01 February 2023
EMA/PRAC/947562/2022
Human Medicines Division

Pharmacovigilance Risk Assessment Committee (PRAC)

Minutes of the meeting on 26-29 September 2022

Chair: Sabine Straus – Vice-Chair: Martin Huber

Health and safety information

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

Disclaimers

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

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

Note on access to documents

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

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Table of contents

1. Introduction

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

The Chair opened the meeting by welcoming all participants. Due to the current coronavirus (COVID-19) pandemic, and the associated EMA Business Continuity Plan (BCP), the meeting was held in-person with some members connected remotely (hybrid setting).

In accordance with the Agency's policy on handling of declarations of interests of scientific Committees' members and experts, based on the declarations of interest submitted by the Committee members, alternates and experts and on the topics in the agenda of the meeting, the Committee Secretariat announced the restricted involvement of some Committee members, alternates and experts for concerned agenda topics. Participants were asked to declare any changes, omissions or errors to their declared interests concerning the matters for discussion. No new or additional competing interests were declared. Restrictions applicable to this meeting are captured in the List of participants included in the minutes.

Discussions, deliberations and voting took place in full respect of the restricted involvement of Committee members and experts in line with the relevant provisions of the Rules of Procedure (EMA/PRAC/567515/2012 Rev.3). All decisions taken at this meeting were made in the presence of a quorum of members. All decisions, recommendations and advice were agreed by consensus, unless otherwise specified.

The Chair welcomed the new member(s) and alternate(s) and thanked the departing members/alternates for their contributions to the Committee (see section 12.1.1.)

1.2. Agenda of the meeting on 26-29 September 2022

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

1.3. Minutes of the previous meeting on 29 August - 01 September 2022

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 29 August – 01 September 2022 were published on the EMA website on 02 February 2023 (EMA/PRAC/938468/2022).

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. Janus kinase (JAK) inhibitors[1]: abrocitinib - CIBINQO (CAP); baricitinib - OLUMIANT (CAP); filgotinib - JYSELECA (CAP); tofacitinib - XELJANZ (CAP); upadacitinib - RINVOQ (CAP) – EMEA/H/A-20/1517

Applicant(s): AbbVie Deutschland GmbH & Co. KG (Rinvoq), Eli Lilly Nederland B.V. (Olumiant), Galapagos N.V. (Jyseleca), Pfizer Europe MA EEIG (Cibinqo, Xeljanz)

PRAC Rapporteur: Ulla Wändel Liminga; PRAC Co-rapporteur(s): Liana Gross-Martirosyan (Olumiant, Xeljanz), Nikica Mirošević Skvrce (Cibinqo, Jyseleca, Rinvoq)

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

Background

A referral procedure under Article 20 of Regulation (EC) No 726/2004 is ongoing for Janus kinase inhibitors (JAKi), namely Xeljanz (tofacitinib), Cibinqo (abrocitinib), Olumiant (baricitinib), Jyseleca (filgotinib) and Rinvoq (upadacitinib) indicated in the treatment of several chronic inflammatory disorders such as rheumatoid arthritis, atopic dermatitis, psoriatic arthritis, juvenile idiopathic arthritis, ankylosing spondylitis and ulcerative colitis. This follows the final results from study A3921133[2] (ORAL surveillance) for Xeljanz (tofacitinib) showing an increase incidence of major adverse cardiovascular events (MACE), a higher risk of malignancy with tofacitinib compared to tumour necrosis fibrosis (TNF)-inhibitors in patients with rheumatoid arthritis, as well as a higher incidence of venous thromboembolism (VTE), all-cause of mortality and serious infections in patients treated with tofacitinib compares to TNF-inhibitors. This also follows preliminary results from study I4V-MC-B023[3] for Olumiant (baricitinib) suggesting also an increased risk of MACE and VTE in patients with rheumatoid arthritis treated with Olumiant (baricitinib) compared to those treated with TNF-inhibitors. For further background, see PRAC minutes February 2022, PRAC minutes June 2022 and PRAC minutes September 2022[4].

Summary of recommendation(s)/conclusions

[1] Indicated for the treatment of inflammatory disorders
[2] A phase 3b/4 randomised safety endpoint study of 2 doses of tofacitinib in comparison to a tumour necrosis fibrosis (TNF) inhibitor in subjects with rheumatoid arthritis
[3] A retrospective observational study to compare baricitinib relative to the standard of care
[4] Held 29 August – 01 September 2022

- PRAC noted the feedback provided by the ad-hoc expert group (AHEG) Chair following the AHEG meeting held on 19 September 2022.

3.3. Procedures for finalisation

3.3.1. Terlipressin[5] (NAP) - EMEA/H/A-31/1514

Applicant(s): various

PRAC Rapporteur: Krõõt Aab; PRAC Co-rapporteur: Anette Kirstine Stark

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

Background

A referral procedure under Article 31 of Directive 2001/83/EC for the review of terlipressin-containing product(s) indicated in the treatment of hepatorenal syndrome (HRS) is to be concluded. This procedure was initiated following the assessment of the results from a large clinical trial CONFIRM[6] involving patients with type 1 HRS within the PSUR single assessment (PSUSA) procedure on terlipressin (PSUSA/00002905/202104) concluded in December 2021. Following this assessment, serious safety concerns were raised due to an increased risk of respiratory failure in patients treated with terlipressin, sometimes with fatal outcome, within 90 days after the first dose compared to those who were given a placebo. In addition, the frequency of respiratory failure observed in the study was higher than expected based on frequency stated in the current product information. For further background, see PRAC minutes January 2022, PRAC minutes April 2022, PRAC minutes June 2022 and PRAC minutes July 2022.

Discussion

PRAC discussed the conclusion reached by the Rapporteurs.

PRAC considered the totality of the data submitted during the referral procedure, including the clinical data from the CONFIRM trial, pooled data for 3 clinical trials (OT-0401, REVERSE, CONFIRM), the responses submitted by the MAH(s) in writing as well as the outcome of the ad-hoc expert group meeting.

Based on the available efficacy data, PRAC concluded that the evidence does not raise serious doubts on the established efficacy on the outcome of reversal of type 1 HRS, whereas the survival benefit remains uncertain.

PRAC also concluded that use of terlipressin-containing products for treatment of type 1 HRS is associated with an increased risk of respiratory failure and a risk of sepsis/septic shock. PRAC also noted the potential additive effect of concomitant use of albumin and terlipressin, as albumin itself is associated with a risk of volume overload and respiratory failure, and overall higher albumin doses were used in CONFIRM compared to the EU clinical guidelines.

Therefore, PRAC recommended that the product information should be updated to take into consideration the current clinical knowledge on safety of terlipressin when used in the treatment of type 1 HRS with warnings and precautions regarding respiratory failure and sepsis/septic shock. PRAC also recommended that a warning to use albumin when

[5] Indicated for the treatment of hepatorenal syndrome (HRS)
[6] Wong F, et al. Terlipressin plus albumin for the treatment of type 1 hepatorenal syndrome. N Engl J Med. 2021 Mar 4;384(9):818-828. doi: 10.1056/NEJMoa2008290

administered together with terlipressin with caution should be included in the product information.

Moreover, PRAC was of the view that the data reviewed raises concerns about the benefit and the risk of terlipressin treatment in specific groups of patients, namely in patients with advanced renal dysfunction and severe liver disease, as the use of terlipressin in these patient groups is associated with an increased risk of mortality, reduced efficacy and increased risk of adverse events, including respiratory failure (specifically for patients with severe liver disease). Therefore, PRAC agreed that the product information should be updated accordingly.

Additionally, PRAC considered further evidence concerning the administration of terlipressin via continuous intravenous (IV) infusion, alternatively to the approved method of administration (bolus injection). Nevertheless, although the available evidence is limited, PRAC noted that it is indicative that continuous infusion improves the overall safety profile of terlipressin to an extent that is clinically significant, while efficacy is maintained. Therefore, as a risk minimisation measure, PRAC recommended the addition of continuous IV infusion to the product information as an alternative method of administration.

The Committee considered that the benefit-risk balance of terlipressin-containing medicinal products indicated in the treatment of type 1 HRS remains favourable subject to the agreed amendments to the product information.

Summary of recommendation(s)/conclusions

- PRAC adopted a recommendation to vary[7] the terms of the marketing authorisation(s) for terlipressin-containing medicines indicated in HRS and adopted a recommendation to be considered by CMDh for a position – see EMA Press release (EMA/781753/2022).
- PRAC agreed on the content of a direct healthcare professional communication (DHPC) along with a communication plan for its distribution.

Post-meeting note: the press release entitled 'New recommendations for terlipressin-containing medicines in the treatment of hepatorenal syndrome' (EMA/862470/2022) representing the position adopted by the CMDh was published on the EMA website on 11 November 2022.

3.4. Re-examination procedures[8]

None

3.5. Others

None

[7] Update of SmPC sections 4.2, 4.4, 4.8 and 5.1. The package leaflet is updated accordingly
[8] Re-examination of PRAC recommendation under Article 32 of Directive 2001/83/EC

4. Signals assessment and prioritisation[9]

4.1. New signals detected from EU spontaneous reporting systems

See Annex I 14.1.

4.2. New signals detected from other sources

See Annex I 14.2.

4.3. Signals follow-up and prioritisation

4.3.1. Codeine, ibuprofen (NAP)

Applicant(s): various

PRAC Rapporteur: Rhea Fitzgerald

Scope: Signal of renal tubular acidosis and hypokalaemia

EPITT 19820 – Follow-up to June 2022

Background

For background information, see PRAC minutes June 2022.

The MAHs of the originator product(s) containing codeine/ibuprofen (Viatris and Reckitt Benckiser) replied to the request for information on the signal of renal tubular acidosis and hypokalaemia and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence from EudraVigilance and the literature, the reviews provided by the MAHs together with the Rapporteur's assessment, PRAC recommended an update of the product information for codeine/ibuprofen combination medicines to include a warning that serious clinical outcomes, including fatalities, have been reported in association with abuse and dependence with codeine/ibuprofen combinations, particularly when taken for prolonged periods at higher than recommended doses. PRAC further concluded that there is sufficient evidence to establish a causal association between codeine/ibuprofen-containing products and renal tubular acidosis and hypokalaemia, due to prolonged use of ibuprofen at higher than recommended doses. This risk is increased with the use of codeine/ibuprofen as patients may become dependent on the codeine component. Therefore, PRAC agreed that renal tubular acidosis and hypokalaemia should be added to the product information as a warning and as undesirable effects with a frequency 'not known'. In addition, PRAC agreed that the existing warning on dependence should be amended and include reference to opioid use disorder upon repeated use.

PRAC additionally recommended an amendment to the existing warning on overdose, including that prolonged use of codeine/ibuprofen combination medicines at higher than recommended doses may result in severe hypokalaemia and renal tubular acidosis.

[9] 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

Summary of recommendation(s)

- The MAHs for codeine/ibuprofen-containing products should submit to the National Competent Authorities (NCAs) of the Member States, within 60 days, a variation to amend[10] the product information.

For the full PRAC recommendation, see EMA/PRAC/781568/2022 published on 24 October 2022 on the EMA website.

PRAC agreed on a set of key elements for a direct healthcare professional communication (DHPC), including a proposed target healthcare professional audience. Further consideration is to be given at the level of the EU Member States, as deemed necessary.

PRAC also noted that there are codeine/ibuprofen-containing product(s) in the EU which are available as medicinal products not subject to medical prescription. Taking into account that the assessment of the signal of renal tubular acidosis and hypokalaemia showed that reports of adverse reactions from codeine/ibuprofen-containing products in association with prolonged use at high doses were predominantly from territories where these products are available as non-prescription medicines, PRAC considered that prescription-only medicines status would be the most effective risk minimisation measure to mitigate the harms associated with abuse and dependence of these products. Further consideration is to be given at the level of the EU Member States where these products are available without prescription.

4.3.2. Gemtuzumab ozogamicin – MYLOTARG (CAP) - EMEA/H/C/004204/SDA/005.1

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Signal of atypical haemolytic reactions

EPITT 19788 – Follow-up to June 2022

Background

For background information, see PRAC minutes June 2022.

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

Discussion

Having considered the available evidence from case reports in the literature and EudraVigilance along with the cumulative review provided by the MAH together with the Rapporteur's assessment, PRAC agreed that at present, there is insufficient evidence to establish a causal relationship between atypical haemolytic reactions and gemtuzumab ozogamicin.

Summary of recommendation(s)

- The MAH for Mylotarg (gemtuzumab ozomicin) should continue to closely monitor any new cases of atypical haemolytic reactions as part of routine safety surveillance.

[10] Update of sections 4.4, 4.8 and 4.9 of the SmPC. The package leaflet is to be updated accordingly

For the full PRAC recommendation, see EMA/PRAC/781568/2022 published on 24 October 2022 on the EMA website.

4.3.3. Rivaroxaban - RIVAROXABAN ACCORD (CAP), RIVAROXABAN MYLAN (CAP), XARELTO (CAP); NAP - EMEA/H/C/000944/SDA/051

Applicant(s): Accord Healthcare S.L.U. (Rivaroxaban Accord), Bayer AG (Xarelto), Mylan Ireland Limited (Rivaroxaban Mylan)

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of pemphigoid

EPITT 19785 – Follow-up to April 2022

Background

For background information, see PRAC minutes April 2022.

The MAH for Xarelto (rivaroxaban) replied to the request for information on the signal of pemphigoid and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence from case reports in EudraVigilance, the literature, studies along with the data submitted by the MAH together with the Rapporteur's assessment, PRAC agreed there is insufficient evidence to establish a causal relationship between treatment with rivaroxaban and pemphigoid and pemphigus at present.

Summary of recommendation(s)

- The MAHs of rivaroxaban-containing products should continue to closely monitor any new cases of pemphigoid and pemphigus as part of routine safety surveillance.

4.3.4. Selective serotonin reuptake transporter inhibitors (SSRIs): citalopram (NAP); escitalopram (NAP); fluoxetine (NAP); fluvoxamine (NAP); paroxetine (NAP); sertraline (NAP); serotonin-norepinephrine reuptake inhibitor (SNRIs): desvenlafaxine (NAP); duloxetine – CYMBALTA (CAP) - EMEA/H/C/000572/SDA/050, DULOXETINE LILLY (CAP), DULOXETINE MYLAN (CAP), DULOXETINE ZENTIVA (CAP), YENTREVE (CAP) - EMEA/H/C/000545/SDA/046; NAP; milnacipran (NAP); venlafaxine (NAP); mirtazapine (NAP); vortioxetine - BRINTELLIX (CAP) - EMEA/H/C/002717/SDA/008

Applicant(s): Eli Lilly Nederland B.V. (Cymbalta, Duloxetine Lilly, Yentreve), H. Lundbeck A/S (Brintellix), Mylan Pharmaceuticals Limited (Duloxetine Mylan), Zentiva k.s. (Duloxetine Zentiva), various

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Signal of pulmonary hypertension

EPITT 19772 – Follow-up to March 2022

Background

For background information, see PRAC minutes March 2022.

The originator/brand-leader MAHs (Pfizer, GSK, Eli Lilly, Mylan, H. Lundbeck, Almirall, Pierre Fabre, N.V. Organon) for serotonin reuptake transporter inhibitor (SSRI)-, serotonin-

norepinephrine reuptake inhibitor (SNRI)-, mirtazapine- and vortioxetine-containing products replied to the request for information on the signal of onset pulmonary hypertension (PH) or worsening of PH and the responses were assessed by the Rapporteur.

Discussion

Having considered the evidence from EudraVigilance, the literature, studies, the reviews submitted by the MAHs, together with the Rapporteur's assessment, PRAC agreed that at present, there is insufficient evidence to establish a causal association between the use of SSRIs/SNRIs, mirtazapine or vortioxetine and a new onset of pulmonary hypertension or an increased risk of disease aggravation or increased risk of mortality in patients with existing pulmonary hypertension.

Summary of recommendation(s)

- The MAHs for SSRI-, SNRI-, mirtazapine- and vortioxetine-containing products should continue to closely monitor any new cases of pulmonary hypertension as part of routine safety surveillance.

4.3.5. Temozolomide – TEMODAL (CAP) - EMEA/H/C/000229/SDA/043, TEMOMEDAC (CAP), TEMOZOLOMIDE ACCORD (CAP), TEMOZOLOMIDE HEXAL (CAP), TEMOZOLOMIDE SANDOZ (CAP), TEMOZOLOMIDE SUN (CAP), TEMOZOLOMIDE TEVA (CAP); NAP

Applicant(s): Accord Healthcare S.L.U. (Temozolomide Accord), Hexal AG (Temozolomide Hexal), medac Gesellschaft fur klinische Spezialpraparate mbH (Temomedac), Merck Sharp & Dohme B.V. (Temodal), Sandoz GmbH (Temozolomide Sandoz), Sun Pharmaceutical Industries Europe B.V. (Temozolomide Sun), Teva B.V. (Temozolomide Teva)

PRAC Rapporteur: Martin Huber

Scope: Signal of progressive multifocal leukoencephalopathy (PML)

EPITT 19814 – Follow-up to June 2022

Background

For background information, see PRAC minutes June 2022.

