Regulation (EC) No 726/2004 adopted on 02 April 2020

Scope: Second expedited summary safety report for remdesivir covering the period from 06 May 2020 to 04 June 2020 as a condition for the safety monitoring in frame of the compassionate use for remdesivir, indicated in a compassionate use programme for the treatment of adults with coronavirus disease 2019 (COVID-19) who require invasive mechanical ventilation

Background

Remdesivir is an antiviral medicine recommended, as Veklury, for compassionate use programmes in the European Union (EU) for the treatment of coronavirus disease 2019 (COVID-19) in adults and adolescents from 12 years of age and weighing at least 40 kilograms with pneumonia requiring supplemental oxygen.

The PRAC assessed the second expedited summary safety report for the safety monitoring in frame of the compassionate use for Veklury (remdesivir).

Summary of advice/conclusion(s)

- The PRAC agreed that the safety data included in the report are consistent with the known safety profile of remdesivir and that no new signal was detected during the period of the second monthly summary safety report, except for the validated signal of infusion related reactions and hypersensitivity.
- The Company should provide, in the next summary safety report, or in the first PSUR, information regarding the discontinuation of remdesivir due to adverse events as well as a review of cases of renal events. In addition, the Company should monitor and discuss the information on occupational exposure possibly leading to contact reactions.

7. Post-authorisation safety studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)[38]

See Annex I 17.1.

7.2. Protocols of PASS non-imposed in the marketing authorisation(s)[39]

See also Annex I 17.2.

7.2.1. Solriamfetol - SUNOSI (CAP) - EMEA/H/C/004893/MEA 002

Applicant: Jazz Pharmaceuticals Ireland Limited

PRAC Rapporteur: Julia Pallos

Scope: Protocol for study JZP865-401: a PASS to evaluate the long-term safety of solriamfetol in adult patients with obstructive sleep apnoea (OSA) treated with solriamfetol (from initial opinion/marketing authorisation(s) (MA))

Background

Solriamfetol is a dopamine and norepinephrine reuptake inhibitor (DNRI) indicated, as

[38] In accordance with Article 107n of Directive 2001/83/EC
[39] 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

Sunosi a centrally authorised medicine, to improve wakefulness in adult patients with excessive daytime sleepiness (EDS) associated with narcolepsy or obstructive sleep apnoea (OSA).

As part of the RMP for Sunosi (solriamfetol), the MAH was required to conduct study JZP865-401: a PASS to evaluate the long-term safety of solriamfetol in adult patients with obstructive sleep apnoea (OSA) treated with solriamfetol. The MAH submitted a protocol 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

- Based on the review of the PASS protocol version 1.0 and the assessment from the Rapporteur, the PRAC agreed that the MAH should provide clarification regarding the sample size of the study, discuss the feasibility of having individualised patient follow-up and clarify the minimum duration of the follow-up.

7.3. Results of PASS imposed in the marketing authorisation(s)[40]

7.3.1. Iron[41] [42] (NAP) - EMEA/H/N/PSR/J/0026

Applicant: Mesama Consulting (on behalf of a consortium) (Cosmofer, Ferinject, Monofer, Venofer)

PRAC Rapporteur: Tiphaine Vaillant

Scope: Results for a joint study on intravenous iron: evaluation of the risk of severe hypersensitivity reactions, as imposed in the conclusions of the referral under Article 31 of Directive 2001/83/EC (EMEA/H/A-31/1322) for intravenous (IV) iron-containing medicines in 2013

Background

Intravenous (IV) iron-containing medicines are indicated in iron deficiency situations when the oral route is insufficient or poorly tolerated especially in chronic kidney disease (CKD) patients (haemodialysis), but also in pre- or post-operative situations, or in case of intestinal absorption disorders.

In line with the conclusions reached in 2013 of the referral procedure under Article 31 of Directive 2001/83/EC (EMEA/H/A-31/1322) conducted by the PRAC for IV iron-containing medicines, MAHs were required as a condition to the marketing authorisations (Annex IV) to conduct a PASS to assess the risk of anaphylactic or severe immediate hypersensitivity reactions. For further information see PRAC minutes February 2013, PRAC minutes March 2017 and PRAC minutes October 2019.

The MAH (on behalf of the consortium) submitted a final report version 1.1 dated 6 May 2020 for assessment by the Rapporteur. The PRAC discussed the final study results following assessment.

Summary of recommendation(s) and conclusions

[40] In accordance with Article 107p-q of Directive 2001/83/EC
[41] Intravenous (IV)
[42] Iron(III)-hydroxide dextran complex, iron sucrose complex/iron(III)-hydroxide sucrose complex, ferric carboxymaltose complex, iron(III) isomaltoside complex, sodium ferric gluconate complex

- Based on the review of the final report of the non-interventional PASS entitled 'Intravenous iron post-authorisation safety study (PASS): evaluation of the risk of severe hypersensitivity reactions' and the assessment from the Rapporteur, the PRAC considered that a further request for supplementary information (RSI) was necessary before a recommendation could be made on the benefit-risk balance of IV iron-containing medicines concerned by the PASS final report. The MAHs should provide clarifications on the number of treatments (average) by iron IV received by a third of the patients, the use of databases with potential related bias, provide sensitivity and specificity data as well as further explanations on some interpretations of the analysis. A discussion on the differences observed by comparison with the US studies should be also provided.
- The MAH should submit, to EMA, within 60 days, responses to the RSI. A 60 day-assessment timetable will be followed.

7.4. Results of PASS non-imposed in the marketing authorisation(s)[43]

See also Annex I 17.4.

7.4.1. Degarelix - FIRMAGON (CAP) - EMEA/H/C/000986/II/0037

Applicant: Ferring Pharmaceuticals A/S

PRAC Rapporteur: Tiphaine Vaillant

Scope: Update of Annex II-D on 'Conditions or restrictions with regard to the safe and effective use of the medicinal product' in order to revise the additional risk minimisation measures (educational programme) based on previous assessment and results from study FE 200486 CS39: a prospective observational safety study in patients with advanced prostate cancer treated with Firmagon (degarelix) or a gonadotropin-releasing hormone (GnRH) agonist conducted in multiple countries in the European Economic Area (EEA). As a consequence, the RMP (version 16.0) is updated accordingly. The MAH took the opportunity to bring the RMP in line with revision 2 of GVP module V on 'Risk management systems', to bring the product information in line with the latest quality review of documents (QRD) template (version 10.1) and to propose a combination of different strengths in the product information

Background

Degarelix is a gonadotropin releasing hormone (GnRH) antagonist indicated, as Firmagon a centrally authorised medicine, for the treatment of advanced hormone-dependent prostate cancer.

As stated in the RMP of Firmagon (degarelix), the MAH conducted a non-imposed non-interventional study FE 200486 CS39: a prospective observational safety study in patients with advanced prostate cancer treated with Firmagon (degarelix) or a gonadotropin-releasing hormone (GnRH) agonist conducted in multiple countries in the European Economic Area (EEA) to assess the risks of Firmagon (degarelix). The Rapporteur assessed the MAH's final study report together with the MAH's responses to requests for supplementary information (RSI). For further background, see PRAC minutes May 2020.

[43] 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

Summary of advice

- Based on the available data, the MAH's answers to the RSI and the Rapporteur's review, the PRAC considered that there was nothing unexpected in the pattern of adverse events and that no new safety concerns were identified in the study. As an outcome, the PRAC also agreed to remove the educational programme consisting in an information pack for healthcare professionals (HCPs) as the product information sufficiently addresses the content of the educational programme, risks are well known by HCPs and relevant safety concerns are closely monitored in PSURs. As a consequence, Annex II-D of the marketing authorisation should be updated. As a conclusion, the PRAC agreed that the ongoing variation assessing the final study report could be recommended for approval.

7.4.2. Fampridine - FAMPYRA (CAP) - EMEA/H/C/002097/II/0046

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Update of sections 4.2, 4.3, 4.4, 4.8, 4.9 and 5.2 of the SmPC in order to remove the contraindication for patients with mild renal impairment, add a warning for patients with mild renal impairment, update the frequency of seizure to 'uncommon', add vertigo with frequency common, add dizziness in section 4.9 to reflect safety information based on the final results of study 218MS401 (LIBERATE) (listed as category 3 study in the RMP): a phase 4 prospective, non-interventional, multicentre, observational study in multiple sclerosis (MS) patients who began Fampyra (fampridine) treatment in the post-marketing setting. The package leaflet is updated accordingly. The RMP (version 13.1) is also updated accordingly and in line with revision 2.0 of the guidance on the format of RMP in the EU (template)

Background

Fampridine is a potassium channel blocker indicated, as Fampyra a centrally authorised medicine, for the treatment of multiple sclerosis.

As stated in the RMP of Fampyra (fampridine), the MAH conducted a non-imposed non-interventional study 218MS401 (LIBERATE): a phase 4 prospective, non-interventional, multicentre, observational study in multiple sclerosis (MS) patients to assess the risks of Fampyra (fampridine). The Rapporteur assessed the MAH's final study report together with the MAH's responses to the request for supplementary information (RSI). For further background, see PRAC minutes February 2020.

Summary of advice

- Based on the results of study 218MS401, the MAH's answers to the RSI and the Rapporteur's review, the PRAC agreed with the removal of the existing contraindication in mild renal impairment. Nevertheless, the PRAC supported the addition of a warning to ensure Fampyra (fampridine) is used with caution in patients with mild renal impairment. As a conclusion, the PRAC agreed that the ongoing variation assessing the final study report could be recommended for approval.

7.4.3. Pegfilgrastim - NEULASTA (CAP) - EMEA/H/C/000420/II/0113

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Submission of the final report from study 20160176 (listed as a category 3 study in the RMP): a retrospective cohort study with the time from index date to diagnosis of myelodysplastic syndrome (MDS) or acute myeloid leukaemia (AML) as a primary outcome

Background

Pegfilgrastim is a recombinant human granulocyte colony stimulating factor indicated, as Neulasta a centrally authorised medicine, for the reduction in the duration of neutropenia and the incidence of febrile neutropenia in adult patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes).

As stated in the RMP of Neulasta (pegfilgrastim), the MAH conducted a non-imposed non-interventional PASS study 20160176: a retrospective cohort study with the time from index date to diagnosis of myelodysplastic syndrome (MDS) or acute myeloid leukaemia (AML) to assess these risks for Neulasta (pegfilgrastim). The Rapporteur assessed the MAH's final study report.

Summary of advice

- Based on the available data and the Rapporteur's review, the PRAC considered that further information was necessary before the ongoing variation assessing the final study report can be recommended for approval. In particular, the MAH should provide a proposal to update the product information with 'myelodysplastic syndrome/acute myeloid leukaemia' with a frequency 'uncommon' with a description of the undesirable effect.

7.4.4. Rasagiline - AZILECT (CAP) - EMEA/H/C/000574/WS1749/0084; RASAGILINE RATIOPHARM (CAP) - EMEA/H/C/003957/WS1749/0016

Applicant: Teva B.V.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Submission of the final report from study TV1030-CNS-50024 (listed as a category 3 study in the RMP): a non-interventional retrospective cohort study which was conducted using the United States Medicare research database to assess the potential risk of melanoma associated with the use of rasagilline mesylate in patients with Parkinson's disease

Background

Rasagiline is a selective, irreversible monoamine oxidase type B (MAO-B) inhibitor indicated, as Azilect and Rasagiline ratiopharm centrally authorised medicines, for the treatment of Parkinson's disease (PD).

As stated in the RMP of Azilect and Rasagiline ratiopharm (rasagiline), the MAH conducted a non-imposed non-interventional study TV1030-CNS-50024: a non-interventional retrospective cohort study to assess the potential risk of melanoma associated with the use of rasagilline in patients with PD. The Rapporteur assessed the MAH's final study report together with the MAH's responses to the request for supplementary information (RSI). For further background, see PRAC minutes February 2020.

Summary of advice

- Based on the available data, the MAH's answers to the RSI and the Rapporteur's review, the PRAC considered that further information is required before the ongoing variation assessing the final study report can be recommended for approval. In particular, the MAH should provide a consolidated proposal to update the existing warning on melanoma to ensure that healthcare professionals (HCPs) are aware of the currently available data.

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

See Annex I 17.5.

7.6. Others

See also Annex I 17.6.