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

Discussion

Having considered the available evidence from EudraVigilance and the literature, the review from the MAH together with the Rapporteur's assessment, PRAC concluded that there is insufficient evidence to establish a causal relationship between temozolomide and PML at present.

Summary of recommendation(s)

- The MAHs of temozolomide-containing products should continue to closely monitor any new cases of PML as part of routine safety surveillance.

4.4. Variation procedure(s) resulting from signal evaluation

None

5. Risk management plans (RMPs)

5.1. Medicines in the pre-authorisation phase

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

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

See also Annex I 15.1.

5.1.1. Coronavirus (COVID-19) vaccine (recombinant) - EMEA/H/C/005754

Scope: Active immunisation to prevent coronavirus disease (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2 virus), in individuals 18 years of age and older

5.1.2. Etranacogene dezaparvovec - EMEA/H/C/004827, PRIME, Orphan

Applicant: CSL Behring GmbH, ATMP[11]

Scope: Treatment of adults with haemophilia B

5.1.3. Ruxolitinib - EMEA/H/C/005843

Scope: Treatment of non-segmental vitiligo

5.1.4. Tremelimumab - EMEA/H/C/004650

Scope: Treatment of adults with metastatic non-small cell lung cancer (NSCLC) with no sensitising epidermal growth factor receptor (EGFR) mutation or anaplastic lymphoma kinase (ALK) genomic tumour aberrations

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

See also Annex I 15.2.

5.2.1. Adalimumab - IDACIO (CAP) - EMEA/H/C/004475/II/0017

Applicant: Fresenius Kabi Deutschland GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of an updated RMP version 6 in order to propose the continuation of the observational registry (Rheumatoide Arthritis: Beobachtung der Biologika-Therapie (RABBIT) study#1 (study identifier: FKS0-000-RAB) and the cancellation of the observational registry (Inflammatory Bowel disease UK (IBD UK))) (study identifier: FKS0-000-IBD). In addition, the MAH took the opportunity to align the RMP with the current

[11] Advanced therapy medicinal product

approved RMP of the reference product

Background

For background information on substance(s) and indication(s) of centrally authorised product(s) identified as 'CAP', see Human medicine European public assessment report (EPAR) on the EMA website.

PRAC is evaluating a type II variation procedure for Idacio, a centrally authorised product containing adalimumab, to update the RMP to reflect the proposal of continuing the observational registry: Rheumatoide Arthritis Beobachtung der Biologika-Therapie (RABBIT) study#1 and to close the observational registry (IBD UK)[12]. PRAC is responsible for adopting an outcome based on the assessment report from the PRAC Rapporteur to be further considered at the level of CHMP, responsible for adopting an opinion on this variation.

Summary of advice

- The RMP version 6 for Idacio (adalimumab) in the context of the variation under evaluation by PRAC and CHMP is considered acceptable.
- PRAC agreed with the continuation of the observational registry RABBIT study#1 with reducing the number of targeted patients, as well as with the closure of the observational registry (IBD UK) and its removal from the RMP due to the lack of patient enrolment.

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

See also Annex I 15.3.

5.3.1. Aflibercept - EYLEA (CAP) - EMEA/H/C/002392/II/0077/G

Applicant: Bayer AG

PRAC Rapporteur: Nathalie Gault

Scope: Grouped application consisting of: 1) extension of indication to include as a paediatric indication retinopathy of prematurity (ROP). As a consequence, sections 2, 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2, 5.3 and 6.6 of the SmPC are updated. The package leaflet and the RMP (version 32.1) are updated in accordance. Separate package leaflet is proposed for the guardians of preterm babies; 2) addition of a stand-alone paediatric dosing device, which will be CE marked and cross-labelled to the EU product information

Background

For background information on substance(s) and indication(s) of centrally authorised product(s) identified as 'CAP', see Human medicine European public assessment report (EPAR) on the EMA website.

CHMP is evaluating a type II variation for Eylea, a centrally authorised product containing aflibercept, in order to add ROP as a paediatric indication and to add a stand-alone paediatric dosing device, which will be CE marked and cross-labelled to the EU product information. PRAC is responsible for providing advice to CHMP on the necessary updates to the RMP to support this variation. For further background, see PRAC minutes February

[12] Studies to contribute to the overall evidence base in support of adalimumab, in particular the estimation of incidence rates of adverse events of special interest for adalimumab

2022.

Summary of advice

- The RMP version 32.3 for Eylea (aflibercept) in the context of the variation procedure under evaluation by PRAC and CHMP is considered acceptable.
- PRAC endorsed the addition of 'long-term safety of aflibercept in preterm infants with ROP' as missing information and supported the request for 2-, 3- and 4-year interim data for the ongoing extension study (FIREFLEYE NEXT) listed as a category 3 study to assess the long-term outcomes of subjects previously diagnosed with ROP who were treated in the completed study FIREFLEYE[13]. PRAC reviewed the key elements for the educational materials and concluded that a single set of educational material must be used for both the adult and paediatric populations and that it should reflect the mandatory use and the need of priming of the paediatric dosing device properly in the ROP indication.

5.3.2. Dapagliflozin - EDISTRIDE (CAP) - EMEA/H/C/004161/WS2318/0056/G; FORXIGA (CAP) - EMEA/H/C/002322/WS2318/0077/G; dapagliflozin, metformin - EBYMECT (CAP) - EMEA/H/C/004162/WS2318/0058/G; XIGDUO (CAP) - EMEA/H/C/002672/WS2318/0068/G; saxagliptin, dapagliflozin - QTERN (CAP) - EMEA/H/C/004057/WS2318/0036/G

Applicant: AstraZeneca AB

PRAC Rapporteur: Mari Thorn

Scope: Grouped application consisting of: 1) update of section 4.4 of the SmPC in order to remove the potential risk of lower limb amputation (LLA) based on studies D1690C00018, D1690C00019, DECLARE, DAPA-HF, DAPA-CKD, and DELIVER. The package leaflets are updated accordingly. In addition, the MAH took the opportunity to introduce minor editorial changes to the product information and to align it with the latest QRD template. In addition, the MAH took the opportunity to update the list of local representatives in the Qtern (saxagliptin/dapagliflozin) package leaflet; 2) submission of an updated RMP in order to align the RMPs for Xigduo, Ebymect and Qtern to the recently approved RMP updates for Forxiga (dapagliflozin); 3) update of section 4.5 of the SmPC to include a further product information harmonisation to address the consideration raised during the ongoing dapagliflozin procedure PSUSA/00010029/202110. The RMP for Forxiga (dapagliflozin) and Edistride (dapaliflozn) version 28 has been submitted. The RMP Qtern (saxagliptin/dapagliflozin) version 7 has been submitted. The RMP for Xigduo (dapagliflozin/metformin) and Ebymect (dapagliflozin/metformin) version 13 has been submitted

Background

For background information on substance(s) and indication(s) of centrally authorised product(s) identified as 'CAP', see Human medicine European public assessment report (EPAR) on the EMA website.

CHMP is evaluating a type II work-sharing variation for Edistride (dapagliflozin), Forxiga (dapagliflozin), Ebymect (dapagliflozin/metformin), Xigduo (dapagliflozin/metformin) and Qtern (saxagliptin/dapagliflozin), centrally authorised products containing dapagliflozin

[13] An open-label, randomised, two-arm, controlled study to assess the efficacy, safety, and tolerability of intravitreal (IVT) aflibercept compared to laser photocoagulation in patients with ROP

alone or in combination, in order to remove the potential risk of LLA based on a meta-analysis of studies D1690C00018, D1690C00019, DECLARE, DAPA-HF, DAPA-CKD, and DELIVER and to align the RMPs for the fixed dose combination-medicines Xigduo, Ebymect and Qtern, to the recently approved RMP updates for Forxiga (dapagliflozin). PRAC is responsible for providing advice to CHMP on the necessary updates to the RMP to support this variation.

Summary of advice

- The RMPs (version 28 for Forxiga and Edistride, version 7 for Qtern, version 13 for Xigduo and Ebymect) in the context of the work-sharing variation procedure under evaluation by PRAC and CHMP are considered acceptable.
- PRAC agreed that the safety concern of LLA could be removed as an important potential risk from the RMP since LLA has been sufficiently characterised over the post-marketing experience and no further additional pharmacovigilance activities are planned to address this risk. However, PRAC supported that the existing warning in the product information regarding LLA is maintained and complemented with data from the study meta-analysis. In addition, PRAC agreed with the removal of 'urinary tract infection' and 'renal impairment' as important identified risks and 'liver injury' as an important potential risk from the RMP for Xigduo/Ebymect, in line with the RMPs for Forxiga/Edistride.

5.3.3. Ibrutinib - IMBRUVICA (CAP) - EMEA/H/C/003791/II/0075

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Update of section 4.2 of the SmPC to incorporate information specific for dose modifications for non-cardiac events and events of cardiac failure or cardiac arrhythmias events based on data pooled from clinical studies which included 4 phase 2 (PCYC-1102-CA, PCYC-1104-CA, PCYC-1118E, PCYC-1142-CA) and 8 phase 3 studies (PCYC-1112-CA, PCYC-1115-CA, CLL3001, PCYC-1130-CA, MCL3001, PCYC-1127-CA, CLL3011, and MCL3002). The RMP (version 20.2) is updated accordingly

Background

For background information on substance(s) and indication(s) of centrally authorised product(s) identified as 'CAP', see Human medicine European public assessment report (EPAR) on the EMA website.

CHMP is evaluating a type II variation for Imbruvica, a centrally authorised product containing ibrutinib, to update the product information to include specific information for dose modifications for non-cardiac events and events of cardiac failure or cardiac arrhythmias events. PRAC is responsible for providing advice to CHMP on the necessary updates to the RMP to support this variation.

Summary of advice

- The RMP for Imbruvica (ibrutinib) in the context of type II variation under evaluation by PRAC and CHMP is considered acceptable.
- PRAC agreed on the content of a direct healthcare professional communication (DHPC) along with a communication plan for its distribution to communicate to healthcare providers on the updated dose modification scheme and information on cardiac toxicity.

6. Periodic safety update reports (PSURs)

See also Annex I 16.1.1.

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

6.1.1. Apalutamide - ERLEADA (CAP) - PSUSA/00010745/202202

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

Background

For background information on substance(s) and indication(s) of centrally authorised product(s) identified as 'CAP', see Human medicine European public assessment report (EPAR) on the EMA website.

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Erleada, a centrally authorised medicine containing apalutamide 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 Erleada (apalutamide) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the warning on severe cutaneous adverse reactions (SCARs) and to add drug reaction with eosinophilia and systemic symptoms (DRESS) as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[14].
- In the next PSUR, the MAH should provide an updated cumulative review of cases of interstitial lung disease, as well as a discussion on cases of embolic and thrombotic events focusing on clinical trial data. The MAH should also provide specific data regarding the pharmacokinetics of rivaroxaban and apixaban along with all related cases that could be interpreted as a drug-drug interaction with apalutamide regardless of the occurrence of transient ischemic attack/stroke. The MAH should include a proposal to update the product information as warranted.

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

6.1.2. Bevacizumab - ABEVMY (CAP); ALYMSYS (CAP); AVASTIN (CAP); AYBINTIO (CAP); MVASI (CAP); ONBEVZI (CAP); OYAVAS (CAP); ZIRABEV (CAP) - PSUSA/00000403/202202

Applicants: Amgen Technology (Ireland) Unlimited Company (Mvasi), Mabxience Research

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

SL (Alymsys), Mylan IRE Healthcare Limited (Abevmy), Pfizer Europe MA EEIG (Zirabev), Roche Registration GmbH (Avastin), Samsung Bioepis NL B.V. (Aybintio, Onbevzi), STADA Arzneimittel AG (Oyavas)

PRAC Rapporteur: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

Background

For background information on substance(s) and indication(s) of centrally authorised product(s) identified as 'CAP', see Human medicine European public assessment report (EPAR) on the EMA website.

Based on the assessment of the PSURs, PRAC reviewed the benefit-risk balance of Abevmy, Alymsys, Avastin, Aybintio, Mvasi, Onbevzi, Oyavas and Zirabev, centrally authorised medicines containing bevacizumab and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Abevmy, Alymsys, Avastin, Aybintio, Mvasi, Onbevzi, Oyavas and Zirabev (bevacizumab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add anaphylactic shock to the existing warning on hypersensitivity reactions and as an undesirable effect with a frequency 'rare'. The frequency of hypersensitivity and infusion reactions as undesirable effects should be changed from 'not known' to 'common'. Therefore, the current terms of the marketing authorisation(s) should be varied[15].
- In the next PSUR, the MAHs should provide a detailed review on the risk of renal hyaline occlusive glomerular microangiopathy in cancer patients. In addition, the MAHs should provide cumulative reviews on vasculitis and on systemic adverse drug reactions (ADRs) following intraocular administration in neonates including hypertension and haemorrhage. The MAHs should propose to update the product information as warranted.

The frequency of PSUR submission should be revised from yearly to three-yearly and the next PSUR should be submitted to 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.

6.1.3. Coronavirus (COVID-19) vaccine (Ad26.COV2-S, recombinant) - JCOVDEN (CAP) - PSUSA/00010916/202202

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

Background

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

For background information on substance(s) and indication(s) of centrally authorised product(s) identified as 'CAP', see Human medicine European public assessment report (EPAR) on the EMA website.

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Jcovden, a centrally authorised coronavirus (COVID-19) vaccine (Ad26.COV2-S [recombinant]) 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 Jcovden (coronavirus (COVID-19) vaccine (Ad26.COV2-S [recombinant])) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add facial paralysis including Bell's palsy as an undesirable effect with a frequency 'rare'. Therefore, the current terms of the marketing authorisation(s) should be varied[16].
- In the next PSUR, the MAH should provide an updated cumulative review of cases of neuralgic amyotrophy.

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. Esketamine[17] - SPRAVATO (CAP) - PSUSA/00010825/202203

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

Background

For background information on substance(s) and indication(s) of centrally authorised product(s) identified as 'CAP', see Human medicine European public assessment report (EPAR) on the EMA website.

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Spravato, a centrally authorised medicine containing esketamine 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 Spravato (esketamine) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the existing warning on respiratory depression and to add respiratory depression as an undesirable effect with a frequency 'rare'. Therefore, the current terms of the marketing authorisation(s) should be varied[18].

[16] Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion.
[17] Centrally authorised product(s) only
[18] Update of SmPC sections 4.4. and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion.

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

6.1.5. Isatuximab - SARCLISA (CAP) - PSUSA/00010851/202203

Applicant: sanofi-aventis groupe

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

Background

For background information on substance(s) and indication(s) of centrally authorised product(s) identified as 'CAP', see Human medicine European public assessment report (EPAR) on the EMA website.

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Sarclisa, a centrally authorised medicine containing isatuximab 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 Sarclisa (isatuximab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add tumour lysis syndrome (TLS) as a warning. Therefore, the current terms of the marketing authorisation(s) should be varied[19].
- In the next PSUR, the MAH should provide a cumulative review of cases of thrombocytopenia. The MAH should continue to monitor cases of hepatitis B virus (HBV) reactivation and of tumour lysis syndrome and assess any new relevant data accordingly. The MAH should propose to update the product information as warranted.

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

6.1.6. Lonapegsomatropin - SKYTROFA (CAP) - PSUSA/00010969/202202 (with RMP)

Applicant: Ascendis Pharma Endocrinology Division A/S

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

For background information on substance(s) and indication(s) of centrally authorised product(s) identified as 'CAP', see Human medicine European public assessment report (EPAR) on the EMA website.

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

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Skytrofa, a centrally authorised medicine containing lonapegsomatropin 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 Skytrofa (lonapegsomatropin) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add anaphylactic reactions including angioedema as a warning and as an undesirable effect with a frequency 'uncommon'. Therefore, the current terms of the marketing authorisation(s) should be varied[20].
- In the next PSUR, the MAH should provide a detailed discussion on medication errors with the injection device, including an analysis of their patterns in light of those observed in the US patient support programme (PSP-US-0002). The MAH should include a discussion on the appropriateness of the existing risk minimisation measures on medication errors.

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. Ribociclib - KISQALI (CAP) - PSUSA/00010633/202203

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Evaluation of a PSUSA procedure

Background

For background information on substance(s) and indication(s) of centrally authorised product(s) identified as 'CAP', see Human medicine European public assessment report (EPAR) on the EMA website.

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Kisqali, a centrally authorised medicine containing ribociclib 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 Kisqali (ribociclib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the existing warning on interstitial lung disease (ILD)/pneumonitis and to add ILD/pneumonitis as an undesirable effect with a frequency 'common'. Therefore, the current terms of the marketing authorisation(s) should be varied[21].

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

- In the next PSUR, the MAH should provide a cumulative review on venous thromboembolic events (VTE), considering also cases of deep vein thrombosis (DVT), pulmonary embolism, cerebral venous sinus thrombosis, subclavian, axillary vein thrombosis, DVT inferior vena cava and pelvic venous thrombosis. In addition, the MAH should provide a cumulative review of cornea verticillata (keratitis). Finally, the MAH should propose an update of the product information or other risk minimisation measures as warranted.

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

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

See Annex I 16.2.

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

See also Annex I 16.3.

6.3.1. Carboplatin (NAP) - PSUSA/00000559/202201

Applicant(s): various

PRAC Lead: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

Background

Carboplatin is an antineoplastic agent indicated for the treatment of ovarian carcinoma including second-line/palliative treatment in patients who have previously received cisplatin-containing regimens, small cell lung cancer, cervical cancer, and head and neck cancer.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing carboplatin 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 carboplatin-containing product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add Kounis syndrome 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[22].

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

- In the next PSUR, the MAHs should continue monitoring cases of toxic epidermal necrolysis (TEN), as well as data regarding interaction between carboplatin, pemetrexed, flucytosine and olaparib.

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

6.3.2. Dorzolamide (NAP) - PSUSA/00003168/202202

Applicant(s): various

PRAC Lead: Nathalie Gault

Scope: Evaluation of a PSUSA procedure

Background

Dorzolamide is a potent inhibitor of human carbonic anhydrase II in the ciliary processes of the eye. It is indicated for the treatment of elevated intra-ocular pressure in patients with ocular hypertension, open-angle glaucoma, pseudo-exfoliative glaucoma and as adjunctive therapy to beta-blockers, or as monotherapy in patients unresponsive to beta-blockers or in whom betablockers are contraindicated. It is also indicated in adults with other secondary open-angle glaucomas and in paediatric glaucomas as adjunctive therapy to beta-blockers, as well as in monotherapy.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing dorzolamide 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 dorzolamide-containing product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add tachycardia and hypertension as undesirable effects with a frequency 'unknown'. In addition, the method of administration should be amended in order to mention the need of nasolacrimal occlusion to limit dorzolamide systemic absorption. Therefore, the current terms of the marketing authorisation(s) should be varied[23].
- In the next PSUR, the MAHs should provide cumulative reviews of cases of photophobia, urolithiasis in patients with history of renal calculi, choroidal detachment concomitant with ocular hypotony, corneal disorders and concomitant use with oral carbonic anhydrase inhibitors. The MAHs should also propose to update the product information as warranted.

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

[23] Update of SmPC sections 4.2 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position.

PRAC considered that the risks of tachycardia and hypertension, as well as the need of nasolacrimal occlusion to limit absorption of dorzolamide into the general circulation in patients with glaucoma are also relevant for dorzolamide-containing products in fixed-dose combinations. Further consideration is to be given at the level of CMDh.

6.3.3. Gabapentin (NAP) - PSUSA/00001499/202202

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

Gabapentin is an anticonvulsant indicated as monotherapy for the treatment of partial seizures with and without secondary generalisation in adults and adolescents aged 12 years and above, as adjunctive therapy for the treatment of partial seizures with and without secondary generalisation in adults and children aged 6 years and above, as well as for the treatment of peripheral neuropathic pain such as painful diabetic neuropathy and post-herpetic neuralgia in adults.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing gabapentin 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 gabapentin-containing product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to strengthen the existing warning on abuse and dependence, and to add drug dependence as an undesirable effect with a frequency 'not known'. In addition, the product information should be updated to add withdrawal symptoms as a new warning and the information relating to the existing undesirable effect further expanded. Moreover, the existing warning on drug rash with eosinophilia and systemic symptoms (DRESS) should be replaced by a warning on severe cutaneous adverse reactions (SCARs) to include also toxic epidermal necrolysis (TEN). TEN should be added as an undesirable effect with a frequency 'not known'. Finally, the product information should be updated to add neonatal withdrawal syndrome as a warning. Therefore, the current terms of the marketing authorisation(s) should be varied[24].
- In the next PSUR, the MAHs should provide cumulative reviews of cases of Parkinson-like events, cases of glaucoma, as well as of cases related to the risk of suicidality. In addition, an evaluation of dose-dependency of withdrawal symptoms should be provided. Finally, the MAHs should propose to update the product information as warranted.

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

[24] Update of SmPC sections 4.4, 4.6 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position.

6.3.4. Ketoprofen[25] (NAP) - PSUSA/00009205/202201

Applicant(s): various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

Background

Ketoprofen is a nonsteroidal anti-inflammatory drug (NSAID) indicated, for topical use, for the treatment of signs and symptoms of mild to moderate local pain associated with muscle and/or joints injuries (e.g., sport injuries).

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing ketoprofen for topical use 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 ketoprofen-containing product(s) for topical use in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add the use during the last trimester of pregnancy as a contraindication, as well as to amend the product information on pregnancy with regards to the use during the first and second trimesters of pregnancy. Therefore, the current terms of the marketing authorisation(s) should be varied[26].
- In the next PSUR, the MAHs should provide a cumulative review of cases of drug reaction with eosinophilia and systemic symptoms (DRESS) together with a discussion on the relevance of data from systemic exposure to ketoprofen-containing product(s) for topical use.

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

6.3.5. Levothyroxine (NAP) - PSUSA/00001860/202201

Applicant(s): various

PRAC Lead: Nathalie Gault

Scope: Evaluation of a PSUSA procedure

Background

Levothyroxine is a synthetic thyroid hormone indicated in adults and children for the treatment of a number of conditions associated with hypothyroidism, as well as in suppression therapy for thyroid carcinoma and for diagnostic use for thyroid suppression testing.

[25] For topical use only
[26] Update of SmPC sections 4.3 and 4.6. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing levothyroxine 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 levothyroxine-containing product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add biotin interference on thyroid function tests as a warning, as well as to add drug-drug interactions between levothyroxine and St. John's wort (*Hypericum perforatum L.),* and between levothyroxine and proton pump inhibitors (PPIs). Therefore, the current terms of the marketing authorisation(s) should be varied[27].

The frequency of PSUR submission should be revised from three-yearly to five-yearly and the next PSUR should be submitted to 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.

PRAC agreed on a set of key elements for further communication on the risk of biotin interference with thyroid immunoassays. This includes a proposed target healthcare professional audience. Further consideration is to be given at the levels of the EU Member States, as deemed necessary.

PRAC also considered that drug-drug interactions between levothyroxine and St John's wort and between levothyroxine and PPIs, as well as biotin interference with laboratory tests in patients with hypothyroidism are relevant for levothyroxine-containing product(s) as fixed-dose combinations. Further consideration is to be given at the level of CMDh.

6.3.6. Lisdexamfetamine (NAP) - PSUSA/00010289/202202

Applicant(s): various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

Background

Lisdexamfetamine is a stimulant prodrug of dextroamphetamine, indicated as part of a comprehensive treatment programme for attention deficit/hyperactivity disorder (ADHD) in adults and in children aged 6 years and over when response to previous methylphenidate treatment is considered clinically inadequate.

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

Summary of recommendation(s) and conclusions

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

- Based on the review of the data on safety and efficacy, the benefit-risk balance of lisdexamfetamine-containing 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 Takeda Pharmaceuticals/Shire Pharmaceuticals should provide cumulative reviews of cases of alopecia and of cases of suicidality. The MAHs should propose to update the product information as warranted.

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

PRAC agreed that the signals of intestinal ischaemia, increased bleeding tendency and vasoconstriction/vasospasm need to be further assessed. Further consideration is to be given at the level of CMDh.

6.3.7. Mesalazine (NAP) - PSUSA/00001990/202202

Applicant(s): various

PRAC Lead: Marie Louise Schougaard Christiansen

Scope: Evaluation of a PSUSA procedure

Background

Mesalazine is an intestinal anti-inflammatory agent indicated for the treatment of inflammatory bowel disease, including ulcerative colitis (UC), Crohn's disease and chronic non-classifiable inflammatory bowel disease.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing mesalazine 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 mesalazine-containing product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add a warning on urine discolouration when it comes in contact with sodium hypochlorite bleach and to add drug reaction with eosinophilia and systemic symptoms (DRESS) as a warning and as undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[28].
- In the next PSUR, the MAHs should provide cumulative reviews of cases of benign intracranial hypertension, maternal mesalazine-induced neonatal gastrointestinal bleeding, pericardial effusion as well as of eosinophilia and eosinophil count increase. The MAHs should propose to update the product information as warranted.

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

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.

6.3.8. Mesterolone (NAP) - PSUSA/00010551/202201

Applicant(s): various

PRAC Lead: Melinda Palfi

Scope: Evaluation of a PSUSA procedure

Background

Mesterolone is a derivative of 5α-dihydrotestosterone indicated for the treatment of conditions caused by deficient endogenous androgen production.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing mesterolone 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 mesterolone-containing product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the existing warning on drug abuse and dependence. Therefore, the current terms of the marketing authorisation(s) should be varied[29].

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

6.4. Follow-up to PSUR/PSUSA procedures

See Annex I 16.4.

6.5. Variation procedure(s) resulting from PSUSA evaluation

See Annex I 16.5.

6.6. Expedited summary safety reviews[30]

See also Annex I 16.6.

6.6.1. Coronavirus (COVID-19) vaccine (recombinant, adjuvanted) - NUVAXOVID (CAP) - EMEA/H/C/005808/MEA 014.6

Applicant: Novavax CZ, a.s.

[29] Update of SmPC section 4.4. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position.
[30] Submission of expedited summary safety reports for review in addition to the requirements for submission of PSUR(s) falling within the pandemic period and requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Seventh expedited summary safety report (SSR) for Nuvaxovid (COVID-19 vaccine (recombinant, adjuvanted)) during the coronavirus disease (COVID-19) pandemic

Background

Coronavirus (COVID-19) vaccine (recombinant, adjuvanted) is composed of purified full-length severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) recombinant spike (S) protein that is stabilised in its prefusion conformation. It is indicated, as Nuvaxovid, for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older.

PRAC assessed the seventh expedited SSR for the safety monitoring of Nuvaxovid (COVID-19 vaccine (recombinant, adjuvanted)). At the plenary meeting, PRAC adopted its conclusions.

Summary of advice/conclusion(s)

- PRAC agreed that the safety profile of the Nuvaxovid (COVID-19 vaccine (recombinant, adjuvanted)) is relatively well characterised, although long-term safety remains insufficiently documented. PRAC also agreed that there are no substantial issues that need to be evaluated promptly in the upcoming SSR.
- The SSR frequency for Nuvaxovid (Coronavirus (COVID-19) vaccine (recombinant, adjuvanted)) should be revised from monthly to bimonthly.

7. Post-authorisation safety studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)[31]

See also Annex I 17.1.

7.1.1. Ciltacabtagene autoleucel – CARVYKTI (CAP) - EMEA/H/C/PSP/S/0100

Applicant: Janssen-Cilag International NV, ATMP[32]

PRAC Rapporteur: Jo Robays

Scope: Protocol for study 68284528MMY4004: an observational PASS to evaluate the safety of multiple myeloma patients treated with ciltacabtagene autoleucel

Background

For background information on substance(s) and indication(s) of centrally authorised product(s) identified as 'CAP', see Human medicine European public assessment report (EPAR) on the EMA website.

In order to fulfil the specific obligation to conduct a PASS (Annex II-E) imposed in the marketing authorisation(s) of Carvykti (ciltacabtagene autoleucel), the MAH Janssen-Cilag International NV submitted to EMA protocol version 7.0 for a study entitled: 'a post-authorisation safety study to evaluate the safety of multiple myeloma patients treated with

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

ciltacabtagene autoleucel' for review by PRAC. PRAC is responsible for evaluating the PASS protocol.17.2.

Endorsement/Refusal of the protocol

- Having considered the draft protocol version 7.0 in accordance with Article 107n of Directive 2001/83/EC, PRAC agreed that the PASS is non-interventional and endorsed the protocol.

7.1.2. Ciltacabtagene autoleucel - CARVYKTI (CAP) - EMEA/H/C/PSP/S/0101

Applicant: Janssen-Cilag International NV, ATMP[33]

PRAC Rapporteur: Jo Robays

Scope: Protocol for study 68284528MMY4009: an observational PASS to evaluate the safety of multiple myeloma patients treated with ciltacabtagene autoleucel

Background

For background information on substance(s) and indication(s) of centrally authorised product(s) identified as 'CAP', see Human medicine European public assessment report (EPAR) on the EMA website.

In order to fulfil the specific obligation to conduct a PASS (Annex II-E) imposed in the marketing authorisation(s) of Carvykti (ciltacabtagene autoleucel), the MAH Janssen-Cilag International NV submitted to EMA protocol version 2.0 for a study entitled: 'a post-authorisation safety study to evaluate the safety of multiple myeloma patients treated with ciltacabtagene autoleucel' for review by PRAC. PRAC is responsible for evaluating the PASS protocol.

Endorsement/Refusal of the protocol

- Having considered the draft protocol version 2.0 in accordance with Article 107n of Directive 2001/83/EC, PRAC agreed that the PASS is non-interventional and endorsed the protocol.

7.2. Protocols of PASS non-imposed in the marketing authorisation(s)[34]

See also Annex I 17.2.

7.2.1. Fenofibrate, simvastatin - CHOLIB (CAP) - EMEA/H/C/002559/MEA 002.8

Applicant: Mylan IRE Healthcare Limited

PRAC Rapporteur: Maia Uusküla

Scope: Substantial amendment to a protocol previously agreed in September 2017 (MEA 002.6) for study NCEPPEUPASS15741 (listed as a category 3 study in the RMP): assessment of the clinical practice regarding concomitant use of fenofibrate and simvastatin both as free and fixed combination - a European PASS

Background

[33] Advanced therapy medicinal product
[34] 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

For background information on substance(s) and indication(s) of centrally authorised product(s) identified as 'CAP', see Human medicine European public assessment report (EPAR) on the EMA website.

As part of the RMP for Cholib (fenofibrate/simvastatin), the MAH was required to conduct a PASS to assess the clinical practice regarding concomitant use of fenofibrate and simvastatin both as free and fixed combination in order to evaluate and characterise the important potential risk of off-label use with Cholib (fenofibrate/simvastatin). The MAH submitted to EMA substantial amendments to a previously agreed protocol which were assessed by the Rapporteur. PRAC was requested to provide advice to CHMP on the amended protocol submitted by the MAH.

Summary of advice

- Based on the review of protocol and the assessment from the Rapporteur, taking into account the safety data collected and assessed as part of previous PSUSA as well as the questionable ability of the currently proposed study to provide meaningful results, PRAC considered that the PASS should be removed from the RMP. Consequently, the important potential risk of off-label use with fenofibrate/simvastatin should be removed from the RMP.

7.2.2. Insulin glargine - ABASAGLAR (CAP) - EMEA/H/C/002835/MEA 005

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Amelia Cupelli

Scope: Protocol for study F3Z-MC-B030: a post-approval safety surveillance programme to assess blood glucose data and characterise the frequency of sever hypoglycaemia in patients using a compatible software application for Tempo Pen of Abasaglar/Humalog and to contextualise findings using an appropriate population as comparator [final study report: December 2023]

Background

For background information on substance(s) and indication(s) of centrally authorised product(s) identified as 'CAP', see Human medicine European public assessment report (EPAR) on the EMA website.

As part of the RMP for Abasaglar (insulin glargine), the MAH was required to conduct a PASS in order to address 'severe hypoglycaemia, as a result of incorrect or incomplete data provided to a compatible software application' as an important potential risk for the Tempo pen presentation that may lead to dosing errors. The MAH submitted a protocol for evaluation which was assessed by the Rapporteur. PRAC was requested to provide advice to CHMP on the protocol submitted by the MAH.

Summary of advice

- Having considered the protocol for study F3Z-MC-B030, PRAC considered that the proposed design does not fulfil the study objectives and that it is unlikely that this study can be used to further characterise the risk of hypoglycaemia. Therefore, PRAC agreed that the study can be removed from the RMP. The MAH should continue to monitor cases of medication errors related to the Tempo pen in future PSUR(s).

7.2.3. Insulin lispro - HUMALOG (CAP) - EMEA/H/C/000088/MEA 035

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Mari Thorn

Scope: Protocol for study F3Z-MC-B030: a post-approval safety surveillance programme to assess blood glucose data and characterise the frequency of sever hypoglycaemia in patients using a compatible software application for Tempo Pen of Abasaglar/Humalog and to contextualise findings using an appropriate population as comparator [final study report: December 2023]

Background

For background information on substance(s) and indication(s) of centrally authorised product(s) identified as 'CAP', see Human medicine European public assessment report (EPAR) on the EMA website.

As part of the RMP for Humalog (insulin lispro), the MAH was required to conduct a PASS in order to address 'severe hypoglycaemia, as a result of incorrect or incomplete data provided to a compatible software application' as an important potential risk for the Tempo pen presentation that may lead to dosing errors. The MAH submitted a protocol for evaluation which was assessed by the Rapporteur. PRAC was requested to provide advice to CHMP on the protocol submitted by the MAH.

Summary of advice

- Having considered the protocol for study F3Z-MC-B030, PRAC considered that the proposed design does not fulfil the study objectives and that it is unlikely that this study can be used to further characterise the risk of hypoglycaemia. Therefore, PRAC agreed that the study can be removed from the RMP. The MAH should continue to monitor cases of medication errors related to the Tempo pen in future PSUR(s).

7.2.4. Insulin lispro - LYUMJEV (CAP) - EMEA/H/C/005037/MEA 004

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Mari Thorn

Scope: Protocol for study F3Z-MC-B030: a post-approval safety surveillance programme to assess blood glucose data and characterise the frequency of sever hypoglycaemia in patients using a compatible software application for Tempo Pen of Abasaglar/Humalog and to contextualise findings using an appropriate population as comparator [final study report: December 2023

Background

For background information on substance(s) and indication(s) of centrally authorised product(s) identified as 'CAP', see Human medicine European public assessment report (EPAR) on the EMA website.