7.6.1. Evolocumab - REPATHA (CAP) - EMEA/H/C/003766/MEA 009.2

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Kimmo Jaakkola

Scope: MAH's response to MEA 009.1 [feasibility/futility report for study 20150162 (listed as a category 3 study in the RMP) with a protocol previously agreed in March 2016: a multi-national observational study to evaluate the safety of Repatha (evolocumab) in pregnancy [final report expected in Q2 2027]] as per the request for supplementary information (RSI) adopted in December 2019

Background

Evolocumab is a lipid modifying agent indicated, as Repatha a centrally authorised medicine, in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet, in adults and adolescents aged 12 years and over with homozygous familial hypercholesterolaemia in combination with other lipid-lowering therapies and in adults with established atherosclerotic cardiovascular disease (myocardial infarction, stroke or peripheral arterial disease) to reduce cardiovascular risk by lowering low-density lipoprotein-cholesterol (LDL-C) levels, as an adjunct to correction of other risk factors.

As stated in the RMP of Repatha (evolocumab), the MAH should conduct a study, namely study 20150162: a multi-national observational study to evaluate the safety of Repatha (evolocumab) in pregnancy. The Rapporteur assessed a feasibility/futility report from the MAH in together with the MAH's responses to a request for supplementary information (RSI). For further background, see PRAC minutes December 2019.

Summary of advice

- Based on the available data, the MAH's answers to the RSI and the Rapporteur's review, the PRAC considered that the data do not indicate any safety signals with the use of evolocumab during pregnancy, although data are limited. The PRAC agreed that pregnancy registries have little to no possibility of providing useful information regarding the benefit/risk profile of evolocumab exposure in pregnant women. The PRAC considered alternative options to gather data on evolocumab exposure during pregnancy

and concluded that routine pharmacovigilance could provide the desired data with comprehensive follow-up of the reported post-marketing cases. The PRAC agreed to remove the study from the RMP.

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 Annex I 18.3.

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

10.1.1. Dolutegravir - TIVICAY (CAP) - EMEA/H/C/002753/II/0052; dolutegravir, lamivudine - DOVATO (CAP) - EMEA/H/C/004909/II/0001; dolutegravir, lamivudine, abacavir - TRIUMEQ (CAP) - EMEA/H/C/002754/II/0069; dolutegravir, rilpivirine - JULUCA (CAP) - EMEA/H/C/004427/II/0016

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Martin Huber

Scope: PRAC consultation on variations consisting of an update of section 4.6 of the SmPC in order to update the safety information regarding the occurrence of neural tube defects with the dolutegravir (DTG)-containing regimens based on interim analysis from Tsepamo study: a birth outcomes surveillance study being conducted in Botswana designed to evaluate adverse birth outcomes by human immunodeficiency virus (HIV) status and antiretroviral regimen, and to determine if there is an increased risk of neural tube defects among infants exposed to efavirenz at conception. This surveillance system captures all antiretroviral exposure including dolutegavir

Background

Dolutegravir is an inhibitor of human immunodeficiency virus (HIV) integrase indicated as Tivicay, for the treatment of HIV infected adults, adolescents and children above 6 years of age, in combination with other anti-retroviral medicinal products. In combination with lamivudine, via its active metabolite 5'-triphosphates (TP) (an analogue for cytidine) an reverse transcriptase inhibitor of HIV-1 and HIV-2, dolutegravir/lamivudine is indicated as Dovato for the treatment of HIV-1 infection in adults and adolescents above 12 years of age weighing at least 40 kg, with no known or suspected resistance to the integrase inhibitor class, or lamivudine. Dolutegravir in combination with lamivudine and abacavir, a selective inhibitors of HIV-1 and HIV-2 is indicated as, Triumeq, for the treatment of HIV infected adults and adolescents above 12 years of age weighing at least 40 kg. Dolutegravir in combination with rilpivirine a diarylpyrimidine non-nucleoside reverse transcriptase inhibitor (NNRTI) of HIV-1 is indicated, as Juluca, for the treatment of HIV-1 infection in adults who are virologically-suppressed (HIV-1 RNA[44] < 50 copies/mL) on a stable antiretroviral regimen for at least six months with no history of virological failure and no known or suspected resistance to any non-nucleoside reverse transcriptase inhibitor or integrase inhibitor.

Some type II variations proposing to update the product information of Tivicay, Dovato, Triumeq and Juluca on the occurrence of neural tube defects after treatment with the dolutegravir (DTG)-containing regimens are under evaluation at the CHMP. The PRAC was requested to provide advice on this variation.

Summary of advice

[44] Ribonucleic acid

- Based on the review of the available information, the PRAC agreed that the current data from the Tsepamo study[45] confirm that there is no indication for an overall increased risk of major birth defects in children exposed to dolutegravir during pregnancy. The PRAC agreed that the signal of a potentially increased risk of neural tube defects weakened when the number of exposed patients increased.
- The PRAC advised that the product information of dolutegravir-containing products should be updated to reflect that women of childbearing potential should be counselled about the potential risk of neural tube defects with dolutegravir and to include additional information on the small increase in the risk of neural tube defects. If a pregnancy is confirmed in the first trimester while the patient is on dolutegravir treatment, the risks and benefits of continuing dolutegravir versus switching to another antiretroviral regimen should be discussed with the patient, taking into account the gestational age and the critical time period of neural tube defect development among other factors.

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

11.1.1. Amoxicillin (NAP); amoxicillin, clavulanic acid (NAP) - NL/H/xxxx/WS/371

Applicant(s): Astellas Pharma Europe B.V. (Flemoxin (amoxicillin trihydrate), Forcid Solutab (amoxicillin/clavulanic acid))

PRAC Lead: Liana Gross-Martirosyan

Scope: PRAC consultation on the evaluation of a national variation proposing to add acute pancreatitis as an adverse drug reaction (ADR) with a frequency 'not known', on request of the Netherlands

Background

[45] Observational study capturing birth outcomes data at 8 government hospitals throughout Botswana (~45% of all deliveries) starting August 2014

Amoxicillin is a beta-lactam antibiotic indicated alone or in combination with clavulanic acid, another beta-lactam antibiotic, for the treatment of bacterial infections susceptible to amoxicillin in line with official guidance on the appropriate use of antibacterial agents.

In the context of the evaluation of a national worksharing variation procedure proposing to add acute pancreatitis as an adverse drug reaction for several amoxicillin-containing products, the Netherlands requested PRAC advice on its assessment.

Summary of advice

- Based on the review of the available information, the PRAC agreed that the presented evidence was insufficient to support a change in the product information of amoxicillin-containing products at this stage to include acute pancreatitis. Additionally, the PRAC advised that the MAH(s) should submit in the next PSUR[46], a cumulative review of cases of pancreatitis from all relevant sources, including published literature.

11.1.2. Retinoids[47]: acitretin (NAP), alitretinoin (NAP), isotretinoin (NAP) - DE/H/xxxx/WS/627

Applicant(s): Puren Pharma GmbH & Co. KG. (Acicutan (acitretin), Aknenormin (isotretinoin), Isoderm (isotretinoin), IsoGalen (isotretinoin), Isotret-Hexal (isotretinoin), Isotretinoin Basics (isotretinoin), Isotretinoin Puren (isotretinoin), Isotretinoin-ratiopharm (isotretinoin), Neotigason (acitretin), Toctino (alitretinoin))

PRAC Lead: Martin Huber

Scope: PRAC consultation on the evaluation of a national worksharing variation assessing a protocol for a category 3 study: a patient and prescriber survey: effectiveness measures to investigate awareness, knowledge and adherence to the risk minimisation measures (RMMs) of the pregnancy prevention programme (PPP) for oral retinoids (acitretin, alitretinoin, and isotretinoin), on request of Germany

Background

Acitretin, alitretinoin and isotretinoin are retinoids, vitamin A derivatives indicated for the treatment of several conditions including severe acne and severe forms of psoriasis under certain conditions.

As an outcome of the referral procedure under Article 31 of Directive 2001/83/EC for retinoid-containing medicinal products (EMEA/H/A-31/1446) concluded in 2018, two PASS studies were requested, namely a drug utilisation study (DUS, as a category 1 study) and a complementary survey study (as a category 3 study) in order to evaluate and quantify the effectiveness of risk minimisation measures (RMMs) in women of childbearing potential.

In the context of the evaluation of a national worksharing variation procedure on the protocol for a 'Patient and prescriber survey on the effectiveness measures to investigate awareness, knowledge and adherence to the RMMs of the pregnancy prevention programme (PPP) for oral retinoids (acitretin-, alitretinoin- and isotretinoin-containing products)', Germany requested PRAC advice on its assessment.

Summary of advice

[46] Data lock point (DLP) for amoxicillin: 07/03/2022; DLP for amoxicillin/clavulanic acid: 07/03/2022
[47] Oral presentations

- Based on the review of the available information and the assessment from Germany, the PRAC considered that the protocol could be approvable if the consortium of MAHs amends the protocol to reflect an increase in the threshold level in the knowledge outcome measures from 60% to 80%.

11.2. Other requests

11.2.1. Chlormadinone acetate, ethinylestradiol (NAP)

Applicant: Gedeon Richter Plc (on behalf of a consortium)

PRAC Lead: Martin Huber

Scope: PRAC consultation on the evaluation of interim results for non-interventional imposed study RIVET-CC: a case control study comparing levonorgestrel and chlormadinone acetate in order to evaluate the role of oral contraceptives and the RIsk of VEnous Thromboembolism (VTE), as imposed in the conclusions of referral procedure under Article 31 of Directive 2001/83/EC (EMEA/H/A-31/1356) for combined hormonal contraceptives finalised in 2013, on request of Germany

Background

Chlormadinone acetate is a steroidal synthetic progestin and ethinylestradiol is an oestrogen, indicated in combination as a combined oral contraceptive.

As an outcome of the referral procedure under Article 31 of Directive 2001/83/EC for combined hormonal contraceptive (CHC)-medicinal products (EMEA/H/A-31/1356) concluded in 2013, MAHs of chlormadinone containing CHCs were required to conduct a PASS to compare the risk of venous thromboembolism (VTE) with chlormadinone/ethinyestradiol versus levonorgestrel/ethinyestradiol. In January 2016, the PRAC endorsed the initial protocol. For further background, see PRAC minutes January 2016.

In the context of the evaluation of the interim results for non-interventional imposed study RIVET-CC comparing levonorgestrel and chlormadinone acetate in order to evaluate the risk of VTE, Germany requested PRAC advice on its assessment.

Summary of advice

- Based on the review of the available information, the PRAC supported the assessment conducted by Germany and noted the low recruitment numbers for both cases and controls despite various efforts made to enhance recruitment. The PRAC agreed that it was unlikely that meaningful results on the VTE risk associated with chlormadinone acetate/ethinylestradiol could be generated in a timely manner, and that a meta-analysis of data from previously conducted studies is an acceptable approach to assess the VTE risk adequately, subject to a full assessment of the protocol to be submitted to PRAC for review as a substantial study protocol amendment.

11.2.2. Lenalidomide (pre-authorisation) - IS/H/0376-0388, 0413-0416/001-007/DC

Scope: PRAC consultation on the evaluation of an initial marketing authorisation application under the decentralised procedure for a generic lenalidomide-containing medicinal product in order to consider the need for additional pharmacovigilance activities and risk minimisation measures, on request of Iceland

Background

Lenalidomide is an anti-neoplastic, anti-angiogenic, pro-erythropoietic, and immunomodulatory agent use in the treatment of multiple myeloma, myelodysplastic syndromes, mantle cell lymphoma and follicular lymphoma, under certain conditions.

In the context of the evaluation of an initial marketing authorisation application under the decentralised procedure for a generic lenalidomide-containing medicinal product, Iceland requested PRAC advice on its assessment.

Summary of advice

- Based on the review of the available information, the PRAC supported the assessment from Iceland regarding the applicability of the imposed and non-imposed studies for the generic medicinal product. The PRAC noted that the approved protocols for the studies conducted by the originator medicinal product are designed to address scientific questions and that the results of those studies will be applicable to generic lenalidomide-containing products. Therefore, the PRAC agreed that neither the imposed nor non-imposed studies should be requested from the applicant for the generic medicinal product.

12. Organisational, regulatory and methodological matters

12.1. Mandate and organisation of the PRAC

12.1.1. PRAC working group - Best practice guide on using PRAC plenary time efficiently and effectively – update on the implementation of quantitative goals - Q2 2020

PRAC lead: Ulla Wändel Liminga, Martin Huber, Menno van der Elst, Jan Neuhauser

In line with the adopted PRAC best practice guidance (BPG) on Committee efficiency (see PRAC minutes May 2016 and PRAC minutes June 2018) and the adopted implementation plan for the BPG including goals to measure compliance with the recommendations (see PRAC minutes June 2016 and PRAC minutes June 2018), the EMA secretariat informed the PRAC about the quantitative measures collected for the Q2 2020 of PRAC meetings. For previous update, see PRAC minutes May 2020.