As part of the RMP for Lyumjev (insulin lispro), the MAH was required to conduct a PASS in order to address 'severe hypoglycaemia as a result of incorrect or incomplete data provided to a compatible software application' as an important potential risk for the Tempo pen presentation that may lead to dosing errors. The MAH submitted a protocol for evaluation

which was assessed by the Rapporteur. PRAC was requested to provide advice to CHMP on the protocol submitted by the MAH.

Summary of advice

- Having considered the protocol for study F3Z-MC-B030, PRAC considered that the proposed design does not fulfil the study objectives and that it is unlikely that this study can be used to further characterise the risk of hypoglycaemia. Therefore, PRAC agreed that the study can be removed from the RMP. The MAH should continue to monitor cases of medication errors related to the Tempo pen in future PSUR(s).

7.3. Results of PASS imposed in the marketing authorisation(s)[35]

See also Annex I 17.3.

7.3.1. Aprotinin (NAP) - EMEA/H/N/PSR/S/0030

Applicant: Nordic Group BV

PRAC Rapporteur: Jean-Michel Dogné

Scope: Results of a Nordic aprotinin patient registry to record utilisation information on patients at cardiac surgery centres

Background

Aprotinin is an antifibrinolytic indicated for the prevention of excessive blood loss under certain conditions.

In line with the conclusions reached in 2013 of the referral procedure under Article 31 of Directive 2001/83/EC (EMEA/H/A-1267) conducted by CHMP for antifibrinolytics containing aprotinin, aminocaproic acid and tranexamic acid, the MAH for Trasylol (aprotinin) was required to conduct a registry in order to monitor the pattern of use of aprotinin.

The MAH for Trasylol (aprotinin) submitted to EMA the final results of the study entitled: 'Nordic Aprotinin Patient Registry (NAPaR): a multicentre, non-interventional PASS with active surveillance via patient exposure registry' enrolling patients undergoing cardiac surgery on cardiopulmonary bypass and exposed to aprotinin at all centres in EU. PRAC is responsible for issuing a recommendation on the final study results including the assessment of the MAH's responses to requests for supplementary information (RSI). For further background, see PRAC minutes April 2021 and PRAC minutes September 2021[36] and PRAC minutes February 2022.

Summary of recommendation(s) and conclusions

- Based on the review of the final report of the registry study, the MAH's responses to the RSI and the Rapporteur's assessment, PRAC considered that a further RSI is necessary before a final recommendation can be issued.
- Regarding the risk minimisation measures (RMMs), PRAC did not support the implementation of the proposed certification for prescribers. PRAC considered that the educational material for healthcare professionals (HCPs) (inclunding a multiple choice questionnaire) in printed format would be sufficient to improve the adherence to the

[35] In accordance with Article 107p-q of Directive 2001/83/EC
[36] Held 30 August – 02 September 2021

restricted indication. In addition, PRAC highlighted that learned societies should be involved in the development and distribution of the educational material. With regard to the measures to improve the effectiveness of the RMMs, PRAC did not support the study proposed by the MAH to monitor the outcomes of the RMMs with the aim to collect data on the extent and nature of off-label use following the implementation of the educational material and a direct healthcare professional communication (DHPC) as it will not provide actionable information. PRAC recommended that the monitoring and reporting of off-label use is done in the context of future PSUR(s). The MAH should provide an update to the key elements for the proposed DHPC.

- The MAH should submit responses to the RSI within 60 days to EMA. A 60 day-assessment timetable will be followed.

7.4. Results of PASS non-imposed in the marketing authorisation(s)[37]

See also Annex I 17.4.

7.4.1. Alglucosidase alfa - MYOZYME (CAP) - EMEA/H/C/000636/II/0090

Applicant: Genzyme Europe BV

PRAC Rapporteur: Nathalie Gault

Scope: Submission of the final report from non-interventional study AGLU06909/LTS13930: a prospective safety sub-registry to assess anaphylaxis and severe allergic reactions, and severe cutaneous and systemic immune complex mediated reactions with alglucosidase alfa treatment (Pompe registry report 2020 (in fulfilment of MEA 024.15 and MEA 025.15))

Background

For background information on substance(s) and indication(s) of centrally authorised product(s) identified as 'CAP', see Human medicine European public assessment report (EPAR) on the EMA website.

As stated in the RMP of Myozyme (alglucosidase alfa), the MAH submitted the final report for the non-interventional PASS Pompe safety sub-registry AGLU06909/LTS13930 to address the assessment report conclusion of the Pompe registry report 2020. The Rapporteur assessed the MAH's final study report. For further background, see PRAC minutes May 2022.

Summary of advice

- Based on the available data, the MAH's responses to the request for supplementary information (RSI) and the Rapporteur's review, PRAC considered that the ongoing variation assessing the final study report could be recommended for approval.
- PRAC agreed with the update of product information[38] to add somnolence, throat irritation and infusion site pruritus as undesirable effects with a frequency 'not known'.

[37] 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
[38] Update of sections 4.7 and 4.8 of the SmPC. The package leaflet is updated accordingly.

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

7.5.1. Ulipristal acetate - ESMYA (CAP) - EMEA/H/C/002041/MEA 026.4

Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Third annual report for an observational study using EU registries with biomarker data, as requested in the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 completed in May 2018 (EMEA/H/A-20/1460)]

Background

For background information on substance(s) and indication(s) of centrally authorised product(s) identified as 'CAP', see Human medicine European public assessment report (EPAR) on the EMA website.

As an outcome to the referral procedure under Article 20 of Regulation (EC) No 726/2004 completed in May 2018 (EMEA/H/A-20/1460) for Esmya (ulipristal acetate), the MAH had committed to perform additional pharmacovigilance activities to further characterise the risk of drug-induced liver injury (DILI) with Esmya (ulipristal acetate). The third annual report for an observational study using EU registries with biomarker data was assessed by the Rapporteur for PRAC review.

Summary of advice

- Based on the review of the PASS interim report, PRAC considered that, in view of the current patient exposure and the trend for a further decrease in exposure, it is unlikely that the observational study using EU registries with biomarker data will contribute to further characterise the risk of DILI. Therefore, PRAC agreed to remove this study, as a category 3 study, from the RMP. The MAH should monitor any new cases of DILI in the next PSUR(s).

7.5.2. Ulipristal acetate - ESMYA (CAP) - EMEA/H/C/002041/MEA 027.4

Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Third annual update for a genetic analysis (human leukocyte antigen (HLA)) study using data from EU registries with biomarker data in patients with severe drug-induced liver injury (DILI), as requested in the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 completed in May 2018 (EMEA/H/A-20/1460)

Background

For background information on substance(s) and indication(s) of centrally authorised product(s) identified as 'CAP', see Human medicine European public assessment report (EPAR) on the EMA website.

As an outcome to the referral procedure under Article 20 of Regulation (EC) No 726/2004 completed in May 2018 (EMEA/H/A-20/1460) for Esmya (ulipristal acetate), the MAH had committed to perform observational studies to further characterise the hepatic risk and to evaluate the effectiveness of the risk minimisation measures implemented. The third annual

report for a genetic analysis (human leukocyte antigen (HLA)) study using data from EU registries with biomarker data in patients with severe drug-induced liver injury (DILI) was assessed by the Rapporteur for PRAC review.

Summary of advice

- Based on the review of the PASS interim report, PRAC considered that, in view of the current patient exposure and the trend for a further decrease in exposure, it is unlikely that the genetic analysis (HLA) study using data from EU registries with biomarker data in patients with DILI will contribute to further characterise the risk of DILI. Therefore, PRAC agreed to remove this study, as a category 3 study, from the RMP. The MAH should monitor any new cases of DILI in future PSUR(s).

7.6. Others

7.6.1. Ulipristal acetate - ESMYA (CAP) - EMEA/H/C/002041/MEA 024.4

Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Third yearly report on the feasibility report for study PGL18-002: a retrospective, multi-national, comparative, non-interventional cohort study to investigate the risk of liver injury possibly associated with Esmya (ulipristal acetate) use based on data from various national electronic health record-based databases in Europe, as requested in the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 completed in 2018 (EMEA/H/A-20/1460)

Background

For background information on substance(s) and indication(s) of centrally authorised product(s) identified as 'CAP', see Human medicine European public assessment report (EPAR) on the EMA website.

As an outcome to the referral procedure under Article 20 of Regulation (EC) No 726/2004 completed in May 2018 (EMEA/H/A-20/1460) for Esmya (ulipristal acetate), the MAH had committed to perform additional pharmacovigilance activities to further characterise the risk of drug-induced liver injury (DILI) with Esmya (ulipristal acetate). The MAH submitted the third yearly report on the feasibility report for study PGL18-002, a retrospective, multinational, comparative, non-interventional cohort study to investigate the risk of liver injury possibly associated with Esmya (ulipristal acetate) based on data from various national electronic health record-based databases in Europe, for assessment by the Rapporteur. PRAC was requested to provide advice to CHMP on the report submitted by the MAH.

Summary of advice

- Having considered the updated feasibility report for study PGL18-002, PRAC agreed that, in view of the low patient exposure in the UK and the trend for a further decrease in exposure, the study is not considered feasible any longer. PRAC agreed to remove this study, as a category 3 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 CHMP or EMA

10.1. Safety related variations of the marketing authorisation

None

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

None

10.3. Other requests

None

10.4. Scientific Advice

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

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

11.1. Safety related variations of the marketing authorisation

11.1.1. Bismuth subcitrate potassium, metronidazole, tetracycline (NAP) - DE/H/2467/001/II/052

Applicant: various

PRAC Lead: Martin Huber

Scope: PRAC consultation on a type II variation (DE/H/2467/001/II/052) for Pylera (bismuth subcitrate/metronidazole/tetracycline) on the product information warning for patients with Cockayne syndrome, on request of Germany

Background

Bismuth subcitrate/metronidazole/tetracycline is a medicinal product, as Pylera, containing a combination of a mineral and two antibiotics indicated for the eradication of *Helicobacter pylori* and the prevention of relapse of peptic ulcers in patients with active or a history of *H. pylori* associated ulcers.

In the context of the evaluation of a national type II variation consisting of an update of the product information to add Cockayne syndrome (CS) as a contraindication, Germany as the reference Member State (RMS) requested a PRAC advice on its assessment.

Summary of advice

- Based on the review of the available information and the RMS assessment, PRAC agreed that the use in patients with CS should be contraindicated, as the benefit-risk balance of Pylera (bismuth subcitrate/metronidazole/tetracycline) in the indication of *H. pylori*

eradication is not favourable in this population. As a consequence, the current warning for patients with CS should be deleted.

- PRAC considered that for all the other metronidazole-containing medicines (except for external use on the skin) authorised for indications other than *H. pylori* eradication, the warning for patients with CS should be strengthened.
- Finally, PRAC agreed that there is no need for a direct healthcare professional communication (DHPC). Further consideration and action is to be given at the level of the EU Member States, as deemed necessary.

11.2. Other requests

None

12. Organisational, regulatory and methodological matters

12.1. Mandate and organisation of PRAC

12.1.1. PRAC membership

None

12.1.2. Vote by proxy

None

12.2. Coordination with EMA Scientific Committees or CMDh-v

None

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

None

12.4. Cooperation within the EU regulatory network

12.4.1. Coronavirus (COVID-19) pandemic - update

The EMA Secretariat updated 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. In addition, the EMA Secretariat provided an update on the vaccines and medicinal products to be used for the prevention and treatment of monkey pox disease.

12.4.2. PRAC and CMDh strategic review and learning meeting (SRLM) under the Czech Presidency of the European Union (EU) Council – Prague, 17 – 19 October 2022 - agenda

PRAC lead: Eva Jirsová, Jana Lukačišinová

PRAC was presented with a draft agenda for the 'PRAC strategic review and learning meeting (SRLM)', to be held jointly with the Co-ordination Group for Mutual recognition and Decentralised Procedures – Human (CMDh) on 17-19 October 2022 in Prague, Czechia, under the Czech presidency of the Council of the European Union (EU).

12.5. Cooperation with International Regulators

12.5.1. International Conference on Harmonisation (ICH) E19 - a selective approach to safety data collection in specific late-stage pre-approval or post-approval clinical trials - guideline

Following the last discussion at PRAC in May 2019 (for background, see PRAC minutes May 2019), the EMA Secretariat presented to PRAC the draft International Conference on Harmonisation (ICH) E19 guideline (step 5) following the public consultation that ended in Q3 2019. The guideline provides now internationally harmonised guidance on the use of selective safety data collection that may be applied in specific late-stage clinical trials in the pre-approval or post-approval setting. The guideline (step 5) will become effective as of March 2023.

12.6. Contacts of 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 2022 – planning update dated Q3 2022

The EMA Secretariat presented to PRAC for information a quarterly updated report on marketing authorisation applications (MAA) planned for submission (the business 'pipeline'). For previous update, see PRAC minutes April 2022.

12.9. Pharmacovigilance audits and inspections

12.9.1. Pharmacovigilance systems and their quality systems

None

12.9.2. Pharmacovigilance inspections

None

12.9.3. Pharmacovigilance audits

None

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

12.10.1. Periodic safety update reports

None

12.10.2. Granularity and Periodicity Advisory Group (GPAG)

PRAC lead: Menno van der Elst, Maia Uusküla

The EMA Secretariat presented to PRAC the GPAG recommendation on the implementation of the Union reference date (EURD) list tool in a set of EURD list entries. This set corresponds to around 1,000 entries of the list that at the time of the creation of the list were allocated long PSUR frequency (13 years) and data lock point (DLP) in 2025. PRAC members were invited to send comments in writing

12.10.3. PSURs repository

None

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

In line with the criteria for plenary presentation of updates to the EURD List adopted by PRAC in December 2021, PRAC endorsed the draft revised EURD list, version October 2022, reflecting the PRAC's comments impacting on the data lock point (DLP) and PSUR submission frequencies of the substances/combinations. 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 October 2022, the updated EURD list was adopted by the CHMP and CMDh at their October 2022 meetings and published on the EMA website, see: Home> Human Regulatory>Post-authorisation>Pharmacovigilance>Periodic safety update reports>> List of Union reference dates and frequency of submission of periodic safety update reports (PSURs)

12.11. Signal management

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

PRAC lead: Menno van der Elst

PRAC was updated on the ongoing activities and the progress from the SMART working group meeting on Methods held on 14 September 2022, including some points to consider regarding the further use of observed/expected (O/E) analysis conducted for COVID-19 vaccines, as well as the plan for the safety monitoring of the monkeypox vaccines.

12.12. Adverse drug reactions reporting and additional monitoring

12.12.1. Management and reporting of adverse reactions to medicinal products

None

12.12.2. Additional monitoring

None

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

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 accordingly, see: Home>Human Regulatory>Post-authorisation>Pharmacovigilance>Medicines under additional monitoring>List of medicines under additional monitoring

12.13. EudraVigilance database

12.13.1. Activities related to the confirmation of full functionality

None

12.14. Risk management plans and effectiveness of risk minimisations

12.14.1. Risk management systems

None

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

None

12.15. Post-authorisation safety studies (PASS)

12.15.1. Post-authorisation Safety Studies – imposed PASS

None

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

None

12.16. Community procedures

12.16.1. Referral procedures for safety reasons

None

12.17. Renewals, conditional renewals, annual reassessments

None

12.18. Risk communication and transparency

12.18.1. Public participation in pharmacovigilance

None

12.18.2. Safety communication

None

12.19. Continuous pharmacovigilance

12.19.1. Incident management

None

12.20. Impact of pharmacovigilance activities

12.20.1. Impact of EU label changes on post-referral prescribing trends and risk of long-term/persistent symptoms associated with gadolinium-based contrast agents (GBCA) exposure

The EMA Secretariat presented to PRAC the framework, timelines and proposed study objectives for a study to evaluate the impact of the EU label changes by investigating utilisation patterns of gadolinium-based contrast agents (GBCAs) authorised in the EU before and after implementation of the regulatory actions following the referral procedure dated 2017 (EMEA/H/A-31/1437) and to assess the risk of long-term/persistent symptoms associated with exposure to GBCAs in clinical practice. PRAC in principle endorsed the study's first objective, but raised concerns about the value of crude utilisation data for regulatory decision making in view of the risk minimisation measures (RMM) taken (i.e. suspension and restriction of indications for linear GBCAs but no changes to macrocyclic GBCAs) and the way how GBCAs are dispensed and used in clinical practice. A major concern was the second objective of investigating long-term/persistent symptoms associated with gadolinium exposure, which were not assessed during the 2017 referral procedure and should therefore not be combined in research under the remit of the PRAC Impact Strategy. PRAC also raised concerns whether the envisaged approach for such research – if commissioned by EMA – would be able to deliver sufficiently robust results in order to inform the need for any further regulatory action on the issue of long-term/persistent symptoms. Therefore, PRAC could not endorse the proposed study to be commissioned under EMA's framework contract and recommended instead to further assess the risk of long-term/persistent symptoms and the need for additional research (e.g. in the context of the Data Analysis and Real World Interrogation Network' (DARWIN EU®)) with the next PSUSA procedures.

12.21. Others

12.21.1. Data analysis and real-world interrogation network (DARWIN EU) – introduction of the coordination centre and next steps for real-world evidence (RWE)

The EMA Secretariat presented to PRAC the background and rationale for establishment of 'Data Analysis and Real World Interrogation Network (DARWIN EU)' coordination centre, as well as the data sources, the process for conducting studies, and the types of analyses and studies that DARWIN EU® will deliver. For further background, see PRAC minutes March 2022 and PRAC minutes June 2022.

12.21.2. Launch of EMA coordinated CHMP/PRAC requested GVP inspections in IRIS

The EMA Secretariat presented to PRAC an overview of the changes in the EMA coordinated CHMP/PRAC requested inspections process due to the launch of the IRIS tool, including IRIS access and use in this area.

13. Any other business

None

14. Annex I – Signals assessment and prioritisation[39]

14.1. New signals detected from EU spontaneous reporting systems

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

14.1.1. Enfortumab vedotin - PADCEV (CAP)

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Eva Jirsová

Scope: Signal of interstitial lung disease (ILD)

EPITT 19842 – New signal

Lead Member State(s): CZ

14.1.2. Nivolumab – OPDIVO (CAP)

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Signal of morphoea

[39] 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

EPITT 19839 – New signal

Lead Member State(s): DE

14.2. New signals detected from other sources

14.2.1. Bosutinib – BOSULIF (CAP)

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Martin Huber

Scope: Signal of interstitial lung disease (ILD)

EPITT 19843 – New signal

Lead Member State(s): DE

14.2.2. Colistimethate sodium[40] (NAP)

Applicant(s): various

PRAC Rapporteur: Adam Przybylkowski

Scope: Signal of pseudo-bartter syndrome

EPITT 19845 – New signal

Lead Member State(s): PL

14.2.3. Selpercatinib – RETSEVMO (CAP)

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Signal of hypothyroidism

EPITT 19847 – New signal

Lead Member State(s): NL

15. Annex I – Risk management plans

15.1. Medicines in the pre-authorisation phase

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

15.1.1. Dimethyl fumarate - EMEA/H/C/005950

Scope: Treatment of multiple sclerosis

[40] For intravenous use only

15.1.2. Paclitaxel - EMEA/H/C/005997

Scope: Treatment of metastatic breast cancer

15.1.3. Pegfilgrastim - EMEA/H/C/005810

Scope: Treatment of neutropenia

15.1.4. Tolvaptan - EMEA/H/C/005961

Scope: Treatment of hyponatraemia secondary to syndrome of inappropriate antidiuretic hormone secretion (SIADH)

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

As per the agreed criteria, 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. Aripiprazole - ARIPIPRAZOLE MYLAN PHARMA (CAP); NAP - EMEA/H/C/003803/WS2306/0020

Applicant(s): Mylan Pharmaceuticals Limited

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Submission of an updated RMP (version 6.0) to align the safety concerns in the RMP with the reference product. In addition, the nationally authorised products have been included in the RMP for the company

15.2.2. Caspofungin - CANCIDAS (CAP) - EMEA/H/C/000379/II/0078

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Jo Robays

Scope: Submission of an updated RMP version 4.2 in order to remove safety concerns and align it with the EU GVP Module V (Revision 2)

15.2.3. Elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil - STRIBILD (CAP) - EMEA/H/C/002574/WS2320/0120; emtricitabine, tenofovir disoproxil - TRUVADA (CAP) - EMEA/H/C/000594/WS2320/0177

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: To update Annex II and the RMP for Truvada and Stribild to version 18.1 and 14.1 to remove of the paediatric additional Risk Minimisation Measures (aRMMs) for HIV indication. In addition, the MAH took the opportunity to introduce changes to the PI

15.2.4. Fentanyl - EFFENTORA (CAP); NAP - EMEA/H/C/000833/WS2212/0060

Applicant(s): Teva B.V.

PRAC Rapporteur: Martin Huber

Scope: Submission of an updated RMP (version 5.1) in order to bring it in line with revision 2 of GVP module V on 'Risk management systems' and to implement PRAC requests arising from previous assessments as follows: 1) revision of the list of safety concerns; 2) update of the key messages of the educational materials in line with another centrally authorised product containing fentanyl (Instanyl (fentanyl)). As a result, Annex II on additional risk minimisation measures is updated accordingly

15.2.5. Fentanyl - PECFENT (CAP) - EMEA/H/C/001164/II/0054

Applicant: Kyowa Kirin Holdings B.V.

PRAC Rapporteur: Martin Huber

Scope: Submission of an updated RMP (version 8.0) in line with the outcome of the last PSUR single assessment (PSUSA) procedure (PSUSA 00001369/202004) finalised in January 2021 in order to update the key messages of the educational materials in line with Instanyl (fentanyl). As a result, Annex II-D on 'Conditions or restrictions with regard to the safe and effective use of the medicinal product' is updated accordingly. Finally, the MAH took the opportunity to bring the RMP in line with revision 2 of GVP module V on 'Risk management systems' and the product information in line with the latest quality review of documents (QRD) template (version 10.2)

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

As per the agreed criteria, 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. (1R,2S,5S)-N-((1S)-1-Cyano-2-((3s)-2-oxopyrrolidin-3-yl)ethyl)-3-((2S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido) butanoyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide, ritonavir - PAXLOVID (CAP) - EMEA/H/C/005973/II/0007

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Martin Huber

Scope: Submission of the final report from study C4671010 (listed as a category 3 study in the RMP): a phase 1, non-randomised, open label study to assess the pharmacokinetics, safety and tolerability of PF-07321332 boosted with ritonavir (Paxlovid) in adults with moderate hepatic impairment and individuals with normal hepatic function. The RMP (version 2.0) has also been submitted

15.3.2. Adalimumab - HEFIYA (CAP) - EMEA/H/C/004865/X/0036/G

Applicant: Sandoz GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Grouped application consisting of: 1) Extension application to add a new strength (80 mg/0.8 ml) of the solution for injection grouped with the following quality variations. The package leaflet and labelling are updated in accordance. The RMP (version 9.0) has also

been submitted. Additionally, the applicant takes the opportunity to include editorial changes in the pack sizes (approved (001-003) and new presentations) in Annex A to differentiate packs of pre-filled syringes with or without needle safety device; 2) other quality variations

15.3.3. Adalimumab - HYRIMOZ (CAP) - EMEA/H/C/004320/X/0036/G

Applicant: Sandoz GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Grouped application consisting of: 1) Extension application to add a new strength (80 mg/0.8 ml) of the solution for injection grouped with the following quality variations. The package leaflet and labelling are updated in accordance. The RMP (version 9.0) has also been submitted. Additionally, the applicant takes the opportunity to include editorial changes in the pack sizes (approved (001-003) and new presentations) in the List of All Authorised Presentations (Annex A) to differentiate packs of pre-filled syringes with or without needle safety device; 2) other quality variations

15.3.4. Andexanet alfa - ONDEXXYA (CAP) - EMEA/H/C/004108/II/0033

Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: Update of section 5.1 of the SmPC based on interim results from pharmacokinetic (PK)/pharmacodynamic(PD) study (listed as a specific obligation in the Annex II in order to fulfil SOB 1 and SOB 3): a PK and PK/PD analysis of intravenously administered andexanet after dosing to steady state with a factor Xa inhibitor, rivaroxaban or Apixaban, in healthy subjects and patients who have acute major bleeding. In addition, the MAH took the opportunity implement editorial changes in Annex II of the SmPC. The RMP version 3.0 has also been submitted

15.3.5. Besilesomab - SCINTIMUN (CAP) - EMEA/H/C/001045/II/0015

Applicant: CIS BIO International

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Submission of the final report from study AG-2012 (listed as a category 3 study in the RMP): a non-interventional controlled survey on the impact of Scintimun (besilesomab) administered for scintigraphic imaging on diagnostic thinking and management of patient with suspicion of peripheral osteomyelitis (in fulfilment of MEA 08.4). The RMP (version 15) is updated accordingly

15.3.6. Canagliflozin - INVOKANA (CAP) - EMEA/H/C/002649/II/0060

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Martin Huber

Scope: Submission of the final report from non-clinical studies 1 and 2, listed as category 3 studies in the RMP, in order to fulfil MEA/007.2. Nonclinical study 1 was designed to evaluate the effects of canagliflozin on ketone clearance and production; nonclinical study 2

objective is to evaluate the effects of canagliflozin on ketone clearance and production during prolonged fast. The RMP version 9.1 has also been submitted

15.3.7. Canagliflozin, metformin - VOKANAMET (CAP) - EMEA/H/C/002656/II/0064

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Menno van der Elst

Scope: Submission of the final report from non-clinical studies 1 and 2, listed as category 3 studies in the RMP in order to fulfil MEA/006.2. Nonclinical study 1 was designed to evaluate the effects of canagliflozin on ketone clearance and production; nonclinical study 2 objective is to evaluate the effects of canagliflozin on ketone clearance and production during prolonged fast. The RMP version 9.1 has also been submitted

15.3.8. Casirivimab, imdevimab - RONAPREVE (CAP) - EMEA/H/C/005814/II/0002

Applicant: Roche Registration GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension of indication to include treatment of coronavirus (COVID-19) in hospitalised patients in adults and adolescents aged 12 years and older weighing at least 40 kg. As a consequence, sections 4.2, 4.4, 4.8, 4.9, 5.1 and 5.2 of the SmPC are updated. The package leaflet, the labelling and the RMP (version 1.1) are updated in accordance

15.3.9. Cemiplimab - LIBTAYO (CAP) - EMEA/H/C/004844/II/0026

Applicant: Regeneron Ireland Designated Activity Company (DAC)

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication to include monotherapy treatment of adult patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy. 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 3.0) are updated in accordance

15.3.10. Dalbavancin - XYDALBA (CAP) - EMEA/H/C/002840/II/0043

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Rugile Pilviniene

Scope: Extension of indication to the paediatric population (aged 3 months to < 18 years) for the treatment of acute bacterial skin and skin structure infections (ABSSSI) based on the interim results from the study DUR001-306: a phase 3, multicentre, open-label, randomized, comparator controlled trial of the safety and efficacy of dalbavancin versus active comparator in paediatric subjects with ABSSSI, together with data from three phase 1 pharmacokinetic studies (A8841004, DUR001-106, and DAL-PK-02). Consequently, the sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 6.6 of the SmPC were updated. The package leaflet is updated accordingly. In addition, the applicant took the opportunity to make minor editorial amendments and to bring the product information in line with the latest quality review of documents (QRD) (version 10.2). The RMP (version 7.0) has also been submitted

15.3.11. Dolutegravir, abacavir, lamivudine - TRIUMEQ (CAP) - EMEA/H/C/002754/X/0101/G

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Martin Huber

Scope: Grouped application consisting of: 1) extension application to introduce a new pharmaceutical form associated with a new strength (5 mg/60 mg/30 mg dispersible tablet). The new presentation is indicated for the treatment of human immunodeficiency virus (HIV) infected children weighing at least 14 kg to less than 25 kg; 2) extension of indication to include treatment of human immunodeficiency virus (HIV) infected children weighing at least 25kg for the already approved film-coated tablets. As a consequence, sections 4.1, 4.2, 5.1 and 5.2 of the SmPC are updated. The package leaflet and labelling are updated in accordance. The RMP (version 19) is updated in accordance

15.3.12. Dulaglutide - TRULICITY (CAP) - EMEA/H/C/002825/II/0065

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Amelia Cupelli

Scope: Extension of indication to include treatment of type 2 diabetes mellitus (T2DM) in children and adolescents aged 10 to less than 18 years based on final results from study H9X-MC-GBGC; this is a phase 3, double-blind, randomised, multi-centre, placebo-controlled superiority trial to evaluate PK, PD, safety and efficacy of dulaglutide in children from 10 to less than 18 years of age, with an open label extension to evaluate safety. As a consequence, sections 4.1, 4.2, 4.8, 5.1, and 5.2 of the SmPC are updated. The package leaflet is updated in accordance. Version 7.1 of the RMP has also been submitted

15.3.13. Dupilumab - DUPIXENT (CAP) - EMEA/H/C/004390/II/0060

Applicant: sanofi-aventis groupe

PRAC Rapporteur: Kimmo Jaakkola

Scope: Extension of indication to include treatment of atopic dermatitis in paediatric patients from 6 months to <6 years of age based on final results from study R668-AD-1539: a phase 2/3 study investigating the pharmacokinetics, safety, and efficacy of dupilumab in patients aged ≥6 months to <6 years with moderate-to-severe atopic dermatitis. As a consequence, sections 4.1, 4.2, 4.8, 5.1, 5.2 of the SmPC are updated. The package leaflet and the RMP (version 7.0) are updated in accordance

15.3.14. Durvalumab - IMFINZI (CAP) - EMEA/H/C/004771/II/0041

Applicant: AstraZeneca AB

PRAC Rapporteur: David Olsen

Scope: Extension of indication to include first-line treatment, with durvalumab in combination with tremelimumab and platinum-based chemotherapy, of adults with metastatic non-small-cell lung carcinoma (NSCLC) with no sensitizing epidermal growth factor receptor (EGFR) mutation or anaplastic lymphoma kinase (ALK) genomic tumour aberrations, based on final results from study D419MC00004 (POSEIDON): a phase 3, randomised, multicentre, open-label, comparative global study to determine the efficacy

and safety of tremelimumab and durvalumab or durvalumab in combination with platinum based chemotherapy for first-line treatment in patients with metastatic NSCLC. 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 is updated in accordance. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet. Furthermore, the product information is brought in line with the latest quality review of documents (QRD) template (version 10.2). The RMP (version 5.1) is updated accordingly

15.3.15. Durvalumab - IMFINZI (CAP) - EMEA/H/C/004771/II/0046

Applicant: AstraZeneca AB

PRAC Rapporteur: David Olsen

Scope: Extension of indication to include Imfinzi in combination with chemotherapy for the treatment of adults with locally advanced or metastatic biliary tract cancer (BTC), based on the second interim analysis from the ongoing pivotal study D933AC00001 (TOPAZ-1): a phase III randomised, double-blind, placebo-controlled, multi-regional, international study conducted to assess the efficacy and safety of durvalumab in combination with the current standard of care Gemcitabine/Cisplatin for the first-line treatment of patients with locally advanced or metastatic BTC. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated and the package leaflet has been updated accordingly. Version 7.1 of the RMP has also been submitted

15.3.16. Elasomeran - SPIKEVAX (CAP) - EMEA/H/C/005791/II/0067

Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Extension of indication to include immunisation of paediatric individuals from 6 months through 5 years of age based on results from the study P204 (KidCove); this is a phase 2/3, two-part, open-label, dose-escalation, age de-escalation and randomised, observer-blind, placebo-controlled expansion study to evaluate the safety, tolerability, reactogenicity, and effectiveness of mRNA-1273 SARS-CoV-2 vaccine in healthy children 6 months to less than 12 years of age. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated and the package leaflet is updated in accordance. The MAH also took the opportunity to implement minor editorial changes in the product information. The submission includes a revised RMP version 4.1

15.3.17. Emicizumab - HEMLIBRA (CAP) - EMEA/H/C/004406/II/0027

Applicant: Roche Registration GmbH

PRAC Rapporteur: Amelia Cupelli

Scope: Extension of indication to include treatment of adult and paediatric patients with haemophilia A without factor VIII (FVIII) inhibitors who have mild or moderate disease for whom prophylaxis is clinically indicated. Consequently, sections 4.1, 4.8, 5.1 and 5.2 of the SmPC are updated. In addition, section 4.2 of the SmPC is updated to make clearer that the maintenance dose for Hemlibra (emicizumab) applies from week 5 of dosing. The package leaflet and the RMP (version 4.0) are updated accordingly

15.3.18. Fenfluramine - FINTEPLA (CAP) - EMEA/H/C/003933/II/0012, Orphan

Applicant: Zogenix ROI Limited

PRAC Rapporteur: Martin Huber

Scope: Extension of indication to include treatment of seizures associated with Lennox-Gastaut syndrome as an add on therapy to other anti-epileptic medicines for patients 2 years of age and older. As a consequence, sections 4.1, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 2.3) are updated accordingly

15.3.19. Fenfluramine - FINTEPLA (CAP) - EMEA/H/C/003933/II/0015, Orphan

Applicant: Zogenix ROI Limited

PRAC Rapporteur: Martin Huber

Scope: Update of sections 4.2 and 5.2 of the SmPC to update the safety information based on final results from study ZX008-1903 listed as a category 3 study in the RMP: a phase 1, open-label, single-dose study to evaluate the safety, tolerability, and pharmacokinetics of ZX008 (fenfluramine hydrochloride) in subjects with varying degrees of hepatic impairment. The primary objective of this study was to compare the pharmacokinetics (PK) of a single dose of ZX008 (fenfluramine hydrochloride) in subjects with varying degrees of hepatic impairment with that of healthy matched control subjects. The RMP (version 2.7) was updated accordingly

15.3.20. Filgotinib - JYSELECA (CAP) - EMEA/H/C/005113/II/0018

Applicant: Galapagos N.V.