12.2. Coordination with EMA Scientific Committees or CMDh-v

None

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

None

12.4. Cooperation within the EU regulatory network

12.4.1. Coronavirus (COVID-19) pandemic - update

The EMA secretariat updated the PRAC on the activities of the COVID-19 EMA pandemic Task Force (ETF), including an overview of ongoing clinical trials and epidemiological studies

and initiatives, as well as a summary of medicines in development and medicines authorised for other indications, as potential treatments for COVID-19, and their safety surveillance.

The EMA secretariat also updated the PRAC on the progress of the EMA-funded study on COVID-19 disease and medicines in pregnancy.

12.4.2. Pharmaceutical strategy for Europe

The European Commission (EC) representative provided an overview of the EC's proposal for the Pharmaceutical strategy for Europe. It was highlighted that the strategy will address challenges in the current pharmaceutical system including shortages, unequal access and affordability of medicines. It will also support competitiveness, innovation and sustainability of the EU's pharmaceutical industry. PRAC members were informed that the strategy is open for public consultation until 15 September 2020.

Post-meeting note: On 25 November 2020, the European Commission adopted the 'Pharmaceutical strategy for Europe' (SWD(2020) 286 final).

12.5. Cooperation with International Regulators

None

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

None

12.7. PRAC work plan

None

12.8. Planning and reporting

12.8.1. Marketing authorisation applications (MAA) forecast for 2020 – planning update dated Q2 2020

The EMA Secretariat presented to PRAC for information a quarterly updated report on marketing authorisation applications planned for submission (the business 'pipeline').

12.8.2. PRAC workload statistics – Q2 2020

The EMA secretariat informed the PRAC of the quarterly and cumulative figures to estimate the evolution of the workload of the PRAC for Q2 2020, by reflecting on the number of procedures and agenda items covered at each PRAC plenary meeting. For previous update, see PRAC minutes May 2020.

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

None

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 2020, 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 2020, the updated EURD list was adopted by the CHMP and CMDh at their July 2020 meetings and published on the EMA website on 29/07/2020, 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)

12.10.5. Periodic safety update reports single assessment (PSUSA) – Joint PRAC/CMDh action group on 'other consideration' section - update to the assessment report template

PRAC lead: Martin Huber, Menno van der Elst, Jana Lukacisinova, Michal Radik

The EMA secretariat updated the PRAC on the update of the assessment report (AR) template for the assessment of PSUSA procedures, to provide further instructions to assessors with pre-defined options, for section 6 on 'Other considerations', to highlight issues to MAHs which require follow-up outside PSUSA procedures. The PRAC adopted the amended template.

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 signal management review technical (SMART) working group updated the PRAC on the activities in preparation for the monitoring of the safety of vaccines for the prevention of coronavirus (COVID-19), building on lessons learnt from the monitoring of pandemic A/H1N1 influenza vaccines in 2009-2010.

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 – status of lenalidomide-containing product(s)

PRAC lead: Eva Segovia, Maria del Pilar Rayon

The PRAC was consulted on the additional monitoring (AM) status of lenalidomide-containing products, considering the inclusion of Revlimid (lenalidomide - originator, centrally authorised product) and Lenalidomide Accord (lenalidomide - generic, centrally authorised product) in the AM list and the existence of other nationally authorised lenalidomide-containing products which are not included in the AM list.

Further to the discussion in March 2020 (for further background, see PRAC minutes March 2020),the PRAC agreed that Lenalidomide Accord (lenalidomide), which is currently under AM due to restrictions with regards to the safe and effective use of the medicinal product (optional scope), should be removed from the AM list (black triangle and accompanying statement should be removed from the product information). This change was agreed to be implemented via the PSUSA procedure due for recommendation this month (see under 6.2.4.). Additionally, the PRAC agreed that generics of nationally authorised lenalidomide-containing products do not require additional monitoring status using optional scope, and that the AM status and the black triangle should be removed via the next regulatory opportunity or via a variation procedure.

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

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

Post-meeting note: The updated additional monitoring list was published on the EMA website on 29/07/2020, see: Home>Human Regulatory>Post-authorisation>Pharmacovigilance>Medicines under additional monitoring>List of medicines under additional monitoring

12.13. EudraVigilance database

12.13.1. Activities related to the confirmation of full functionality

None

12.14. Risk management plans and effectiveness of risk minimisations

12.14.1. Risk management systems

None

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

None

12.14.3. Good pharmacovigilance practice (GVP) module XVI on 'Risk minimisation measures: selection of tools and effectiveness indicators' – revision 3

PRAC lead: Sabine Straus

In line with the PRAC work plan 2020, the EMA Secretariat on behalf of the drafting group together with the PRAC Impact group presented to PRAC for discussion the proposed major changes to the current GVP module XVI on 'Risk minimisation measures: selection of tools and effectiveness indicators'. Based on the comments received, further discussion will be planned in October 2020. In the meantime, PRAC members were invited to provide written comments by 31 August 2020 on the draft GVP XVI guidance on Risk minimisation measures: selection of tools and effectiveness indicators and the addendum II on methods for effectiveness evaluation.

12.14.4. Initial marketing authorisation applications (MAA) – review of PRAC rapporteur assessment report templates for RMP (D-94) - revision

The EMA secretariat provided the PRAC with an update on the revision of the template for the RMP assessment report (AR) in initial marketing authorisation applications (MAA), based on feedback from PRAC on other Rapporteurs' AR templates. PRAC members were invited to provide written comments by 31 August 2020 on the proposed revision. Further discussion will be scheduled in 2021.

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. Drug-induced hepatotoxicity - PRAC assessors' guide - final

PRAC lead: Menno van der Elst, Martin Huber

In line with the PRAC work plan 2020, and agreed as an outcome of the last discussion (for further background, see PRAC minutes June 2020), the EMA secretariat presented to PRAC the updated version of the assessors' guide reflecting the comments from the PRAC, following discussion in May 2020 and June 2020 PRAC. The PRAC adopted the updated guide.

12.20.2. Rapid data analytical process - Interim results

Following the presentation of the pilot initiative on rapid data analytics in 2019 (for background, see PRAC minutes July 2019), the pilot was initiated in November 2019 to support PRAC discussions. The PRAC was updated on the progress of the pilot, the process for assessing feasibility of studies and the process for data analysis.

13. Any other business

None

14. Annex I – Signals assessment and prioritisation[48]

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[49].

14.1.1. Anakinra - KINERET (CAP); canakinumab – ILARIS (CAP)

Applicant(s): Novartis Europharm Limited (Ilaris), Swedish Orphan Biovitrum (Kineret)

PRAC Rapporteur: Hans-Christian Siersted

Scope: Signal of drug reaction with eosinophilia and systemic symptoms (DRESS)

EPITT 19566 – New signal

Lead Member State(s): DE, DK

14.1.2. Dabrafenib - TAFINLAR (CAP); trametinib - MEKINIST (CAP)

Applicant(s): Novartis Europharm Limited

PRAC Rapporteur: David Olsen

Scope: Signal of sarcoidosis

EPITT 19574 – New signal

Lead Member State(s): NO, SE

14.1.3. Ibrutinib – IMBRUVICA (CAP)

Applicant(s): Janssen-Cilag International

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Signal of hepatitis E

EPITT 19569 – New signal

Lead Member State(s): HR

14.1.4. Palbociclib - IBRANCE (CAP)

Applicant(s): Pfizer Europe MA EEIG

PRAC Rapporteur: Hans Christian Siersted

Scope: Signal of cutaneous lupus erythematosus

[48] 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

[49] 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

EPITT 19571 – New signal

Lead Member State(s): DK

14.2. New signals detected from other sources

None

15. Annex I – Risk management plans

15.1. Medicines in the pre-authorisation phase

None

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. Alemtuzumab - LEMTRADA (CAP) - EMEA/H/C/003718/II/0031

Applicant: Sanofi Belgium

PRAC Rapporteur: Anette Kirstine Stark

Scope: Submission of an updated RMP (version 7.0) in order to reflect all amendments and additional activities as per the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 completed in November 2019 (EMEA/H/A-20/1483)

15.2.2. Herpes zoster vaccine (recombinant, adjuvanted) - SHINGRIX (CAP) - EMEA/H/C/004336/II/0031

Applicant: GlaxoSmithkline Biologicals SA

PRAC Rapporteur: Sonja Hrabcik

Scope: Submission of an updated RMP (version 3.0) to reflect a potential increased risk of exacerbation of pre-existing potentially immune-mediated diseases (pIMDs) following vaccination with Shingrix (herpes zoster vaccine (recombinant, adjuvanted)). The implementation of the change is further substantiated by new additional data on post-hoc analyses and spontaneous reports of potential exacerbations of pIMDS from a worldwide safety database

15.2.3. Tacrolimus - ADVAGRAF (CAP) - EMEA/H/C/000712/WS1805/0057; MODIGRAF (CAP) - EMEA/H/C/000954/WS1805/0035

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Ronan Grimes

Scope: Submission of an updated RMP (version 3) in order to add a non-interventional study related to the safety concerns of use during pregnancy and use during lactation. The MAH took the opportunity combine the two important potential risks of 'exchangeability

between the granule and capsule formulations of tacrolimus' for Modigraf (tacrolimus) and 'if administered accidentally either arterially or perivascularly, the reconstituted solution may cause irritation at the injection site' for Prograf (tacrolimus) concentrate for solution for infusion into the important identified risk of 'medication errors'. Finally, the RMP is updated in line with revision 2 of the guidance on the format of RMP in the EU (template)

15.2.4. Umeclidinium, vilanterol - ANORO ELLIPTA (CAP) - EMEA/H/C/002751/WS1850/0030; LAVENTAIR ELLIPTA (CAP) - EMEA/H/C/003754/WS1850/0033

Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Ilaria Baldelli

Scope: Submission of an updated RMP (version 8.2) following completion of study WWE117397 (listed as a category 3 in the RMP): a post-authorisation safety electronic medical records database retrospective cohort study of new users of inhaled umeclidinium/vilanterol (UMEC/VI) or new users of inhaled umeclidinium (UMEC) in the primary care setting. In addition, updates are reflected in the RMP with regard to study 201038 (listed as a category 1 in the RMP/Annex II): a post authorisation safety observational cohort study to quantify the incidence of selected cardiovascular and cerebrovascular events in chronic obstructive pulmonary disease (COPD) patients using inhaled UMEC/VI combination or inhaled UMEC versus tiotropium, as requested in the conclusions of procedure PSA/S/0032.3 adopted in November 2019. These include updates of the primary and secondary objectives to include the composite endpoint and the sample size for the study

15.2.5. Umeclidinium - INCRUSE ELLIPTA (CAP) - EMEA/H/C/002809/WS1589/0029; ROLUFTA ELLIPTA (CAP) - EMEA/H/C/004654/WS1589/0014

Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Ilaria Baldelli

Scope: Submission of an updated RMP (version 7.1) following completion of study WWE117397 (listed as a category 3 in the RMP): a post-authorisation safety electronic medical records database retrospective cohort study of new users of inhaled umeclidinium/vilanterol (UMEC/VI) or new users of inhaled umeclidinium (UMEC) in the primary care setting. In addition, updates are reflected in the RMP with regard to study 201038 (listed as a category 1 in the RMP/Annex II): a post authorisation safety observational cohort study to quantify the incidence of selected cardiovascular and cerebrovascular events in chronic obstructive pulmonary disease (COPD) patients using inhaled UMEC/VI combination or inhaled UMEC versus tiotropium, as requested in the conclusions of procedure PSA/S/0032.3 adopted in November 2019. These include updates of the primary and secondary objectives to include the composite endpoint and the sample size for the study. Finally, the RMP is brought in line with revision 2 of GVP module V on 'Risk management systems'

15.2.6. Vedolizumab - ENTYVIO (CAP) - EMEA/H/C/002782/II/0050

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Adam Przybylkowski

Scope: Submission of an updated RMP (version 6.0) with regards to the measures to evaluate the effectiveness of the patient alert card as an additional risk minimisation measure (aRMM). The MAH took the opportunity to add the completion date of the interim report for study MLN0002_401: an international observational prospective cohort study comparing vedolizumab to other biologic agents in patients with ulcerative colitis or Crohn's disease