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Update of sections 4.4, 4.6 and 5.1 of the SmPC in order to update information on fertility based on interim results from studies GLPG0634-CL-227 (MANTA Ray) and GS-US-418-4279 (MANTA) listed as a category 3 study in the RMP. The package leaflet and Annex II are updated accordingly. The RMP version 4.1 has also been submitted

15.3.21. Givosiran - GIVLAARI (CAP) - EMEA/H/C/004775/II/0011/G, Orphan

Applicant: Alnylam Netherlands B.V.

PRAC Rapporteur: Martin Huber

Scope: Grouped application consisting of: 1) Update of section 5.3 of the SmPC based on final results from study AS1-GLP18-007 listed as a category 3 study in the RMP: a 104-week subcutaneous injection carcinogenicity study in rats; 2) Update of section 5.3 of the SmPC based on final results from study AS1-GLP18-004: a 26-week subcutaneous injection carcinogenicity study in mice. The RMP version 2.1 has also been submitted. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet

15.3.22. Givosiran - GIVLAARI (CAP) - EMEA/H/C/004775/II/0013/G, Orphan

Applicant: Alnylam Netherlands B.V.

PRAC Rapporteur: Martin Huber

Scope: Submission of the final reports from studies ALN-AS1-003 (Study 003) and ALN-AS1-002 (Study 002) listed as a category 3 studies in the RMP. Study 003 is a phase 3 randomised, double-blind, placebo-controlled multicentre study with an open-label extension to evaluate the efficacy and safety of givosiran in patients with acute hepatic porphyrias, while Study 002 is a multicentre, open-label extension study to evaluate the long-term safety and clinical activity of subcutaneously administered ALN AS1 in patients with acute intermittent porphyria who have completed a previous clinical study with ALN-AS1. The RMP version 2.2 has also been submitted

15.3.23. Ibrutinib - IMBRUVICA (CAP) - EMEA/H/C/003791/II/0073

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Extension of indication to include treatment with Imbruvica (ibrutinib) in combination with bendamustine and rituximab (BR) of adult patients with previously untreated mantle cell lymphoma (MCL) who are unsuitable for autologous stem cell transplantation, based on final results from study PCI-32765MCL3002 (SHINE) (listed as a category 3 study in the RMP): a randomized, double-blind, placebo-controlled phase 3 study of ibrutinib in combination with BR in subjects with newly diagnosed MCL. 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 19.1) are updated in accordance

15.3.24. Lenvatinib - KISPLYX (CAP) - EMEA/H/C/004224/II/0052

Applicant: Eisai GmbH

PRAC Rapporteur: David Olsen

Scope: Update of section 4.8 of the SmPC based on pooled safety data including results of Study 307, an ongoing, multicentre, randomised, open-label study that is being conducted to compare the efficacy and safety of lenvatinib in combination with everolimus or pembrolizumab versus sunitinib as first-line (1L) treatment in adults with advanced renal cell carcinoma (RCC). The provision of the clinical study report (CSR) addresses the post-authorisation measure MEA/FSR 009.3. The package leaflet is updated accordingly. An updated RMP version 15.0 has been submitted

15.3.25. Lumacaftor, ivacaftor - ORKAMBI (CAP) - EMEA/H/C/003954/X/0078/G

Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Grouped application consisting of: 1) Extension application to add a new strength of 75 mg of lumacaftor and 94 mg of ivacaftor fixed dose combination granules; 2) Extension of indication to include treatment of cystic fibrosis for children aged 1 to less than 2 years old of age who are homozygous for the F508del mutation in the CFTR gene, based on final results from study 122, a 2-part study of CF subjects 1 to <2 years of age homozygous for F508del. As a consequence, sections 4.1, 4.2, 4.5, 4.6, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet is updated in accordance. Version 11.2 of the RMP has also

been submitted

15.3.26. Olaparib - LYNPARZA (CAP) - EMEA/H/C/003726/II/0053

Applicant: AstraZeneca AB

PRAC Rapporteur: Amelia Cupelli

Scope: Extension of indication to include treatment of adults with metastatic castration resistant prostate cancer (mCRPC) with olaparib in combination with abiraterone and prednisone or prednisolone, based on the results of the pivotal study D081SC00001 (PROpel study): a phase 3, randomised, double-blind, placebo-controlled, multicentre study evaluating olaparib vs placebo in combination with abiraterone as first line treatment for men with mCRPC, and supportive evidence from study D081DC00008 (study 8): a randomised, double-blind, placebo-controlled, multicentre phase 2 study to compare the efficacy, safety and tolerability of olaparib versus placebo when given in addition to abiraterone treatment in patients with mCRPC who have received prior chemotherapy containing docetaxel. Consequently, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC for Lynparza (olaparib) tablets are updated. In addition, sections 4.4 and 4.8 of the SmPC for Lynparza (olaparib) hard capsules are revised based on the updated safety data analysis. The package leaflet and the RMP (version 24) are updated accordingly

15.3.27. Peginterferon alfa-2a - PEGASYS (CAP) - EMEA/H/C/000395/II/0112

Applicant: Zr Pharma& GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of section 4.8 of the SmPC in order to include information on post-treatment recovery in growth based on final results from study YV25718 listed as a category 3 study in the RMP; this is a Phase 3b parallel group, open label study of pegylated interferon alfa-2a monotherapy (PEG-IFN, RO0258310) compared to untreated control in children with HBeAg-Positive Chronic Hepatitis B in the immune active phase. The RMP version 9.1 has also been submitted. In addition, the MAH took the opportunity to implement editorial changes in the package leaflet

15.3.28. Pembrolizumab - KEYTRUDA (CAP) - EMEA/H/C/003820/II/0121

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication to include Keytruda as monotherapy for the adjuvant treatment of adults with stage IB (T2a ≥ 4 cm), II or IIIA non-small cell lung carcinoma (NSCLC) who have undergone complete resection, based on study KEYNOTE-091: an ongoing phase 3, randomized, triple-blinded, placebo-controlled, multicentre study of pembrolizumab versus placebo in patients with early-stage NSCLC after resection and completion of standard adjuvant therapy. As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are being updated and the package leaflet is updated in accordance. An updated RMP version 39.1 was also submitted

15.3.29. Pirfenidone - ESBRIET (CAP) - EMEA/H/C/002154/II/0074

Applicant: Roche Registration GmbH

PRAC Rapporteur: Rhea Fitzgerald

Scope: Extension of indication to include treatment of 'advanced' idiopathic pulmonary fibrosis (IPF) by the deletion of the current qualifier 'mild to moderate', based on the results from study MA29957: a 52-week phase 2b, multicentre, randomised, double-blind, placebo-controlled clinical trial in IPF-patients with advanced lung function impairment (carbon monoxide diffusion capacity (DLco) < 40% of predicted) and at high risk of grade 3 pulmonary hypertension, and additional analyses performed on the original pivotal trials for pirfenidone in IPF. As a consequence, sections 4.1, 4.8 and 5.1 of the SmPC are updated. In addition, the MAH took the opportunity to include information in section 4.4 of the SmPC related to the content of sodium. The package leaflet and the RMP (version 12.0) are updated accordingly

15.3.30. Polatuzumab vedotin - POLIVY (CAP) - EMEA/H/C/004870/II/0018, Orphan

Applicant: Roche Registration GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of the final report from study GO29365 listed as a category 3 study in the RMP in order to address MEA/002. This is a phase Ib/II, multicentre, open-label study evaluating the safety, tolerability, and anti-tumor activity of polatuzumab vedotin in combination with rituximab or obinutuzumab plus bendamustine in patients with relapsed/refractory follicular lymphoma or relapsed/refractory diffuse large B-cell lymphoma. The RMP version 3.0 has also been submitted

15.3.31. Ravulizumab - ULTOMIRIS (CAP) - EMEA/H/C/004954/X/0027/G

Applicant: Alexion Europe SAS

PRAC Rapporteur: Kimmo Jaakkola

Scope: Grouped application consisting of: 1) extension application to introduce a new pharmaceutical form (solution for injection) associated with new strength (245 mg) and route of administration (subcutaneous use); 2) type II variation (C.I.4) to align the Summary of product characteristics and Labelling of Ultomiris intravenous formulation (IV) with the proposed Ultomiris subcutaneous formulation (SC). The RMP (version 5.0) is updated in accordance

15.3.32. Risdiplam - EVRYSDI (CAP) - EMEA/H/C/005145/II/0005/G, Orphan

Applicant: Roche Registration GmbH

PRAC Rapporteur: Jan Neuhauser

Scope: Grouped variations consisting of: 1) extension of indication to include treatment of patients below 2 months of age based on interim results from pivotal study BN40703 (RAINBOWFISH): an ongoing phase 2 multicentre, open-label, and single-arm study designed to evaluate the efficacy, safety, tolerability, and pharmacokinetic/pharmacodynamic (PK/PD) of risdiplam in pre-symptomatic infants below

2 months of age who were genetically diagnosed with spinal muscular atrophy (SMA). As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. In addition, the MAH took the opportunity to make some editorial improvements in the product information; 2) update of Evrysdi (risdiplam) pack configuration. As a consequence, section 6.5 of the SmPC and the labelling are updated; 3) removal of a device. As a consequence, section 6.5 of the SmPC and the labelling are updated. The package leaflet and the RMP (version 1.1) are updated in accordance

15.3.33. Tadalafil - ADCIRCA (CAP) - EMEA/H/C/001021/X/0035/G

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Grouped application consisting of: 1) extension application to introduce a new pharmaceutical form associated with a new strength (2 mg/ml oral suspension); 2) extension of indication to paediatric use from 6 months to 17 years based on study 4 (H6D-MC-LVHV [LVHV]): a 24-week placebo-controlled efficacy and safety study with an open-label long-term extension phase. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and labelling are updated accordingly. Furthermore, the product information is brought in line with the latest quality review of documents (QRD) template and editorial changes have been implemented. The RMP (version 9.1) is updated in accordance

15.3.34. Tixagevimab, cilgavimab - EVUSHELD (CAP) - EMEA/H/C/005788/II/0003

Applicant: AstraZeneca AB

PRAC Rapporteur: Kimmo Jaakkola

Scope: Update of sections 4.2, 4.8, 4.9, 5.1 and 5.2 of the SmPC in order to change the posology recommendations in the pre-exposure prophylaxis indication based on study TACKLE (D8851C00001). The package leaflet is updated accordingly. The RMP (version 2) has also been submitted

15.3.35. Tozinameran - COMIRNATY (CAP) - EMEA/H/C/005735/X/138

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Extension application to add a new strength of 3 µg for individuals 6 months to 4 years of age. The RMP (version 5.1) is updated accordingly

15.3.36. Treosulfan - TRECONDI (CAP) - EMEA/H/C/004751/II/0013, Orphan

Applicant: medac Gesellschaft fur klinische Spezialpraparate mbH

PRAC Rapporteur: Julia Pallos

Scope: Update of section 5.3 of the SmPC in order to update the description of non-clinical information regarding musculoskeletal and connective tissue disorders in form of lympho-histiocytic infiltration in the skeletal muscles and renal and urinary disorders which show up as haematuria. These new determinations are based on results from study LPT 37259. A

revised RMP version 1.0 was also submitted

15.3.37. Zanubrutinib - BRUKINSA (CAP) - EMEA/H/C/004978/II/0003

Applicant: BeiGene Ireland Ltd

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication to include treatment of adult patients with chronic lymphocytic leukaemia (CLL) or small lymphocytic leukaemia (SLL) based on results from: 1) study BGB-3111-304: an ongoing, international, phase 3, open-label, multiple-cohort, randomised study designed to evaluate the efficacy of zanubrutinib versus bendamustine plus rituximab (B+R) in patients with previously untreated CLL/SLL; 2) study BGB-3111-305: an ongoing, international phase 3, open-label, randomised study of zanubrutinib versus ibrutinib with relapsed/refractory (R/R) CLL/SLL. As a consequence, sections 4.1, 4.2, 4.4, 4,5, 4.6, 4.8, 5.1 and 5.2 of the SmPC are being updated. The package leaflet and the RMP (version 1.1) are updated in accordance. In addition, as part of the application the MAH requested a 1-year extension of the market protection

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

Based on the assessment of the following PSURs, PRAC concluded that the benefit-risk balance of the medicines mentioned below 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 the agreed criteria, the procedures listed below were finalised at 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).

16.1.1. Abrocitinib - CIBINQO (CAP) - PSUSA/00010976/202203

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Evaluation of a PSUSA procedure

16.1.2. Axitinib - INLYTA (CAP) - PSUSA/00010022/202201

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: David Olsen

Scope: Evaluation of a PSUSA procedure

16.1.3. Baloxavir marboxil - XOFLUZA (CAP) - PSUSA/00010895/202202

Applicant: Roche Registration GmbH

PRAC Rapporteur: Sonja Hrabcik

Scope: Evaluation of a PSUSA procedure

16.1.4. Baricitinib - OLUMIANT (CAP) - PSUSA/00010578/202202

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.5. Bempedoic acid - NILEMDO (CAP); bempedoic acid, ezetimibe - NUSTENDI (CAP) - PSUSA/00010841/202202

Applicant: Daiichi Sankyo Europe GmbH

PRAC Rapporteur: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

16.1.6. Bimekizumab - BIMZELX (CAP) - PSUSA/00010953/202202

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

16.1.7. Burosumab - CRYSVITA (CAP) - PSUSA/00010669/202202

Applicant: Kyowa Kirin Holdings B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.8. Ceftazidime, avibactam - ZAVICEFTA (CAP) - PSUSA/00010513/202202

Applicant: Pfizer Ireland Pharmaceuticals

PRAC Rapporteur: Rugile Pilviniene

Scope: Evaluation of a PSUSA procedure

16.1.9. Degarelix - FIRMAGON (CAP) - PSUSA/00000944/202202

Applicant: Ferring Pharmaceuticals A/S

PRAC Rapporteur: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

16.1.10. Dexamethasone[41] - OZURDEX (CAP) - PSUSA/00000985/202201

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Maria del Pilar Rayon

[41] Centrally authorised product(s) only, indicated in the treatment of uveitis and macular oedema

Scope: Evaluation of a PSUSA procedure

16.1.11. Eptinezumab - VYEPTI (CAP) - PSUSA/00010966/202202

Applicant: H. Lundbeck A/S

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

16.1.12. Eravacycline - XERAVA (CAP) - PSUSA/00010718/202202

Applicant: Paion Deutschland GmbH

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.13. Evinacumab - EVKEEZA (CAP) - PSUSA/00010945/202202

Applicant: Ultragenyx Germany GmbH

PRAC Rapporteur: Mari Thorn

Scope: Evaluation of a PSUSA procedure

16.1.14. Ex vivo expanded autologous human corneal epithelial cells containing stem cells - HOLOCLAR (CAP) - PSUSA/00010352/202202

Applicant: Holostem Terapie Avanzate s.r.l., ATMP[42]

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

16.1.15. Fedratinib - INREBIC (CAP) - PSUSA/00010909/202202

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Sonja Hrabcik

Scope: Evaluation of a PSUSA procedure

16.1.16. Fenofibrate, simvastatin - CHOLIB (CAP) - PSUSA/00010096/202202

Applicant: Mylan IRE Healthcare Limited

PRAC Rapporteur: Maia Uusküla

Scope: Evaluation of a PSUSA procedure

16.1.17. Ferric maltol - FERACCRU (CAP) - PSUSA/00010476/202202

Applicant: Norgine B.V.

PRAC Rapporteur: Adam Przybylkowski

[42] Advanced therapy medicinal product

Scope: Evaluation of a PSUSA procedure

16.1.18. Hepatitis B (rDNA[43]) vaccine (adjuvanted, adsorbed) - FENDRIX (CAP) - PSUSA/00001598/202202

Applicant: GlaxoSmithKline Biologicals

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

16.1.19. Ibalizumab - TROGARZO (CAP) - PSUSA/00010797/202203

Applicant: Theratechnologies Europe Limited

PRAC Rapporteur: David Olsen

Scope: Evaluation of a PSUSA procedure

16.1.20. Imlifidase - IDEFIRIX (CAP) - PSUSA/00010870/202202

Applicant: Hansa Biopharma AB

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.21. Influenza vaccine (surface antigen, inactivated, prepared in cell cultures) - FLUCELVAX TETRA (CAP) - PSUSA/00010737/202203

Applicant: Seqirus Netherlands B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.22. Lefamulin - XENLETA (CAP) - PSUSA/00010872/202202

Applicant: Nabriva Therapeutics Ireland DAC

PRAC Rapporteur: Eva Jirsová

Scope: Evaluation of a PSUSA procedure

16.1.23. Nitisinone - ORFADIN (CAP) - PSUSA/00002169/202202

Applicant: Swedish Orphan Biovitrum International AB

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

[43] Recombinant deoxyribonucleic acid

16.1.24. Pegfilgrastim - CEGFILA (CAP); FULPHILA (CAP); GRASUSTEK (CAP); NEULASTA (CAP); NYVEPRIA (CAP); PELGRAZ (CAP); PELMEG (CAP); ZIEXTENZO (CAP) - PSUSA/00002326/202201

Applicant: Accord Healthcare S.L.U. (Pelgraz), Amgen Europe B.V. (Neulasta), Juta Pharma GmbH (Grasustek), Mundipharma Corporation (Ireland) Limited (Cegfila, Pelmeg), Pfizer Europe MA EEIG (Nyvepria), Sandoz GmbH (Ziextenzo), Viatris Limited (Fulphila)

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.25. Plasmodium falciparum and hepatitis B vaccine (recombinant, adjuvanted) - MOSQUIRIX (Art 58[44]) - EMEA/H/W/002300/PSUV/0062

Applicant: GlaxoSmithkline Biologicals SA

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUR procedure

16.1.26. Pralsetinib - GAVRETO (CAP) - PSUSA/00010961/202203

Applicant: Roche Registration GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.27. Pretomanid - DOVPRELA (CAP) - PSUSA/00010863/202202

Applicant: Mylan IRE Healthcare Limited

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

16.1.28. Ropeginterferon alfa-2b - BESREMI (CAP) - PSUSA/00010756/202202

Applicant: AOP Orphan Pharmaceuticals GmbH

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Evaluation of a PSUSA procedure

16.1.29. Ruxolitinib - JAKAVI (CAP) - PSUSA/00010015/202202

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

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

16.1.30. Somapacitan - SOGROYA (CAP) - PSUSA/00010920/202202

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.31. Sotrovimab - XEVUDY (CAP) - PSUSA/00010973/202202

Applicant: Glaxosmithkline Trading Services Limited

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

16.1.32. Telotristat - XERMELO (CAP) - PSUSA/00010639/202202

Applicant: SERB S.A.S.

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.33. Tezacaftor, ivacaftor - SYMKEVI (CAP) - PSUSA/00010730/202202

Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

16.1.34. Tivozanib - FOTIVDA (CAP) - PSUSA/00010636/202202

Applicant: EUSA Pharma (Netherlands) B.V.

PRAC Rapporteur: Rugile Pilviniene

Scope: Evaluation of a PSUSA procedure

16.1.35. Trastuzumab emtansine - KADCYLA (CAP) - PSUSA/00010136/202202

Applicant: Roche Registration GmbH

PRAC Rapporteur: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

16.1.36. Ulipristal acetate[45] - ESMYA (CAP) - PSUSA/00009325/202202

Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

[45] Indication(s) for the treatment of moderate to severe symptoms of uterine fibroids only

16.1.37. Upadacitinib - RINVOQ (CAP) - PSUSA/00010823/202202

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Evaluation of a PSUSA procedure

16.1.38. Vosoritide - VOXZOGO (CAP) - PSUSA/00010952/202202

Applicant: BioMarin International Limited

PRAC Rapporteur: Zane Neikena

Scope: Evaluation of a PSUSA procedure

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

16.2.1. Anidulafungin - ECALTA (CAP); NAP - PSUSA/00000215/202201

Applicant: Pfizer Europe MA EEIG (Ecalta), various

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

16.2.2. Dexrazoxane - SAVENE (CAP); NAP - PSUSA/00001001/202202

Applicant: Clinigen Healthcare B.V. (Savene), various

PRAC Rapporteur: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

16.2.3. Influenza vaccine (surface antigen, inactivated, adjuvanted) - FLUAD TETRA (CAP); NAP - PSUSA/00010300/202203

Applicant: Seqirus Netherlands B.V. (Fluad Tetra), various

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.2.4. Orlistat - ALLI (CAP); XENICAL (CAP); NAP - PSUSA/00002220/202202

Applicant: GlaxoSmithKline Dungarvan Ltd (Alli), CHEPLAPHARM Arzneimittel GmbH (Xenical), various

PRAC Rapporteur: Nathalie Gault

Scope: Evaluation of a PSUSA procedure

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

16.3.1. Acetylsalicylic acid (NAP) - PSUSA/00000039/202202

Applicant(s): various

PRAC Lead: Melinda Palfi

Scope: Evaluation of a PSUSA procedure

16.3.2. Alverine (NAP) – PSUSA/00000124/202202

Applicant(s): various

PRAC Lead: Željana Margan Koletić

Scope: Evaluation of a PSUSA procedure

16.3.3. Alverine, simeticone (NAP) - PSUSA/00000125/202202

Applicant(s): various

PRAC Lead: Nathalie Gault

Scope: Evaluation of a PSUSA procedure

16.3.4. Amlodipine, atorvastatin (NAP) – PSUSA/00000177/202201

Applicant(s): various

PRAC Lead: Nathalie Gault

Scope: Evaluation of a PSUSA procedure

16.3.5. Carbomers (NAP) - PSUSA/00000557/202201

Applicant(s): various

PRAC Lead: Polona Golmajer

Scope: Evaluation of a PSUSA procedure

16.3.6. Cromoglicic acid (NAP) - PSUSA/00000883/202202

Applicant(s): various

PRAC Lead: Ronan Grimes

Scope: Evaluation of a PSUSA procedure

16.3.7. Glipizide (NAP) - PSUSA/00001535/202201

Applicant(s): various

PRAC Lead: Željana Margan Koletić

Scope: Evaluation of a PSUSA procedure

16.3.8. Hydroxyethyl starch (HES) (NAP) - PSUSA/00001694/202203

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.3.9. Influenza vaccine[46] (split virion, inactivated) (NAP) - PSUSA/00010298/202203

Applicant(s): various

PRAC Lead: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.3.10. Influenza vaccine (surface antigen, inactivated) (NAP) - PSUSA/00001744/202203

Applicant(s): various

PRAC Lead: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.3.11. Interferon gamma (NAP) - PSUSA/00001760/202201

Applicant(s): various

PRAC Lead: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

16.3.12. Ketoprofen[47] (NAP) - PSUSA/00001809/202201

Applicant(s): various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.3.13. Loratadine (NAP) - PSUSA/00001907/202202

Applicant(s): various

PRAC Lead: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

16.3.14. Loratadine, pseudoephedrine (NAP) - PSUSA/00001908/202202

Applicant(s): various

PRAC Lead: Jean-Michel Dogné

[46] Non-centrally authorised product(s) only
[47] All formulations except topical

Scope: Evaluation of a PSUSA procedure

16.3.15. Lorazepam (NAP) - PSUSA/00001909/202201

Applicant(s): various

PRAC Lead: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

16.3.16. Moxonidine (NAP) - PSUSA/00002095/202201

Applicant(s): various

PRAC Lead: Melinda Palfi

Scope: Evaluation of a PSUSA procedure

16.3.17. Zanamivir (NAP) - PSUSA/00003141/202201

Applicant(s): various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

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

16.4.1. Ocrelizumab - OCREVUS (CAP) - EMEA/H/C/004043/LEG 008.1

Applicant: Roche Registration GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: MAH's response to LEG 008 [cumulative review of cases of colitis, diarrhoea, alopecia/alopecia aerate and appendicitis, as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00010662/202103) adopted in November 2021] as per the request for supplementary information (RSI) adopted in July 2022

16.5. Follow-up to PSUR/PSUSA procedures

16.5.1. Coronavirus (COVID-19) vaccine (recombinant, adjuvanted) - NUVAXOVID (CAP) - EMEA/H/C/005808/II/0022

Applicant: Novavax CZ, a.s.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of sections 4.4 and 4.8 of the SmPC in order to add a new warning on pericarditis and myocarditis and to add pericarditis and myocarditis to the list of adverse drug reactions (ADRs) with frequency not known following the outcome of MEA/014.4 (5th monthly summary safety report) based on PRAC assessment on pericarditis and myocarditis concluded in August 2022. The package leaflet is updated accordingly

16.5.2. Elasomeran - SPIKEVAX (CAP) - EMEA/H/C/005791/II/0077

Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Update of section 4.8 of the SmPC to include acute and delayed urticaria as an adverse reaction, with a frequency 'rare', as requested by PRAC in the 13th Safety Summary Report (EMEA/H/C/005791/MEA/011.12) concluded in June 2022. The package leaflet is updated accordingly

16.6. Expedited summary safety reviews[48]

16.6.1. Coronavirus (COVID-19) vaccine (inactivated, adjuvanted, adsorbed) - COVID-19 VACCINE (INACTIVATED, ADJUVANTED) VALNEVA (CAP) - EMEA/H/C/006019/MEA 009

Applicant: Valneva Austria GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Justification letter submitted by the MAH for not submitting a monthly summary safety report (letter covering reporting period of 24 June 2022 to 31 July 2022) for (COVID-19 vaccine (inactivated, adjuvanted) Valneva during the coronavirus disease (COVID-19) pandemic

16.6.2. Coronavirus (COVID-19) vaccine (inactivated, adjuvanted, adsorbed) - COVID-19 VACCINE (INACTIVATED, ADJUVANTED) VALNEVA (CAP) - EMEA/H/C/006019/MEA 009.1

Applicant: Valneva Austria GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Justification letter submitted by the MAH for not submitting the second summary monthly safety report (SSR) (letter covering reporting period of 01 August 2022 to 31 August 2022)] for (COVID-19 vaccine (inactivated, adjuvanted) Valneva during the coronavirus disease (COVID-19) pandemic

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, PRAC adopted the conclusion of the Rapporteurs on their assessment for the medicines listed below without further plenary discussion.

[48] Submission of expedited summary safety reports for review in addition to the requirements for submission of PSUR(s) falling within the pandemic period and requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC

17.1. Protocols of PASS imposed in the marketing authorisation(s)[49]

17.1.1. Alemtuzumab – LEMTRADA (CAP) - EMEA/H/C/PSA/S/0089

Applicant: Sanofi Belgium

PRAC Rapporteur: Anette Kirstine Stark

Scope: Substantial amendment to an agreed protocol for a non-interventional PASS to investigate the risk of mortality in multiple sclerosis patients treated with Lemtrada (alemtuzumab) relative to comparable multiple sclerosis patients using other disease modifying therapies: a cohort study

17.1.2. Pomalidomide – IMNOVID (CAP) - EMEA/H/C/PSA/S/0090

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Substantial amendment to a non-interventional post authorisation registry of patients treated with pomalidomide for relapsed and refractory multiple myeloma who have received at least two prior treatment regimens, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy

17.1.3. Teduglutide – REVESTIVE (CAP) - EMEA/H/C/PSA/S/0086

Applicant: Shire Pharmaceuticals Ireland Limited

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Substantial amendment (version 8.0) to a protocol previously agreed in June 2022 (PSA/S/0082.1) for study TED-R13-002: a prospective, multicentre registry for patients with short bowel syndrome]

17.1.4. Valproate[50] (NAP) - EMEA/H/N/PSP/J/0075.8

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

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: MAH's response to PSP/J/0075.7 [submission of the third interim report for drug utilisation study (DUS) extension to assess the effectiveness of the risk minimisation measures and to further characterise the prescribing patterns for valproate and related substances, in Europe, using databases, in Germany, France, Netherlands, Spain, Sweden and United Kingdom , as required in the outcome of the referral procedure under Article 31 of Directive 2001/83/EC on valproate and related substances, completed in February 2018 (EMEA/H/A-31/1454)]. The MAH also provided an updated protocol (version 9.0), in response to the request included in the assessment report evaluating the second interim report, as well as to describe for which country data are expected to be available in the third and fourth interim report

[49] In accordance with Article 107n of Directive 2001/83/EC
[50] Valproic acid, sodium valproate, valproate pivoxil, valproate semisodium, valpriomide, valproate bismuth, calcium valproate, valproate magnesium

17.1.5. Valproate[51] (NAP) - EMEA/H/N/PSA/J/0091

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

PRAC Rapporteur: Jean-Michel Dogné

Scope: Substantial amendment (protocol version 7.0, including amendment 3.0, dated 11 July 2022) to an agreed protocol for a non-interventional retrospective longitudinal study, conducted in the United Kingdom and France to evaluate and identify the best practices for switching of valproate and related substances in clinical practice [VALSE study (VALNAC09344)], as required in the outcome of the referral procedure under Article 31 of Directive 2001/83/EC on valproate and related substances, completed in February 2018 (EMEA/H/A-31/1454)]

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

17.2.1. Cinacalcet - MIMPARA (CAP) - EMEA/H/C/000570/MEA 035.4

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Mari Thorn

Scope: Amendment to a previously agreed protocol for study 20180204 (listed as category 3 study in the RMP): an observational registry study to evaluate the use and safety of cinacalcet among paediatric patients with secondary hyperparathyroidism

17.2.2. Cladribine - MAVENCLAD (CAP) - EMEA/H/C/004230/MEA 002.3

Applicant: Merck Europe B.V.

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Amendment to a previously agreed protocol for study MS 700568-0002 (CLARION) (listed as category 3 study in the RMP): a prospective, observational cohort study evaluating the safety profile, in terms of incidence of adverse events of special interest, in patients with highly active relapsing multiple sclerosis (RMS) newly started on oral cladribine

17.2.3. Coronavirus (COVID-19) vaccine (recombinant, adjuvanted) - NUVAXOVID (CAP) - EMEA/H/C/005808/MEA 006

Applicant: Novavax CZ, a.s.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Updated protocol for study 2019nCoV-404: US post-authorisation safety study to evaluate the pooled of risk of selected adverse events of special interest (AESI) within specified time periods after vaccination with Nuvaxovid using a claim and/or electronic healthcare record (her) database

[51] Valproic acid, sodium valproate, valproate pivoxil, valproate semisodium, valpriomide, valproate bismuth, calcium valproate, valproate magnesium
[52] In accordance with Article 107m of Directive 2001/83/EC, supervised by PRAC in accordance with Article 61a (6) of Regulation (EC) No 726/2004

17.2.4. Darbepoetin alfa - ARANESP (CAP) - EMEA/H/C/000332/MEA 092.4

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Martin Huber

Scope: MAH's response to MEA 092.3 [amendment to a previously agreed protocol for study 20190404 (listed as a category 3 study in the RMP): a retrospective cohort study to assess the use of erythropoiesis stimulating agents (ESAs) in subjects receiving myelosuppressive chemotherapy in Europe] as per the request for supplementary information (RSI) adopted in May 2022

17.2.5. Diroximel fumarate - VUMERITY (CAP) - EMEA/H/C/005437/MEA 002.1

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Martin Huber

Scope: MAH's response to MEA 002 [protocol for study SE-VUM-12146 (listed as category 3 study in the RMP): an observational study utilising data from 'big data' multiple sclerosis registries to evaluate the long-term safety of Vumerity (diroximel fumarate) and Tecfidera (dimethyl fumarate)] as per RSI (request for supplementary information) adopted in May 2022

17.2.6. Dulaglutide - TRULICITY (CAP) - EMEA/H/C/002825/MEA 006.4

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Amelia Cupelli

Scope: Amendment to a previously agreed protocol for study H9X-MC-B013 (listed as category 3 study in the RMP): a non-interventional retrospective study to estimate the incidence rates of events of interest among type 2 diabetes mellitus (T2DM) patients treated with dulaglutide compared to other glucagon-like peptide 1 (GLP-1) receptor agonists in order to better characterise the safety profile of dulaglutide in terms of acute pancreatitis, pancreatic and thyroid malignancies

17.2.7. Empagliflozin - JARDIANCE (CAP) - EMEA/H/C/002677/MEA 004.6

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Maria del Pilar Rayon

Scope: MAH's response to MEA 004.5 [fifth monitoring interim report for study 1245.97: a non-interventional PASS assessing the risk of urinary tract malignancies in relation to empagliflozin exposure in patients with type 2 diabetes mellitus (T2DM): a multi-database European study] as per the request for supplementary information (RSI) adopted in May 2022

17.2.8. Empagliflozin, metformin - SYNJARDY (CAP) - EMEA/H/C/003770/MEA 006.8

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Maria del Pilar Rayon

Scope: MAH's response to MEA 006.7 [fifth monitoring interim report for study 1245.97: a non-interventional PASS assessing the risk of urinary tract malignancies in relation to empagliflozin exposure in patients with type 2 diabetes mellitus (T2DM): a multi-database European study] as per the request for supplementary information (RSI) adopted in May 2022

17.2.9. Filgotinib - JYSELECA (CAP) - EMEA/H/C/005113/MEA 016.1

Applicant: Galapagos N.V.