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

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

15.3.1. Adalimumab - HULIO (CAP) - EMEA/H/C/004429/X/0016

Applicant: Mylan S.A.S

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension application to add a new strength of 20 mg solution for injection. The RMP (version 3.1) is updated in accordance

15.3.2. Adalimumab - HUMIRA (CAP) - EMEA/H/C/000481/II/0198

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension of indication to include treatment of moderately to severely active ulcerative colitis in paediatric patients. As a consequence, sections 4.1, 4.2, 5.1 and 5.2 of the SmPC for the 40mg/0.8mL, 40mg/0.4mL and 80mg/0.8mL presentations are updated. Furthermore, sections 5.1 and 5.2 of the SmPC for the 20mg/0.2mL presentation are updated. The package leaflet and the RMP (version 15.0) are updated in accordance

15.3.3. Albutrepenonacog alfa - IDELVION (CAP) - EMEA/H/C/003955/II/0042, Orphan

Applicant: CSL Behring GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Update of section 4.2 of the SmPC to update the posology by expanding the once weekly routine prophylaxis regimen from 35-to 50 IU/kg to 25- to 50 IU/kg. The RMP (version 3.3) is updated accordingly

15.3.4. Atezolizumab - TECENTRIQ (CAP) - EMEA/H/C/004143/II/0036

Applicant: Roche Registration GmbH

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Submission of the final report from study GO28915 (OAK) (listed as a category 3 study in the RMP): a phase 3, open-label multicentre, randomised study to investigate the efficacy and safety of atezolizumab compared with docetaxel in patients with non-small cell lung cancer (NSCLC) after failure with platinum-containing chemotherapy. In addition, the

MAH submitted integrated analyses of the potential relationship of ADA and safety we based on studies IMvigor210, IMvigor211, OAK, POPLAR, IMpower150, IMpower130, IMpower131, IMpower132, IMpower133 and IMpassion130 as recommended by the CHMP

15.3.5. Avelumab - BAVENCIO (CAP) - EMEA/H/C/004338/II/0015

Applicant: Merck Europe B.V.

PRAC Rapporteur: Hans Christian Siersted

Scope: Update of sections 4.2, 4.4 and 4.8 of the SmPC in order to change posology recommendations, to amend an existing warning and to add myasthenia gravis and myasthenic syndrome as new adverse drug reactions (ADRs) with a frequency uncommon. The update results from an update of the company core data sheet (CCDS) based on the review of cases of myasthenia gravis/myasthenic syndrome. The package leaflet is updated accordingly. The RMP (version 2.2) is updated with a proposal to reclassify 'other immune-related events (myasthenic syndrome)' from an important potential risk to an important identified risk of 'other immune-related events (myasthenia gravis/myasthenic syndrome)'

15.3.6. Beclometasone dipropionate, formoterol fumarate dihydrate, glycopyrronium - TRIMBOW (CAP) - EMEA/H/C/004257/X/0012

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Jan Neuhauser

Scope: Extension application to add a new pharmaceutical form (inhalation powder) associated with a new strength (88µg/5µg/9µg). The RMP (version 6.2) is updated in accordance

15.3.7. Bortezomib - BORTEZOMIB FRESENIUS KABI (CAP) - EMEA/H/C/005074/II/0001/G

Applicant: Fresenius Kabi Deutschland GmbH

PRAC Rapporteur: Amelia Cupelli

Scope: Grouped variations consisting of: 1) addition of a new pack size (EU number-EU/1/19/1397/002) for the sterile parenteral biological medicinal product Bortezomib Fresenius Kabi (bortezomib) powder for solution for injection with a fill volume for a single dose vial of 1 mg per vial in addition to the authorised 3.5 mg per vial; 2) addition of a new pack size within a range (EU number-EU/1/19/1397/003) for the sterile parenteral biological medicinal product Bortezomib Fresenius Kabi (bortezomib) powder for solution for injection with a fill volume for a single dose vial of 2.5 mg per vial in addition to the authorised 3.5 mg per vial. The RMP (version 2.0) is updated accordingly

15.3.8. Cannabidiol - EPIDYOLEX (CAP) - EMEA/H/C/004675/II/0005, Orphan

Applicant: GW Pharma (International) B.V.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Extension of indication for use as adjunctive therapy of seizures associated with tuberous sclerosis complex (TSC) for patients 1 year of age and older. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The package

leaflet and the RMP (version 1.1) are updated accordingly. The MAH took the opportunity to correct typographic errors in the product information, to introduce editorial updates and to implement the updated ethanol statement in compliance with the European Commission (EC) guideline on 'excipients in the labelling and package leaflet of medicinal products for human use'

15.3.9. Catridecacog - NOVOTHIRTEEN (CAP) - EMEA/H/C/002284/II/0026/G

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Tiphaine Vaillant

Scope: Grouped variations consisting of an extension of indication to include treatment of bleeding episodes in patients with congenital factor XIII A-subunit deficiency as well as minor surgery based on the results of: 1) study NN1841-3868: use of recombinant factor XIII (rFXIII) in treatment of congenital FXIII deficiency, a prospective multi-centre observational study; 2) registry PRO-RBDD: a prospective rare bleeding disorders database registry. As a consequence, sections 4.1, 4.2, 4.4, 4.6, 5.1 and 5.2 of the SmPC are updated. The package leaflet, Annex II-D on 'Conditions or restrictions with regard to the safe and effective use of the medicinal product' and the RMP (version 15) are updated accordingly. Furthermore, the product information is brought in line with the latest quality review of documents (QRD) template (version 10.1). Finally, the MAH took the opportunity to introduce minor editorial changes to the product information

15.3.10. 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

15.3.11. Darunavir - PREZISTA (CAP) - EMEA/H/C/000707/II/0107

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Extension of indication for Prezista (darunavir) 800 mg in combination with cobicistat (COBI) 150 mg for the treatment of human imunodeficiency virus type 1 (HIV-1) infection in adolescents aged 12 years and older with a body weight of at least 40 kg. 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 27.1) are updated accordingly

15.3.12. Desloratadine - DESLORATADINE RATIOPHARM (CAP) - EMEA/H/C/002404/II/0023/G

Applicant: Ratiopharm GmbH

PRAC Rapporteur: Laurence de Fays

Scope: Grouped variations consisting of: 1) change in the legal status of Desloratadine ratiopharm from 'medicinal product subject to medical prescription' to 'medicinal product not subject to medical prescription' in view of the safety profile of Desloratadine ratiopharm and the post-marketing experience already available with other medicinal products containing similar long acting histamine antagonists. The RMP (version 1.0) is updated accordingly. In addition, the MAH also took the opportunity to bring the product information (PI) in line with the latest quality review of documents (QRD) template (version 10.1), to update the list of local representatives in the package leaflet and to introduce editorial changes.; 2) deletion of the therapeutic indication in adolescents aged 12 years and older for the relief of symptoms associated with allergic rhinitis and urticaria. As a consequence, section 4.1 of the SmPC is updated. The package leaflet is updated accordingly

15.3.13. Dulaglutide - TRULICITY (CAP) - EMEA/H/C/002825/X/0045

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Ilaria Baldelli

Scope: Extension application to introduce two new strengths of 3 mg and 4.5 mg solution for injection. The RMP (version 4.1) is updated accordingly

15.3.14. Dupilumab - DUPIXENT (CAP) - EMEA/H/C/004390/II/0027

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Kimmo Jaakkola

Scope: Extension of indication to include atopic dermatitis patients from 6 years to 11 years. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 5.0) are updated accordingly

15.3.15. Herpes zoster vaccine (recombinant, adjuvanted) - SHINGRIX (CAP) - EMEA/H/C/004336/II/0022

Applicant: GlaxoSmithkline Biologicals SA

PRAC Rapporteur: Sonja Hrabcik

Scope: Extension of indication to include adults of 18 years of age or older at increased risk of herpes zoster, supported by clinical studies: 1) study ZOSTER-002: a phase 3, randomised, observer-blind, placebo-controlled, multicentre, clinical trial to assess the prophylactic efficacy, safety, and immunogenicity of Shingrix (herpes zoster vaccine) when administered intramuscularly on a two-dose schedule to adult autologous haematopoietic stem cell transplant (HCT) recipients (MEA 001); 2) study ZOSTER-039: a phase 3, randomised, observer-blind, placebo-controlled, multicentre study to assess the safety and immunogenicity of Shingrix (herpes zoster vaccine) when administered intramuscularly on a two-dose schedule to adults aged 18 years and older with haematologic malignancies (MEA 002); 3) study ZOSTER-041: a phase 3, randomised, observer-blind, placebo-controlled, multicentre clinical study to assess the immunogenicity and safety of Shingrix (herpes zoster vaccine) when administered intramuscularly on a 0- and 1- to 2-months schedule to adults ⩾ 18 years of age with renal transplant (MEA 003); 4) study ZOSTER-028: a phase 2/3, randomised, observer-blind, placebo-controlled, multicentre, clinical trial to assess the immunogenicity and safety of Shingrix (herpes zoster vaccine) when administered intramuscularly on a 0 and 1 to 2 months schedule to adults of 18 years of age with solid tumours receiving chemotherapy (MEA 004); 5) study ZOSTER-001: a phase 1/2a, randomised, observer-blind, placebo-controlled, multicentre study to evaluate the safety and immunogenicity of Shingrix (herpes zoster vaccine) and to saline (placebo) when administered as 2 doses or 3 doses to autologous HCT recipients ; 6) study ZOSTER-015: a phase 1/2a, randomised, observer-blind, placebo-controlled, multicentre study to evaluate the safety and immunogenicity of Shingrix (herpes zoster vaccine) in comparison to placebo when administered as 3 doses to adult human immunodeficiency virus (HIV)-infected subjects.. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated in order to add the indication, delete a warning and add new safety and efficacy information. The package leaflet and the RMP (version 2.1) are updated in accordance

15.3.16. Human normal immunoglobulin - HYQVIA (CAP) - EMEA/H/C/002491/II/0056

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to replace the therapeutic indications of replacement therapy in hypogammaglobulinaemia and recurrent bacterial infections in patients with chronic lymphocytic leukaemia and multiple myeloma and hypogammaglobulinaemia in patients with hematopoietic stem cell transplantation (HSCT), by the therapeutic indication of replacement therapy in secondary immunodeficiencies (SID) in patients who suffer from severe or recurrent infections, ineffective antimicrobial treatment and either proven specific antibody failure (PSAF) or serum immunoglobulin G (IgG) level of <4 g/L. As a consequence, sections 4.1 and 4.2 of the SmPC are updated. The package leaflet and the RMP (version 10.0) are updated in accordance

15.3.17. Human normal immunoglobulin - PRIVIGEN (CAP) - EMEA/H/C/000831/II/0161/G

Applicant: CSL Behring GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Grouped variations consisting of: 1) update of sections 4.4, 4.8 and 5.1 of the SmPC

in order to amend an existing warning on haemolytic anaemia and to update safety information based on final results from study IgPro10_5003 (listed as a category 3 study in the RMP): an observational hospital-based cohort study in the US to evaluate Privigen (human normal immunoglobulin) use and haemolytic anaemia in adults and children and the Privigen (human normal immunoglobulin) safety profile in children with chronic inflammatory demyelinating polyneuropathy (CIDP). The package leaflet is updated accordingly; 2) update of sections 4.8 and 5.1 of the SmPC in order to update the list of adverse drug reactions based on final results from study IgPro10_3004: a prospective open-label single-arm study of the pharmacokinetics and safety of intravenous IgPro10 in Japanese subjects with primary immunodeficiency. The RMP (version 8.0) is updated accordingly. In addition, the MAH took the opportunity to align the SmPC with the EU core SmPC for human normal immunoglobulin for intravenous administration (IVIg) (EMA/CHMP/BPWP/94038/2007 Rev. 5), to update the local representative for Bulgaria in the package leaflet and to bring the product information in line with the latest quality review of documents (QRD) template (version 10.1)

15.3.18. Ibrutinib - IMBRUVICA (CAP) - EMEA/H/C/003791/II/0059, Orphan

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Extension of indication to add the combination with rituximab or obinutuzumab for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL), based on results from study E1912 (PCYC-1126e-CA): a randomized phase 3 study of ibrutinib-based therapy vs standard fludarabine, cyclophosphamide, and rituximab (FCR) chemo-immunotherapy in untreated younger patients with CLL. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated to include information related to the new indication. The package leaflet and the RMP (version 16.1) are updated accordingly. The MAH took the opportunity to introduce minor editorial changes in Annex II and the labelling (Annex III-A)

15.3.19. Imipenem, cilastatin, relebactam - RECARBRIO (CAP) - EMEA/H/C/004808/II/0001

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Extension of indication to include the treatment of hospital-acquired pneumonia (HAP) including ventilator-associated pneumonia (VAP), with or without concurrent bacteraemia in adults. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated. The Package Leaflet and the RMP (version 1.1) are updated in accordance. Furthermore, the MAH introduced editorial corrections in the product information and brought it in line with the latest quality review of documents (QRD) template (version 10.1)

15.3.20. Insulin glargine - ABASAGLAR (CAP) - EMEA/H/C/002835/WS1587/0028/G; insulin lispro - HUMALOG (CAP) - EMEA/H/C/000088/WS1587/0178/G

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Annika Folin

Scope: Grouped variations consisting of: 1) introduction of an additional prefilled pen presentation for Abasaglar (insulin glargine), solution for injection, Humalog (insulin lispro) solution for injection, Humalog (insulin lispro) Kwikpen solution for injection and Humalog (insulin lispro) Junior Kwikpen solution for injection. Each pack contains 5 pre-filled pens; 2) extension to two x5 multipacks. As a consequence, sections 1, 4.2, 4.4, 6.2, 6.4, 6.5, 6.6 and 8 of the SmPC are updated. The package leaflet and labelling are updated accordingly. In addition, the MAH took the opportunity to introduce an editorial change in the Slovakian address of the package leaflet

15.3.21. Ivacaftor - KALYDECO (CAP) - EMEA/H/C/002494/II/0085, Orphan

Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Extension of indication to include the combination regimen of the ivacaftor 150 mg tablets with elexacaftor/tezacaftor/ivacaftor fixed dose combination (FDC) tablets for the treatment of adults and adolescents aged 12 years and older with cystic fibrosis who have at least one phenylalanine in position 508 deletion (F508del) mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 8.8) are updated in accordance

15.3.22. Ivacaftor - KALYDECO (CAP) - EMEA/H/C/002494/II/0086, Orphan

Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Extension of indication to extend the indication of Kalydeco (ivacaftor) granules in the treatment of infants aged at least 4 months, toddlers and children weighing 5 kg to less than 25 kg with cystic fibrosis who have one of the following gating (class III) mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 8.9) are updated in accordance

15.3.23. Lacosamide - LACOSAMIDE UCB (CAP) - EMEA/H/C/005243/WS1782/0006; VIMPAT (CAP) - EMEA/H/C/000863/WS1782/0088

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension of indication to include the treatment as adjunctive therapy of primary generalised tonic-clonic seizures in adults, adolescents and children from 4 years of age with idiopathic generalised epilepsy. 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 15.1) are updated in accordance. Furthermore, the MAH took the opportunity to bring the product information in line with the latest quality review of documents (QRD) template (version 10.1), to align the product information of Lacosamide UCB (lacosamide) with the product information of Vimpat (lacosamide) and to implement some minor corrections in the Bulgarian, Czech, Danish, French, German, Hungarian, Polish and Spanish versions of the product information

15.3.24. Levetiracetam - KEPPRA (CAP) - EMEA/H/C/000277/WS1664/0187

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Laurence de Fays

Scope: Update of section 4.2 of the SmPC to recommend the same dosing for monotherapy and adjunctive therapy based on data from modelling and simulation project. The package leaflet and the RMP (version 9.1) are updated accordingly. The MAH took the opportunity to move Braille to another box section and to review and adapt the German product information in line with the latest quality review of documents (QRD) template (version 10.1)

15.3.25. Lumacaftor, ivacaftor - ORKAMBI (CAP) - EMEA/H/C/003954/II/0055

Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Update of section 4.8 of the SmPC following results from study VX16-809-116 (study 106, safety study in children): a phase 3, open-label, rollover extension study evaluating the long-term safety of lumacaftor/ivacaftor in patients with cystic fibrosis aged 2 and older, homozygous for the deletion of phenylalanine in position 508 of the cystic fibrosis transmembrane conductance regulator (F508del-CFTR) mutation, who initiated treatment in parent study 115. The package leaflet and the RMP (version 7.1) are updated accordingly. The MAH took the opportunity to bring the product information in line with the latest quality review of documents (QRD) template (version 10.1)

15.3.26. Meningococcal group B vaccine (recombinant, adsorbed) - TRUMENBA (CAP) - EMEA/H/C/004051/II/0027/G

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Jean-Michel Dogné

Scope: Grouped variations consisting of: 1) a revised protocol outline for study B1971060: a phase 4, open-label, single-arm trial, to describe the safety, tolerability and immunogenicity of Trumenba (meningococcal group B vaccine/bivalent rLP2086 vaccine) when administered in immunocompromised subjects ≥ 10 years of age in order to change from a 3 dose-regimen of Trumenba (meningococcal group B vaccine) administered on a 0-, 2-, and 6-month schedule to a 2-dose regimen administered on 0- and 6-month schedule; 2) a proposal to replace study B1971062 aimed at investigating the co-administration of Trumenba (meningococcal group B vaccine) with measles, mumps, and rubella (MMR) and pneumococcal vaccines, with study C3511006 (MenABCWY): a phase 2b, randomised, controlled, open-label trial to describe the safety, tolerability, and immunogenicity of bivalent rLP2086-containing MenABCWY when administered concomitantly with MMR and 13-valent pneumococcal vaccine (13vPnC) in healthy participants ≥12 to < 16 months of age. A protocol outline is included. The RMP (version 4.0) is updated accordingly

15.3.27. Metreleptin - MYALEPTA (CAP) - EMEA/H/C/004218/II/0012, Orphan

Applicant: Amryt Pharmaceuticals DAC

PRAC Rapporteur: Adam Przybylkowski

Scope: Update of section 4.4 of the SmPC in order to add a new warning on the risk of autoimmune disease following exposure to metreleptin. The package leaflet and the key elements to be included in the guide/training material for healthcare professionals are updated accordingly. The RMP (version 2.0) is also updated in accordance

15.3.28. Natalizumab - TYSABRI (CAP) - EMEA/H/C/000603/X/0116

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension application to introduce a new pharmaceutical form (solution for injection), associated with a new strength (150 mg) and a new route of administration (subcutaneous use). The RMP (version 26.1) is updated accordingly

15.3.29. Nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/II/0080

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include treatment of adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma (OSCC) after prior fluoropyrimidine- and platinum-based chemotherapy. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 16.0) are updated in accordance

15.3.30. Rivaroxaban - XARELTO (CAP) - EMEA/H/C/000944/X/0074/G

Applicant: Bayer AG

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Grouped applications consisting of: 1) extension application to introduce a new pharmaceutical form, granules for oral suspension, 1 mg/mL; 2) extension of indication to include treatment of venous thromboembolism (VTE) and prevention of VTE recurrence in term neonates, infants and toddlers, children and adolescents aged less than 18 years following initiation of standard anticoagulation treatment for Xarelto (rivaroxaban) 15 mg and 20 mg tablets. As a consequence, sections 4.2, 4.4, 4.5, 4.8, 4.9, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 12.1) are updated accordingly. In addition, sections 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated for all other dose strengths (2.5/10 mg and 15/20 mg initiation packs). Furthermore, the MAH took the opportunity to update the product information with regards to sodium content in line with the Annex to the European Commission (EC) guideline on 'excipients in the labelling and package leaflet of medicinal products for human use'

15.3.31. Sebelipase alfa - KANUMA (CAP) - EMEA/H/C/004004/II/0026/G, Orphan

Applicant: Alexion Europe SAS

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Grouped variations consisting of: 1) update of sections 4.2, 4.4, 4.8 and 5.1 of the SmPC in order to update the clinical information based on the pooled safety and efficacy

analysis of already submitted studies (namely study LAL-CL04: an open label multicentre extension study to evaluate the long-term safety, tolerability, and efficacy of sebelipase alfa (SBC-102) in adult subjects with liver dysfunction due to lysosomal acid lipase deficiency (LAL-D) who previously received treatment in study LAL-CL01; study LAL-CL03: an open label, multicentre, dose escalation study to evaluate the safety, tolerability, efficacy, pharmacokinetics, and pharmacodynamics of SBC-102 in children with growth failure due to LAL-D; study LAL-CL06: a multicentre, open-label study of sebelipase alfa in patients with LAL-D; study LAL-CL08: a phase 2, open label, multicentre study to evaluate the safety, tolerability, efficacy, and pharmacokinetics of sebelipase alfa in infants with rapidly progressive LAL-D; study LAL-CL02: a multicentre, randomized, placebo-controlled study of SBC-102 in patients with LAL-D) and updated population pharmacokinetic (PK) analyses in children and adults. The package leaflet and the RMP (version 4.0) are updated accordingly. Annex II is also updated to remove the obligation related to the provision of study LAL-CL08; 2) submission of the final report from study LAL-EA01: an open-label study with sebelipase alfa 1 mg/kg every other week for up to 78 weeks or until drug commercialisation in the United States (US) patients who did not otherwise qualify for an active sebelipase alfa trial (expanded access protocol)

15.3.32. Tocilizumab - ROACTEMRA (CAP) - EMEA/H/C/000955/II/0097

Applicant: Roche Registration GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of section 4.2 of the SmPC for the 20 mg/mL concentrate for solution for infusion presentation in order to amend the existing recommendations for monitoring of laboratory abnormalities in systemic juvenile idiopathic arthritis (sJIA) patients based on final results from study WA28029 (ARTHUR) (listed as a category 3 study in the RMP): a phase 4 study to evaluate decreased dose frequency in sJIA who experience laboratory abnormalities during treatment with tocilizumab. The RMP (version 26.0) is updated in accordance and also reflects the completion of study WA22480 (ARTIS) as assessed in variation II/0094 finalised in May 2020

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. Allopurinol, lesinurad - DUZALLO (CAP) - PSUSA/00010704/201912

Applicant: Grunenthal GmbH

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

16.1.2. Angiotensin II - GIAPREZA (CAP) - PSUSA/00010785/201912

Applicant: La Jolla Pharmaceutical II B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.3. Betibeglogene autotemcel - ZYNTEGLO (CAP) - PSUSA/00010769/201911

Applicant: Bluebird bio (Netherlands) B.V, ATMP[50]

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.4. Binimetinib - MEKTOVI (CAP) - PSUSA/00010717/201912

Applicant: Pierre Fabre Medicament

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Evaluation of a PSUSA procedure

16.1.5. Blinatumomab - BLINCYTO (CAP) - PSUSA/00010460/201912

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Eva Jirsová

Scope: Evaluation of a PSUSA procedure

16.1.6. Cannabidiol[51] - EPIDYOLEX (CAP) - PSUSA/00010798/201912

Applicant: GW Pharma (International) B.V.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

[50] Advanced therapy medicinal product
[51] Centrally authorised product(s) only

16.1.7. Dengue tetravalent vaccine (live, attenuated) - DENGVAXIA (CAP) - PSUSA/00010740/201912

Applicant: Sanofi Pasteur

PRAC Rapporteur: Sonja Hrabcik

Scope: Evaluation of a PSUSA procedure

16.1.8. Elotuzumab - EMPLICITI (CAP) - PSUSA/00010500/201911

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.9. Encorafenib - BRAFTOVI (CAP) - PSUSA/00010719/201912

Applicant: Pierre Fabre Medicament

PRAC Rapporteur: Rugile Pilviniene

Scope: Evaluation of a PSUSA procedure

16.1.10. Ertugliflozin - STEGLATRO (CAP) - PSUSA/00010682/201912

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.11. Ertugliflozin, metformin - SEGLUROMET (CAP); ertugliflozin, sitagliptin - STEGLUJAN (CAP) - PSUSA/00010784/201912

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.12. Ethinylestradiol, norelgestromin - EVRA (CAP) - PSUSA/00001311/201911

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.13. Follitropin delta - REKOVELLE (CAP) - PSUSA/00010554/201911

Applicant: Ferring Pharmaceuticals A/S

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.14. Hydroxocobalamin[52] - CYANOKIT (CAP) - PSUSA/00010228/201911

Applicant: SERB SA

PRAC Rapporteur: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

16.1.15. Indacaterol - HIROBRIZ BREEZHALER (CAP); ONBREZ BREEZHALER (CAP); OSLIF BREEZHALER (CAP) - PSUSA/00001730/201911

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Hans Christian Siersted

Scope: Evaluation of a PSUSA procedure

16.1.16. Inotuzumab ozogamicin - BESPONSA (CAP) - PSUSA/00010659/201912

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.17. Lesinurad - ZURAMPIC (CAP) - PSUSA/00010470/201912

Applicant: Grunenthal GmbH

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

16.1.18. Lutetium (^{177}Lu) oxodotreotide - LUTATHERA (CAP) - PSUSA/00010643/201912

Applicant: Advanced Accelerator Applications

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.19. Lutropin alpha - LUVERIS (CAP) - PSUSA/00001918/201911

Applicant: Merck Europe B.V.

PRAC Rapporteur: Hans Christian Siersted

Scope: Evaluation of a PSUSA procedure

16.1.20. Mexiletine[53] - NAMUSCLA (CAP) - PSUSA/00010738/201912

Applicant: Lupin Europe GmbH

PRAC Rapporteur: Eva Jirsová

[52] Indicated for the treatment of chemical poisoning only
[53] Centrally authorised product(s) only

Scope: Evaluation of a PSUSA procedure

16.1.21. Netarsudil - RHOKIINSA (CAP) - PSUSA/00107812/201912

Applicant: Aerie Pharmaceuticals Ireland Ltd

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

16.1.22. Nonacog beta pegol - REFIXIA (CAP) - PSUSA/00010608/201911

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.23. Nusinersen - SPINRAZA (CAP) - PSUSA/00010595/201911

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.24. Pegvisomant - SOMAVERT (CAP) - PSUSA/00002328/201911

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

16.1.25. Peramivir - ALPIVAB (CAP) - PSUSA/00010687/201912

Applicant: BioCryst Ireland Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.26. Pneumococcal polysaccharide conjugate vaccine (adsorbed)[54] - SYNFLORIX (CAP) - PSUSA/00009262/201912

Applicant: GlaxoSmithkline Biologicals SA

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.27. Ponatinib - ICLUSIG (CAP) - PSUSA/00010128/201912

Applicant: Incyte Biosciences Distribution B.V.

[54] 10-valent

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

16.1.28. Ravulizumab - ULTOMIRIS (CAP) - PSUSA/00010787/201912

Applicant: Alexion Europe SAS

PRAC Rapporteur: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

16.1.29. Rucaparib - RUBRACA (CAP) - PSUSA/00010694/201912

Applicant: Clovis Oncology Ireland Limited

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

16.1.30. Saquinavir - INVIRASE (CAP) - PSUSA/00002684/201912

Applicant: Roche Registration GmbH

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.1.31. Selexipag - UPTRAVI (CAP) - PSUSA/00010503/201912

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

16.1.32. Sofosbuvir - SOVALDI (CAP) - PSUSA/00010134/201912

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.1.33. Sonidegib - ODOMZO (CAP) - PSUSA/00010408/201912

Applicant: Sun Pharmaceutical Industries Europe B.V.

PRAC Rapporteur: Željana Margan Koletić

Scope: Evaluation of a PSUSA procedure

16.1.34. Treosulfan[55] - TRECONDI (CAP) - PSUSA/00010777/201912

Applicant: Medac Gesellschaft fur klinische Spezialpraparate mbH

[55] Centrally authorised product(s) only

PRAC Rapporteur: Julia Pallos

Scope: Evaluation of a PSUSA procedure

16.1.35. Turoctocog alfa pegol - ESPEROCT (CAP) - PSUSA/00010782/201912

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.36. Venetoclax - VENCLYXTO (CAP) - PSUSA/00010556/201912

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Eva Jirsová

Scope: Evaluation of a PSUSA procedure

16.1.37. Vonicog alfa - VEYVONDI (CAP) - PSUSA/00010714/201912

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Ulla Wändel Liminga

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. Edotreotide - SOMAKIT TOC (CAP); NAP - PSUSA/00010552/201912

Applicants: Advanced Accelerator Applications (SomaKit TOC), various

PRAC Rapporteur: Ronan Grimes

Scope: Evaluation of a PSUSA procedure

16.2.2. Erlotinib - TARCEVA (CAP); NAP - PSUSA/00001255/201911

Applicants: Roche Registration GmbH (Tarceva), various

PRAC Rapporteur: Hans Christian Siersted

Scope: Evaluation of a PSUSA procedure

16.2.3. Riluzole - RILUTEK (CAP); RILUZOLE ZENTIVA (CAP); NAP - PSUSA/00002645/201912

Applicants: Sanofi Mature IP (Rilutek), Zentiva, k.s. (Riluzole Zentiva), various

PRAC Rapporteur: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

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

16.3.1. Anthrax vaccine (NAP) - PSUSA/00010771/201912

Applicant(s): various

PRAC Lead: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.3.2. Apomorphine (NAP) - PSUSA/00000227/201911

Applicant(s): various

PRAC Lead: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

16.3.3. Brotizolam (NAP) - PSUSA/00000444/201912

Applicant(s): various

PRAC Lead: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.3.4. Chloroquine phosphate, proguanil hydrochloride (NAP) - PSUSA/00010207/201911

Applicant(s): various

PRAC Lead: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.3.5. Cinolazepam (NAP) - PSUSA/00000769/201912

Applicant(s): various

PRAC Lead: Marek Juracka

Scope: Evaluation of a PSUSA procedure

16.3.6. Dienogest (NAP) - PSUSA/00003167/201912

Applicant(s): various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.3.7. Domperidone (NAP) - PSUSA/00001158/201911

Applicant(s): various

PRAC Lead: Laurence de Fays

Scope: Evaluation of a PSUSA procedure

16.3.8. Drospirenone, estradiol (NAP) - PSUSA/00001184/201912

Applicant(s): various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.3.9. Human coagulation factor VIII[56] (NAP) - PSUSA/00001620/201911

Applicant(s): various

PRAC Lead: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.3.10. Hydroxycarbamide[57] (NAP) - PSUSA/00009182/201912

Applicant(s): various

PRAC Lead: Nikica Mirošević Skvrce

Scope: Evaluation of a PSUSA procedure

16.3.11. Idarubicin (NAP) - PSUSA/00001720/201911

Applicant(s): various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.3.12. Sodium fluoride (^{18}F) (NAP) - PSUSA/00010706/201911

Applicant(s): various

PRAC Lead: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

16.3.13. Sulbactam (NAP) - PSUSA/00002800/201911

Applicant(s): various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.3.14. Tibolone (NAP) - PSUSA/00002947/201912

Applicant(s): various

PRAC Lead: Annika Folin

Scope: Evaluation of a PSUSA procedure

[56] Antihemophilic factor A
[57] Nationally approved product(s) only

16.4. Follow-up to PSUR/PSUSA procedures

None

16.5. Variation procedure(s) resulting from PSUSA evaluation

None

16.6. Expedited summary safety reviews[58]

None

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)[59]

17.1.1. Aprotinin (NAP) - EMEA/H/N/PSA/J/0046.1

Applicant: Nordic Group BV (Trasylol) (on behalf of a consortium)

PRAC Rapporteur: Laurence de Fays

Scope: MAH's response to PSA/J/0046 [substantial amendment to a previously agreed protocol (N/PSP/0004.1) in March 2015 for a joint non-interventional study: Nordic aprotinin patient registry to record utilisation information on patients at cardiac surgery centres] as per the request for supplementary information (RSI) adopted in February 2020

17.1.2. Sotagliflozin – ZYNQUISTA (CAP) - EMEA/H/C/PSP/S/0084.2

Applicant: Navigant Germany GmbH

PRAC Rapporteur: Martin Huber

Scope: MAH's response to PSP/S/0084.1 [protocol for an observational retrospective cohort study using existing data sources on the incidence of diabetic ketoacidosis (DKA) in adult patients with type 1 diabetes mellitus (T1DM) treated with sotagliflozin as an adjunct to insulin versus insulin alone, as required in the outcome of the initial opinion/marketing authorisation (EMEA/H/C/004889) finalised in February 2019] as per the request for supplementary information (RSI) adopted in February 2020

[58] Requirement to the compassionate use opinion to submit expedited summary safety reports for review accompanied by a summary of remdesivir distribution, In addition to the 6-monthly or annual PSURs falling within the pandemic period
[59] In accordance with Article 107n of Directive 2001/83/EC

17.1.3. Valproate[60] (NAP) - EMEA/H/N/PSP/J/0074.3

Applicant: Sanofi-Aventis Recherche & Développement (on behalf of a consortium)

PRAC Rapporteur: Jean-Michel Dogné

Scope: MAH's response to PSP/J/0074.2 [protocol for a joint observational study to evaluate and identify the best practices for switching of valproate in clinical practice, as required in the outcome of the referral procedure under Article 31 of Directive 2001/83/EC on valproate-containing products completed in February 2018 (EMEA/H/A-31/1454)] as per the request for supplementary information (RSI) adopted in March 2020

17.1.4. Volanesorsen – WAYLIVRA (CAP) - EMEA/H/C/PSP/S/0080.3

Applicant: Akcea Therapeutics Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: MAH's response to PSP/S/0080.2 [protocol for study WAY4001: a multinational observational registry of patients treated with volanesorsen to evaluate the safety on severe thrombocytopenia and bleeding in patients with familial chylomicronemia syndrome (FCS)] as per the request for supplementary information (RSI) adopted in April 2020

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

17.2.1. Fostamatinib - TAVLESSE (CAP) - EMEA/H/C/005012/MEA 002

Applicant: Instituto Grifols, S.A.

PRAC Rapporteur: Menno van der Elst

Scope: Protocol for study BIG-CL-PRT-000015: a post-authorisation long term safety surveillance study of fostamatinib in adult patients with chronic immune thrombocytopenia (cITP) who are refractory to other treatments (from initial opinion/marketing authorisation(s) (MA)) [final clinical study report (CSR) expected in March 2025]

17.2.2. Givosiran - GIVLAARI (CAP) - EMEA/H/C/004775/MEA 006

Applicant: Alnylam Netherlands B.V.

PRAC Rapporteur: Martin Huber

Scope: Protocol for study ALN-AS1-006: a global observational longitudinal prospective registry of patients with acute hepatic porphyria (AHP) [ELEVATE]

17.2.3. Lenvatinib - LENVIMA (CAP) - EMEA/H/C/003727/MEA 014.3

Applicant: Eisai GmbH

PRAC Rapporteur: Annika Folin

[60] Valproic acid, sodium valproate, valproate pivoxil, valproate semisodium, valpriomide, valproate bismuth, calcium valproate, valproate magnesium
[61] 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

Scope: MAH's response to MEA 014.2 [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 2020

17.2.4. Loxapine - ADASUVE (CAP) - EMEA/H/C/002400/MEA 001.5

Applicant: Ferrer Internacional s.a.

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Substantial amendment to a protocol previously agreed in May 2018 for study AMDC-204-401: a post-authorisation observational study to evaluate the safety of Adasuve (loxapine for inhalation) in agitated persons in routine clinical care and study

17.2.5. Lutetium (^{177}Lu) oxodotreotide - LUTATHERA (CAP) - EMEA/H/C/004123/MEA 001.4

Applicant: Advanced Accelerator Applications

PRAC Rapporteur: Adam Przybylkowski

Scope: MAH's response to MEA 001.3 [first progress report for study A-LUT-T-E02-402 (SALUS study) (listed as a category 3 study in the RMP): an international post-authorisation safety registry to assess the long-term safety of Lutathera (lutetium (^{177}Lu)) for unresectable or metastatic, somatostatin receptor positive gastroenteropancreatic neuroendocrine tumours (GEP-NETs) [final clinical study report (CSR) expected in December 2025]] as per the request for supplementary information (RSI) adopted in March 2020

17.2.6. Naloxegol - MOVENTIG (CAP) - EMEA/H/C/002810/MEA 002.6

Applicant: Kyowa Kirin Holdings B.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: Substantial amendment to a protocol previously agreed in November 2015 for study D3820R00006: a post-marketing observational drug utilisation study (DUS) of Moventig (naloxegol) conducted in selected European populations in order to describe demographic, clinical, and treatment characteristics in the baseline of patients treated with naloxegol as well as to describe treatment pattern characteristics of naloxegol utilisation at initiation and follow-up

17.2.7. Patisiran - ONPATTRO (CAP) - EMEA/H/C/004699/MEA 002.4

Applicant: Alnylam Netherlands B.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: MAH's response to MEA 002 [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 April 2020

17.2.8. Tocilizumab - ROACTEMRA (CAP) - EMEA/H/C/000955/MEA 041.6

Applicant: Roche Registration GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Substantial amendment to a protocol previously agreed in November 2018 for study WA29358: an observational safety and effectiveness study of patients with polyarticular juvenile idiopathic arthritis treated with tocilizumab

17.2.9. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/MEA 014

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Protocol for study A3921321: a drug utilisation study (DUS) on the utilisation and prescribing patterns of Xeljanz (tofacitinib) in two European countries using administrative claims databases and national registries for assessment, as requested in the conclusions of the referral procedure under Article 20 of Regulation (EC) No 726/2004 (EMEA/H/A-20/1485) finalised in November 2019

17.2.10. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/MEA 015

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Protocol for study A3921334: a non-interventional PASS to evaluate the effectiveness of additional risk minimisation measures (aRMM) materials for Xeljanz (tofacitinib) in Europe via a survey of healthcare professionals (HCPs), as requested in the conclusions of the referral procedure under Article 20 of Regulation (EC) No 726/2004 (EMEA/H/A-20/1485) finalised in November 2019

17.2.11. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/MEA 044.8

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Rhea Fitzgerald

Scope: Substantial amendment to a protocol previously agreed in October 2019 for study CNTO1275PSO4056: an observational PASS of ustekinumab in the treatment of paediatric patients aged 12 years and older with moderate to severe plaque psoriasis (adolescent registry) as requested in the conclusion of variation II/0073 finalised in December 2019

17.3. Results of PASS imposed in the marketing authorisation(s)[62]

None

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

17.4. Results of PASS non-imposed in the marketing authorisation(s)[63]

17.4.1. Aclidinium - BRETARIS GENUAIR (CAP) - EMEA/H/C/002706/WS1795/0043; EKLIRA GENUAIR (CAP) - EMEA/H/C/002211/WS1795/0043

Applicant: AstraZeneca AB

PRAC Rapporteur: Adam Przybylkowski

Scope: Submission of the final report from study D6570R00002 (listed as a category 3 study in the RMP): a descriptive, non-interventional, multinational European cohort study of new users of aclidinium, aclidinium/formoterol, and other selected chronic obstructive pulmonary disease (COPD) medications to describe the characteristics and patterns of use. As a consequence, the following safety concerns listed as missing information in the RMP are removed: 'safety in patients with hepatic or severe renal impairment', 'safety in patients with benign hyperplasia or urinary retention' and 'use in pregnancy or lactation'. The RMP (version 8.0) is updated accordingly

17.4.2. Aclidinium, formoterol fumarate dihydrate - BRIMICA GENUAIR (CAP) - EMEA/H/C/003969/WS1794/0029; DUAKLIR GENUAIR (CAP) - EMEA/H/C/003745/WS1794/0029

Applicant: AstraZeneca AB

PRAC Rapporteur: Adam Przybylkowski

Scope: Submission of the final report from study D6570R00002 (listed as a category 3 study in the RMP): a descriptive, non-interventional, multinational European cohort study of new users of aclidinium, aclidinium/formoterol, and other selected chronic obstructive pulmonary disease (COPD) medications to describe the characteristics and patterns of use. As a consequence, the following safety concerns listed as missing information in the RMP are removed 'safety in patients with hepatic or severe renal impairment', 'safety in patients with benign hyperplasia or urinary retention' and 'use in pregnancy or lactation'. The RMP (version 5.0) is updated accordingly

17.4.3. Alglucosidase alfa - MYOZYME (CAP) - EMEA/H/C/000636/II/0079

Applicant: Genzyme Europe BV

PRAC Rapporteur: Adrien Inoubli

Scope: Submission of the final report from study ALGMYC07390: prevalence of immunology testing in patients treated with alglucosidase alfa with significant hypersensitivity/anaphylactic reactions to test the effectiveness of the approved safety information packet (SIP) (in fulfilment of MEA 053)

17.4.4. Baricitinib - OLUMIANT (CAP) - EMEA/H/C/004085/II/0017

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Adam Przybylkowski

[63] 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

Scope: Submission of the final report from study I4V-MC-B010 (listed as a category 3 study in the RMP): an observational, multinational cross-sectional survey amongst rheumatologists to assess the effectiveness of the risk minimisation measures (RMM) for Olumiant (baricitinib). The RMP (version 9.2) is updated accordingly. The MAH took the opportunity to remove from the RMP three safety concerns listed as missing information namely 'use in combination with biologic disease-modifying anti-rheumatic drugs (bDMARDs) or with other Janus kinase (JAK) inhibitors', 'use in patients with severe hepatic impairment', 'effect on fertility, on pregnancy and the foetus', and 'use in breastfeeding' as requested in the conclusions of variation II/006 finalised in July 2018

17.4.5. Dulaglutide - TRULICITY (CAP) - EMEA/H/C/002825/II/0048

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Ilaria Baldelli

Scope: Submission of the final study report from study B010 (listed as a category 3 study in the RMP) investigating the utilisation of dulaglutide in European countries: a cross-sectional, multi-country and multi-source drug utilisation study using electronic health record databases (in fulfilment of MEA 001). The RMP (version 5.1) is updated accordingly

17.4.6. Dulaglutide - TRULICITY (CAP) - EMEA/H/C/002825/II/0051

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Ilaria Baldelli

Scope: Submission of the final study report for study B009 (listed as a category 3 study in the RMP): a multi-database collaborative research programme of observational studies to monitor the drug utilisation and safety of dulaglutide in the EU (in fulfilment of MEA 002). The RMP (version 6.1) is updated accordingly

17.4.7. Estrogens conjugated, bazedoxifene - DUAVIVE (CAP) - EMEA/H/C/002314/II/0025

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Martin Huber

Scope: Submission of the final clinical study report (CSR) for study B2311061 (listed as a category 3 study in the RMP): a non-interventional EU drug utilisation study (DUS) to describe baseline characteristics and utilisation patterns of EU patients initiating Duavive (estrogens conjugated/bazedoxifene) or oestrogen + progestin (E+P) combination hormone replacement therapy (HRT) (in fulfilment of MEA 003)

17.4.8. Hydroxycarbamide - SIKLOS (CAP) - EMEA/H/C/000689/II/0045

Applicant: Addmedica S.A.S.

PRAC Rapporteur: Laurence de Fays

Scope: Update of sections 4.2, 4.3, 4.4, 4.5, 4.6, 4.8 and 4.9 of the SmPC in order to reflect the final study results of non-interventional cohort study ESCORT-HU (European Sickle Cell Disease Cohort-Hydroxyurea): an observational prospective cohort study to measure the occurrence of adverse events and serious adverse events and to harmonise

the product information with other hydroxyurea (HU)-containing products. In addition, Annex II-D on 'Conditions or restrictions with regard to the safe and effective use of the medicinal product' is amended to delete the reference to the treatment guide for physicians. The package leaflet and the RMP (version 20) are updated accordingly

17.4.9. Ranibizumab - LUCENTIS (CAP) - EMEA/H/C/000715/II/0085

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of the results of study RFB002F2401 (OBTAIN): a 36-month observational study to describe the long-term efficacy and safety of ranibizumab 0.5 mg treatment, in patients with visual impairment due to choroidal neovascularisation (CNV) secondary to pathologic myopia (PM)

17.4.10. Teriparatide - FORSTEO (CAP) - EMEA/H/C/000425/II/0054

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Adrien Inoubli

Scope: Submission of the final report for the European Union (EU) component of study B3D-MC-GHBX(2.1): registry to estimate the incidence of osteosarcoma in patients who have received treatment with Forteo (teriparatide)

17.4.11. Umeclidinium - INCRUSE ELLIPTA (CAP) - EMEA/H/C/002809/WS1761/0028; ROLUFTA ELLIPTA (CAP) - EMEA/H/C/004654/WS1761/0013; umeclidinium, vilanterol - ANORO ELLIPTA (CAP) - EMEA/H/C/002751/WS1761/0029; LAVENTAIR ELLIPTA (CAP) - EMEA/H/C/003754/WS1761/0032

Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Ilaria Baldelli

Scope: Submission of the final report from study WWE117397 (listed as a category 3 study in the RMP): a retrospective longitudinal non-interventional observational study of new users of inhaled umeclidinium/vilanterol (UMEC/VI) or new users of inhaled umeclidinium (UMEC) or new users of long-acting bronchodilators (LABD) in the primary care setting

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

17.5.1. Elosulfase alfa - VIMIZIM (CAP) - EMEA/H/C/002779/ANX 005.5

Applicant: BioMarin International Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Sixth annual report (reporting period: 14 February 2019 to 13 February 2020) 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]

17.5.2. Infliximab - FLIXABI (CAP) - EMEA/H/C/004020/MEA 002.2

Applicant: Samsung Bioepis NL B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Annual interim report for a prospective study (listed as a category 3 study in the RMP) to treat patients with rheumatological disorders with biological agents to assess long-term toxicity of these agents in routine clinical practice using the British Society of Rheumatology Biologics Register for Rheumatoid Arthritis (BSRBR-RA): an established nationwide register [final clinical study report (CSR) expected in 2027]

17.5.3. Infliximab - FLIXABI (CAP) - EMEA/H/C/004020/MEA 003

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 national prospective, observational, uncontrolled cohort study whose objectives are to evaluate the risk of selected adverse events (AEs) in rheumatoid arthritis (RA), juvenile idiopathic arthritis, and other rheumatic disease patients treated with infliximab using the Anti-Rheumatic Therapies in Sweden (ARTIS) national surveillance programme [final clinical study report (CSR) expected in 2027]

17.5.4. Infliximab - FLIXABI (CAP) - EMEA/H/C/004020/MEA 005.2

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 (TNF)-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 (CSR) expected in 2027]

17.5.5. Infliximab - FLIXABI (CAP) - EMEA/H/C/004020/MEA 006.2

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 (CSR) expected in 2027]

17.5.6. Influenza vaccine (live attenuated, nasal) - FLUENZ TETRA (CAP) - EMEA/H/C/002617/MEA 004.11

Applicant: AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

Scope: Annual interim report for the passive enhanced safety surveillance study (ESS) D2560C00008: a postmarketing non-interventional cohort study of the safety of live attenuated influenza vaccine (LAIV) in subjects 2 through 17 years of age for the 2019-2020 influenza season in England

17.5.7. Octocog alfa - KOVALTRY (CAP) - EMEA/H/C/003825/MEA 005.2

Applicant: Bayer AG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Annual interim results 2019 for epidemiological study 15689: an evaluation of adverse events of special interest (AESI) in the PEDiatric NETwork (PedNet) haemophilia registry

17.5.8. Vedolizumab - ENTYVIO (CAP) - EMEA/H/C/002782/MEA 001

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Adam Przybylkowski

Scope: Interim analysis report for study MLN-0002-401 (listed as a category 3 study in the RMP): an international prospective, observational, cohort safety study comparing vedolizumab to other biologic agents in patients with ulcerative colitis or Crohn's disease [final clinical study report (CSR) expected in June 2022] (from initial opinion/marketing authorisation(s) (MA))

17.6. Others

17.6.1. Avatrombopag - DOPTELET (CAP) - EMEA/H/C/004722/MEA 002.1

Applicant: Dova Pharmaceuticals Ireland Limited

PRAC Rapporteur: Eva Segovia

Scope: MAH's response to MEA 002 [feasibility assessment for study AVA-CLD-402: evaluation of the feasibility of conducting a PASS of Doptelet (avatrombopag) in patients with severe chronic liver disease (CLD) and potential utilisation of data from TARGET PharmaSolutions' ongoing observational studies in patients with severe CLD] as per the request for supplementary information (RSI) adopted in January 2020

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/0014 (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/0087 (without RMP)

Applicant: Shire Human Genetic Therapies AB

PRAC Rapporteur: Liana Gross-Martirosyan

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/0079 (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/0021 (without RMP)

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Annika Folin

Scope: Conditional renewal of the marketing authorisation

18.2.3. Recombinant vesicular stomatitis virus-Zaire ebolavirus vaccine (live) - ERVEBO (CAP) - EMEA/H/C/004554/R/0004 (without RMP)

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Conditional renewal of the marketing authorisation

18.3. Renewals of the marketing authorisation

18.3.1. Aripiprazole - ARIPIPRAZOLE ACCORD (CAP) - EMEA/H/C/004021/R/0019 (without RMP)

Applicant: Accord Healthcare S.L.U.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: 5-year renewal of the marketing authorisation

18.3.2. Birch bark extract - EPISALVAN (CAP) - EMEA/H/C/003938/R/0018 (without RMP)

Applicant: Amryt GmbH

PRAC Rapporteur: Zane Neikena

Scope: 5-year renewal of the marketing authorisation

18.3.3. Brivaracetam - BRIVIACT (CAP) - EMEA/H/C/003898/R/0025 (with RMP)

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Adam Przybylkowski

Scope: 5-year renewal of the marketing authorisation

Action: For adoption of advice to CHMP

18.3.4. Cabazitaxel - JEVTANA (CAP) - EMEA/H/C/002018/R/0042 (with RMP)

Applicant: sanofi-aventis groupe

PRAC Rapporteur: Tiphaine Vaillant

Scope: 5-year renewal of the marketing authorisation

18.3.5. Cinacalcet - CINACALCET MYLAN (CAP) - EMEA/H/C/004014/R/0011 (without RMP)

Applicant: Mylan S.A.S

PRAC Rapporteur: Ulla Wändel Liminga

Scope: 5-year renewal of the marketing authorisation

18.3.6. Diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA), poliomyelitis (inactivated) and haemophilus type b conjugate vaccine (adsorbed) - VAXELIS (CAP) - EMEA/H/C/003982/R/0065 (with RMP)

Applicant: MCM Vaccine B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: 5-year renewal of the marketing authorisation

18.3.7. Elvitegravir, cobicistat, emtricitabine, tenofovir alafenamide - GENVOYA (CAP) - EMEA/H/C/004042/R/0069 (with RMP)

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ilaria Baldelli

Scope: 5-year renewal of the marketing authorisation

18.3.8. Eptifibatide - EPTIFIBATIDE ACCORD (CAP) - EMEA/H/C/004104/R/0010 (without RMP)

Applicant: Accord Healthcare S.L.U.

PRAC Rapporteur: Adrien Inoubli

Scope: 5-year renewal of the marketing authorisation

18.3.9. Lopinavir, ritonavir – LOPINAVIR/RITONAVIR MYLAN (CAP) - EMEA/H/C/004025/R/0014 (without RMP)

Applicant: Mylan S.A.S

PRAC Rapporteur: Adrien Inoubli

Scope: 5-year renewal of the marketing authorisation

18.3.10. Lumacaftor, ivacaftor - ORKAMBI (CAP) - EMEA/H/C/003954/R/0056 (with RMP)

Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: 5-year renewal of the marketing authorisation

18.3.11. Octocog alfa - KOVALTRY (CAP) - EMEA/H/C/003825/R/0030 (without RMP)

Applicant: Bayer AG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: 5-year renewal of the marketing authorisation

18.3.12. Pemetrexed - PEMETREXED ACCORD (CAP) - EMEA/H/C/004072/R/0012 (without RMP)

Applicant: Accord Healthcare S.L.U.

PRAC Rapporteur: Tiphaine Vaillant

Scope: 5-year renewal of the marketing authorisation

18.3.13. Rasagiline - RASAGILINE MYLAN (CAP) - EMEA/H/C/004064/R/0006 (without RMP)

Applicant: Mylan S.A.S

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: 5-year renewal of the marketing authorisation

18.3.14. Sufentanil - ZALVISO (CAP) - EMEA/H/C/002784/R/0016 (without RMP)

Applicant: Grunenthal GmbH

PRAC Rapporteur: Adam Przybylkowski

Scope: 5-year renewal of the marketing authorisation

19. Annex II – List of participants

including any restrictions with respect to involvement of members / alternates / experts following evaluation of declared interests for the 06-09 July 2020 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
Laurence de Fays	Alternate	Belgium	No restrictions applicable to this meeting	Full involvement
Maria Popova-Kiradjieva	Member	Bulgaria	No interests declared	Full involvement
Nikica Mirošević Skvrce	Member	Croatia	No interests declared	Full involvement
Željana Margan Koletić	Alternate	Croatia	No interests declared	Full involvement
Helena Panayiotopoulou	Member	Cyprus	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 Lukacisinovà	Alternate	Czech Republic	No interests declared	Full involvement
Anette Kirstine 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

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Kimmo Jaakkola	Alternate	Finland	No interests declared	Full involvement
Adrien Inoubli	Member	France	No interests declared	Full involvement
Tiphaine Vaillant	Alternate	France	No interests declared	Full involvement
Martin Huber	Member (Vice-Chair)	Germany	No interests declared	Full involvement
Brigitte Keller-Stanislawski	Alternate	Germany	No interests declared	Full involvement
Sophia Trantza	Alternate	Greece	No interests declared	Full involvement
Julia Pallos	Member	Hungary	No restrictions applicable to this meeting	Full involvement
Melinda Palfi	Alternate	Hungary	No interests declared	Full involvement
Guðrún Stefánsdóttir	Member	Iceland	No participation in discussion, final deliberations and voting on:	4.3.1. Adalimumab - AMGEVITA (CAP); HALIMATOZ (CAP); HEFIYA (CAP); HULIO (CAP); HUMIRA (CAP) - HYRIMOZ (CAP); IDACIO (CAP); IMRALDI (CAP) 4.3.5. Tumour necrosis factor (TNF) inhibitors: adalimumab - AMGEVITA (CAP), AMSPARITY (CAP), HALIMATOZ (CAP), HEFIYA (CAP), HULIO (CAP), HUMIRA (CAP), HYRIMOZ (CAP), IDACIO (CAP), IMRALDI (CAP); certolizumab pegol - CIMZIA (CAP); etanercept - BENEPALI (CAP), ENBREL (CAP), ERELZI (CAP);

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				golimumab - SIMPONI (CAP); infliximab - FLIXABI (CAP), INFLECTRA (CAP), REMICADE (CAP), REMSIMA (CAP), ZESSLY (CAP) 7.4.3. Pegfilgrastim - NEULASTA (CAP) 7.6.1. Evolocumab - REPATHA (CAP) 11.1.1. Amoxicillin (NAP); amoxicillin, clavulanic acid (NAP) 15.2.3. Tacrolimus - ADVAGRAF (CAP); MODIGRAF (CAP) 16.1.5. Blinatumomab - BLINCYTO (CAP)
Rhea Fitzgerald	Member	Ireland	No restrictions applicable to this meeting	Full involvement
Ronan Grimes	Alternate	Ireland	No interests declared	Full involvement
Amelia Cupelli	Member	Italy	No interests declared	Full involvement
Ilaria Baldelli	Alternate	Italy	No interests declared	Full involvement
Zane Neikena	Member	Latvia	No interests declared	Full involvement
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 final deliberations and voting on:	6.1.1. Aflibercept - EYLEA (CAP) 6.3.2. Flurbiprofen (NAP) 15.3.30.

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				Rivaroxaban - XARELTO (CAP) 7.3.1. Iron (NAP) 17.5.7. Octocog alfa - KOVALTRY (CAP) 18.3.11. Octocog alfa - KOVALTRY (CAP)
Karen Pernille Harg	Alternate	Norway	No interests declared	Full involvement
Adam Przybylkowski	Member	Poland	No interests declared	Full involvement
Katarzyna Ziolkowska	Alternate	Poland	No interests declared	Full involvement
Ana Diniz Martins	Member	Portugal	No interests declared	Full involvement
Marcia Silva	Alternate	Portugal	No interests declared	Full involvement
Roxana Stefania Stroe	Member	Romania	No interests declared	Full involvement
Alexandra - Maria Spurni	Alternate	Romania	No interests declared	Full involvement
Michal Radik	Member	Slovakia	No restrictions applicable to this meeting	Full involvement
Marek Juracka	Alternate	Slovakia	No interests declared	Full involvement
Jasmina Klopcic	Alternate	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
Daniel Morales	Member	Independent scientific expert	No interests declared	Full involvement
Antoine Pariente	Member	Independent scientific expert	No restrictions applicable to this meeting	Full involvement
Stefan Weiler	Member	Independent scientific expert	No participation in discussion, final deliberations and voting on:	3.2.2 - Ulipristal acetate – ESMYA (CAP); NAP

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Raymond Anderson	Member	Healthcare Professionals' Representative	No interests declared	Full involvement
Roberto Frontini	Alternate	Healthcare Professionals' Representative	No restrictions applicable to this meeting	Full involvement
Cathalijne van Doorne	Member	Patients' Organisation Representative	No interests declared	Full involvement
Virginie Hivert	Alternate	Patients' Organisation Representative	No restrictions applicable to this meeting	Full involvement
Christelle Bizimungu	Expert - via telephone*	Belgium	No restrictions applicable to this meeting	Full involvement
Fabrice Moore	Expert - via telephone*	Belgium	No interests declared	Full involvement
Ivona Bahnik Biševac	Expert - via telephone*	Croatia	No restrictions applicable to this meeting	Full involvement
Katica Milčić	Expert - via telephone*	Croatia	No restrictions applicable to this meeting	Full involvement
Maja Tabak Slošić	Expert - via telephone*	Croatia	No interests declared	Full involvement
Nikolina Torti	Expert - via telephone*	Croatia	No interests declared	Full involvement
Karin Susanne Erneholm	Expert - via telephone*	Denmark	No restrictions applicable to this meeting	Full involvement
Moritz Sander	Expert - via telephone*	Denmark	No interests declared	Full involvement
Krõõt Aab	Expert - via telephone*	Estonia	No interests declared	Full involvement
Alice Aribaud	Expert - via telephone*	France	No interests declared	Full involvement
Florent Arinal	Expert - via telephone*	France	No interests declared	Full involvement
Jeremie Botton	Expert - via telephone*	France	No interests declared	Full involvement
Matthew Burbank	Expert - via telephone*	France	No restrictions applicable to this meeting	Full involvement
Emiliano Gemma	Expert - via telephone*	France	No interests declared	Full involvement
Emilie Patras-de-Campaigno	Expert - via telephone*	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
Faustine Vidil	Expert - via telephone*	France	No interests declared	Full involvement
Nicole Bick	Expert - via telephone*	Germany	No interests declared	Full involvement
Ines Fluegge	Expert - via telephone*	Germany	No interests declared	Full involvement
Dennis Lex	Expert - via telephone*	Germany	No participation in discussion, final deliberations and voting on:	7.4.2. Fampridine - FAMPYRA (CAP) 15.3.28. Natalizumab - TYSABRI (CAP)
Kerstin Loeschcke	Expert - via telephone*	Germany	No interests declared	Full involvement
Tania Meirer	Expert - via telephone*	Germany	No interests declared	Full involvement
Nerina Pflanz	Expert - via telephone*	Germany	No interests declared	Full involvement
Szabina Luca Papp	Expert - via telephone*	Hungary	No interests declared	Full involvement
Elena Ukhatskaya	Expert - via telephone*	Iceland	No restrictions applicable to this meeting	Full involvement
Paolo Foggi	Expert - via telephone*	Italy	No interests declared	Full involvement
Ida Bergva Aas	Expert - via telephone*	Norway	No interests declared	Full involvement
Ana Catarina Fonseca	Expert - via telephone*	Portugal	No interests declared	Full involvement
Silvia de Orbe Izquierdo	Expert - via telephone*	Spain	No interests declared	Full involvement
Mónica Martínez Redondo	Expert - via telephone*	Spain	No restrictions applicable to this meeting	Full involvement
Charlotte Backman	Expert - via telephone*	Sweden	No interests declared	Full involvement
Angelica Lindén Hirschber	Expert - via telephone*	Sweden	No restrictions applicable to this meeting	Full involvement
A representative from the European Commission attended the meeting				
Meeting run with support from relevant EMA staff				

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

20. Annex III - List of acronyms and abbreviations

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

21. Explanatory notes

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

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

(Items 2 and 3 of the PRAC minutes)

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

Signals assessment and prioritisation

(Item 4 of the PRAC minutes)

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

Risk Management Plans (RMPs)

(Item 5 of the PRAC minutes)

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

Assessment of Periodic Safety Update Reports (PSURs)

(Item 6 of the PRAC minutes)

A PSUR is a report providing an evaluation of the benefit-risk balance of a medicine, which is submitted by marketing authorisation holders at defined time points following a medicine's authorisation. PSURs summarises data on the benefits and risks of a medicine and includes the results of all studies carried out with this medicine (in the authorised and unauthorised indications).

Post-authorisation Safety Studies (PASS)

(Item 7 of the PRAC minutes)

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

Product related pharmacovigilance inspections

(Item 9 of the PRAC minutes)

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

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