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: MAH's response to MEA 016 [protocol for study GLPG0634-CL-413: a non-interventional, PASS of filgotinib in patients with moderately to severely active ulcerative colitis (a European multi registry-based study)] as per the request for supplementary information (RSI) adopted in May 2022

17.2.10. Odevixibat - BYLVAY (CAP) - EMEA/H/C/004691/MEA 003.1

Applicant: Albireo

PRAC Rapporteur: Adam Przybylkowski

Scope: MAH's response to MEA 003 [protocol for study A4250-019 (listed as a category 3 study in the RMP): registry-based safety study in order to collect safety data on hepatotoxicity, diarrhoea, fat-soluble vitamins and fat-soluble nutrients in patients treated with odevixibat] as per request for supplementary information (RSI) adopted in April 2022

17.2.11. Ofatumumab - KESIMPTA (CAP) - EMEA/H/C/005410/MEA 002.2

Applicant: Novartis Ireland Limited

PRAC Rapporteur: Amelia Cupelli

Scope: MAH's response to MEA 002.1 [protocol for study OMB157G2407 (listed as category 3 study in the RMP): pregnancy outcomes intensive monitoring (PRIM) to evaluate pregnancy and infant outcomes in patients taking Kesimpta (ofatumumab)] as per the request for supplementary information (RSI) adopted in May 2022

17.2.12. Ofatumumab - KESIMPTA (CAP) - EMEA/H/C/005410/MEA 004

Applicant: Novartis Ireland Limited

PRAC Rapporteur: Amelia Cupelli

Scope: Protocol for a non-interventional study OMB157G2406: Kesimpta long-term retrospective safety study utilising real-world data from existing multiple sclerosis (MS) registries and databases from multiple countries. The primary objective is to estimate the event rates of malignancy and serious infections following ofatumumab treatment in patients with MS. The secondary objective is to compare the incidence of each serious safety event between ofatumumab exposed patients with relapsed MS and patients with relapsed MS exposed to other approved disease modifying therapies (DMTs)

17.2.13. Pegvaliase - PALYNZIQ (CAP) - EMEA/H/C/004744/MEA 005.4

Applicant: BioMarin International Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Amendment to a previously agreed protocol for study 165-504: a global, multicentre study to assess maternal, fetal and infant outcomes of exposure to Palynziq (pegvaliase) during pregnancy and breastfeeding

17.2.14. Rimegepant - VYDURA (CAP) - EMEA/H/C/005725/MEA 003

Applicant: Biohaven Pharmaceutical Ireland DAC

PRAC Rapporteur: Anette Kirstine Stark

Scope: Submission of protocol for study BHV3000-408: a PASS of rimegepant in patients with migraine and a history of cardiovascular diseases together with a statistical analysis plan (SAP)

17.2.15. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/MEA 018.1

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: MAH's response to MEA 018 [protocol for study A3921407: a PASS surveillance programme among patients treated with tofacitinib for polyarticular course juvenile idiopathic arthritis and juvenile psoriatic arthritis (PsA) within the German Biologics in Paediatric Rheumatology Registry (BIKER) and within the Juvenile Arthritis Methotrexate/Biologics long-term Observation (JuMBO) biological register (from X/0024/G)] as per the request for supplementary information (RSI) adopted in May 2022

17.2.16. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/MEA 019.1

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: MAH's response to MEA 019 [protocol for study A3921408: a PASS surveillance programme among patients treated with tofacitinib for polyarticular course juvenile idiopathic arthritis and juvenile psoriatic arthritis (PsA) within the Swedish juvenile idiopatic arthritis (JIA) clinical registry (from X/0024/G)] as per the request for supplementary information (RSI) adopted in May 2022

17.2.17. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/MEA 020.1

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: MAH's response to MEA 010 [protocol for study A3921409: a PASS surveillance programme among patients treated with tofacitinib for polyarticular course juvenile idiopathic arthritis and juvenile psoriatic arthritis (PsA) within the UK juvenile idiopathic arthritis (JIA) biologics register (from X/0024/G)] as per the request for supplementary

information (RSI) adopted in May 2022

17.2.18. Tozinameran - COMIRNATY (CAP) - EMEA/H/C/005735/MEA 010.5

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Amendment to a previously agreed protocol for study C4591012 to assess the occurrence of safety events of interest, including severe or atypical COVID-10 in real-world use of COVID-19 mRNA vaccine

17.2.19. Tozinameran - COMIRNATY (CAP) - EMEA/H/C/005735/MEA 037.2

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Amendment for a protocol previously agreed in March 2022 [MEA 037.1] for study C4591009: a non-interventional PASS in US to assess the occurrence of safety events of interest, including myocarditis and pericarditis (from variation II/0059 finalised in October 2021)]

17.2.20. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/MEA 053.1

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: MAH's response to MEA 053 [protocol for study CNTO1275PSO4005: a Nordic database initiative for exposure to ustekinumab - a review and analysis of major adverse cardiovascular events (MACE) from the Swedish and Danish national registry systems] as per the request for supplementary information (RSI) adopted in April 2022

17.2.21. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/MEA 054.1

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: MAH's response to MEA 054 [protocol for study PCSIMM004697: an observational longitudinal PASS of Stelara (ustekinumab) in the treatment of psoriasis and psoriatic arthritis - analysis of major adverse cardiovascular events (MACE) using Swedish national health registers] as per the request for supplementary information (RSI) adopted in April 2022

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

17.3.1. Lumacaftor, ivacaftor – ORKAMBI (CAP) - EMEA/H/C/PSR/S/0039

Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Rhea Fitzgerald

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

Scope: Results of an observational study to evaluate the utilisation patterns and long-term effects of lumacaftor and ivacaftor combination therapy in patients with cystic fibrosis

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

17.4.1. Alirocumab - PRALUENT (CAP) - EMEA/H/C/003882/II/0072

Applicant: sanofi-aventis groupe

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Submission of the final report from study ALIROC07997 (listed as a category 3 study in the RMP): PASS using healthcare databases to monitor the safety of alirocumab in HIV patients. The RMP version 7.0 has also been submitted

17.4.2. Hepatitis B surface antigen - HEPLISAV B (CAP) - EMEA/H/C/005063/II/0015

Applicant: Dynavax GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Submission of the final report from study HBV-26 (listed as a category 3 study in the RMP): a post-marketing observational surveillance study to evaluate the incidence of new-onset immune-mediated diseases, herpes zoster, and anaphylaxis in recipients of Heplisav B (hepatitis B surface antigen) with recipients of another hepatitis B vaccine. The RMP (version 1.3) is updated accordingly

17.4.3. Ixazomib - NINLARO (CAP) - EMEA/H/C/003844/II/0041, Orphan

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of the final report from study NSMM-5001 (INSIGHT) (listed as a Specific Obligation in the Annex II of the Product Information. This is a global, prospective, non-interventional, observational study of presentation, treatment patterns, and outcomes in multiple myeloma patients. The Annex II and the RMP (submitted version 9.0) are updated accordingly. In addition, the MAH took the opportunity to introduce minor editorial changes to the PI

17.4.4. Naltrexone hydrochloride, bupropion hydrochloride - MYSIMBA (CAP) - EMEA/H/C/003687/II/0054

Applicant: Orexigen Therapeutics Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: Submission of the final report from study NB-542 (listed as a category 3 study in the RMP): a cross-sectional survey aimed to evaluate the effectiveness of the Mysimba (naltrexone hydrochloride/bupropion hydrochloride) physician prescribing checklist (PPC) among physicians in the EU. The RMP (version 12.6) is updated accordingly

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

17.4.5. Susoctocog alfa - OBIZUR (CAP) - EMEA/H/C/002792/II/0049

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Submission of the final report for study 241501 (listed as a category 2 study in the RMP in order to fulfil SOB/001.4): a prospective and retrospective, non-interventional post-authorisation safety study (PASS) to evaluate the safety and effectiveness of Obizur in real-life practice. The RMP version 6.0 has also been submitted

17.4.6. Vedolizumab - ENTYVIO (CAP) - EMEA/H/C/002782/II/0073

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Adam Przybylkowski

Scope: Submission of the final report from study MLN0002_401 (listed as a category 3 study in the RMP in order to fulfil MEA/001.2): an international observational prospective cohort study comparing vedolizumab to other biologic agents in patients with ulcerative colitis or Crohn's disease. The RMP version 8.0 has also been submitted

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

17.5.1. Dimethyl fumarate - SKILARENCE (CAP) - EMEA/H/C/002157/MEA 001.6

Applicant: Almirall S.A

PRAC Rapporteur: Mari Thorn

Scope: Fourth annual interim results for study M-41008-40 (listed as a category 3 study in the RMP): an observational PASS in European psoriasis registers to evaluate the long-term safety of Skilarence (dimethyl fumarate) used for the treatment of patients with moderate to severe psoriasis

17.5.2. Elosulfase alfa - VIMIZIM (CAP) - EMEA/H/C/002779/ANX 005.7

Applicant: BioMarin International Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Eigth annual report (reporting period: 14 February 2021 to 12 February 2022) 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]

17.5.3. Fenfluramine - FINTEPLA (CAP) - EMEA/H/C/003933/MEA 002

Applicant: Zogenix ROI Limited

PRAC Rapporteur: Martin Huber

Scope: Progress report for study ZX008-1503: an open-label extension trial to assess the

long-term safety of ZX008 (fenfluramine hydrochloride) oral solution as an adjunctive therapy in children and young adults with Dravet syndrome

17.5.4. Luspatercept - REBLOZYL (CAP) - EMEA/H/C/004444/MEA 002.1

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Jo Robays

Scope: Second annual report for study ACE-536-LTFU-001: a study to evaluate the long-term safety, including thromboembolic events (TEEs) and progression to acute myeloid leukaemia (AML) and/or other malignancies/pre malignancies of luspatercept in patients who have participated in company-sponsored luspatercept clinical trials

17.5.5. Ravulizumab - ULTOMIRIS (CAP) - EMEA/H/C/004954/MEA 009

Applicant: Alexion Europe SAS

PRAC Rapporteur: Kimmo Jaakkola

Scope: First interim report for study M11-001 (listed as category 3 study in the RMP): an observational, non-interventional multicentre, multi-national study of patients with atypical hemolyticuremic syndrome (aHUS registry) together with a statistical analysis plan (SAP)

17.5.6. Teriflunomide - AUBAGIO (CAP) - EMEA/H/C/002514/MEA 005.5

Applicant: sanofi-aventis groupe

PRAC Rapporteur: Martin Huber

Scope: MAH's response to MEA 005.4 [1) eighth annual progress report for pregnancy registry OBS13499 (US/CA): teriflunomide pregnancy outcome exposure registry: a 'teratology information specialists (OTIS)' autoimmune diseases in pregnancy project, 2) fifth annual progress report for OBS12751 (international): an international pregnancy exposure registry of women with multiple sclerosis (MS) exposed to Aubagio (teriflunomide)] as per request for supplementary information (RSI) adopted in June 2022

17.5.7. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/MEA 024

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: First interim report for study A3921347 (listed as category 3 study in the RMP): a prospective non-interventional active surveillance study in the US, to quantify the incidence of key safety events of interest in patients with moderate-to-severe ulcerative colitis patients treated with tofacitinib and other systemic therapies in the clinical practice (real world) setting [following variation II/0038, the 2 non-interventional US studies (A3921347 & A3921348) were combined into the A3921347 protocol to allow for the consolidation of resources by using the same US database and vendor]

17.5.8. Tozinameran - COMIRNATY (CAP) - EMEA/H/C/005735/MEA 010.4

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Interim report for study C4591012: clinical study to assess the occurrence of safety events of interest, including severe or atypical COVID-19 in real-world use of COVID-19 mRNA vaccine

17.6. Others

17.6.1. (1R,2S,5S)-N-((1S)-1-Cyano-2-((3s)-2-oxopyrrolidin-3-yl)ethyl)-3-((2S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido) butanoyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide, ritonavir - PAXLOVID (CAP) - EMEA/H/C/005973/LEG/006

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Martin Huber

Scope: A safety review for myalgia covering safety data from ongoing early access worldwide and notably from US (Emergency Use Authorisation) and literature data with cut-off date 31st March should be provided by April 2022, awaiting for a global safety review planned to be submitted covering the 3 applicant's sponsored clinical studies (EPIC-HR, EPIC-SR and study in PEP) in June 2022

17.6.2. (1R,2S,5S)-N-((1S)-1-Cyano-2-((3s)-2-oxopyrrolidin-3-yl)ethyl)-3-((2S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido) butanoyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide, ritonavir - PAXLOVID (CAP) - EMEA/H/C/005973/REC 017

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Martin Huber

Scope: A safety review for myalgia covering safety data from ongoing early access worldwide and notably from US (Emergency Use Authorisation) and literature data with cut-off date 31st March should be provided by April 2022, awaiting for a global safety review planned to be submitted covering the 3 applicant's sponsored clinical studies (EPIC-HR, EPIC-SR and study in PEP) in June 2022

17.6.3. Avatrombopag - DOPTELET (CAP) - EMEA/H/C/004722/MEA 003.2

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Maria del Pilar Rayon

Scope: MAH's response to MEA 003.1 [feasibility assessment for a study to further characterise the long-term safety profile of avatrombopag in patients with primary chronic immune thrombocytopenia in European patient registers and electronic healthcare databases as requested in the conclusions of variation II/0004/G finalised in December 2020] as per the request for supplementary information (RSI) adopted May 2022

17.6.4. Azathioprine - JAYEMPI (CAP) - EMEA/H/C/005055/MEA 001

Applicant: Nova Laboratories Ireland Limited

PRAC Rapporteur: Anette Kirstine Stark

Scope: Monitoring of medication error reports specifically due to 'conversion of patients from tablet to liquid formulation and two dosing syringes' annually and submitted as post authorisation measure (PAM outside the context of azathioprine PSUR) (from initial opinion/MA)

17.6.5. Coronavirus (COVID-19) vaccine (ChAdOx1-S [recombinant]) - VAXZEVRIA (CAP) - EMEA/H/C/005675/MEA 008

Applicant: AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

Scope: Proposal to replace the existing PASS to assess the safety of Vaxzevria (coronavirus (COVID-19) vaccine (ChAdOx1-S[recombinant])) in patients receiving immunosuppressant medication or with primary immunodeficiency with systematic literature review for studies evaluating adverse events of AZD1222 in patients taking immunosuppressant medications and/or with primary immunodeficiency

17.6.6. Radium (Ra223) - XOFIGO (CAP) - EMEA/H/C/002653/ANX 013.2

Applicant: Bayer AG

PRAC Rapporteur: Rugile Pilviniene

Scope: Request for deletion of ANX 013.1 post-approval commitment (study 20511): an open-label, multicentre, non-randomized Phase 1 study that has been requested by the European Commission as a result of the referral procedure (EMEA/H/A-20/1459/C/002653/0028) to further characterize the correlation between the extent of the disease, the dose and the distribution of radium-223 in bone metastases versus sites of impaired bone health versus normal bone structure

17.6.7. Risankizumab - SKYRIZI (CAP) - EMEA/H/C/004759/MEA 002.5

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Revised statistical analysis plan (SAP) for study P16-751: pregnancy exposures and outcomes in psoriasis patients treated with risankizumab: a cohort study utilising large healthcare databases with mother-baby linkage in the United States

17.6.8. Tacrolimus - ADVAGRAF (CAP) - EMEA/H/C/000712/MEA 032.2

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Ronan Grimes

Scope: MAH's response to MEA 032.1 [submission of a critical analysis of the feasibility of using alternative data sources to complement the Transplantation Pregnancy Registry International (TPRI) study outcomes on pregnancy and breastfeeding] as per the request for supplementary information (RSI) adopted in March 2022

17.6.9. Tacrolimus - MODIGRAF (CAP) - EMEA/H/C/000954/MEA 024.2

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: MAH's response to MEA 032.1 [submission of a critical analysis of the feasibility of using alternative data sources to complement the Transplantation Pregnancy Registry International (TPRI) study outcomes on pregnancy and breastfeeding] as per the request for supplementary information (RSI) adopted in March 2022

17.7. New Scientific Advice

None

17.8. Ongoing Scientific Advice

None

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

None

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, 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 the 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. Dinutuximab beta - QARZIBA (CAP) - EMEA/H/C/003918/S/0046 (without RMP)

Applicant: EUSA Pharma (Netherlands) B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Annual reassessment of the marketing authorisation

18.1.2. Ebola vaccine (rDNA55, replication-incompetent) - MVABEA (CAP) - EMEA/H/C/005343/S/0015 (without RMP)

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Jean-Michel Dogné

[55] Ribosomal deoxyribonucleic acid

Scope: Annual reassessment of the marketing authorisation

18.1.3. Ebola vaccine (rDNA56, replication-incompetent) - ZABDENO (CAP) - EMEA/H/C/005337/S/0012 (without RMP)

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Jean-Michel Dogné

Scope: Annual reassessment of the marketing authorisation

18.1.4. Odevixibat - BYLVAY (CAP) - EMEA/H/C/004691/S/0008 (without RMP)

Applicant: Albireo

PRAC Rapporteur: Adam Przybylkowski

Scope: Annual reassessment of the marketing authorisation

18.2. Conditional renewals of the marketing authorisation

18.2.1. (1R,2S,5S)-N-((1S)-1-Cyano-2-((3s)-2-oxopyrrolidin-3-yl)ethyl)-3-((2S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido) butanoyl)- 6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide, ritonavir - PAXLOVID (CAP) - EMEA/H/C/005973/R/0023 (without RMP)

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Martin Huber

Scope: Conditional renewal of the marketing authorisation

18.2.2. Burosumab - CRYSVITA (CAP) - EMEA/H/C/004275/R/0031 (without RMP)

Applicant: Kyowa Kirin Holdings B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Conditional renewal of the marketing authorisation

18.2.3. Coronavirus (COVID-19) vaccine (ChAdOx1-S [recombinant]) - VAXZEVRIA (CAP) - EMEA/H/C/005675/R/0079 (without RMP)

Applicant: AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

Scope: Conditional renewal of the marketing authorisation

18.2.4. Selpercatinib - RETSEVMO (CAP) - EMEA/H/C/005375/R/0018 (without RMP)

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Menno van der Elst

[56] Ribosomal deoxyribonucleic acid

Scope: Conditional renewal of the marketing authorisation

18.3. Renewals of the marketing authorisation

18.3.1. Beclometasone dipropionate, formoterol fumarate dihydrate, glycopyrronium - RIARIFY (CAP) - EMEA/H/C/004836/R/0022 (with RMP)

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Jan Neuhauser

Scope: 5-year renewal of the marketing authorisation

18.3.2. Beclometasone dipropionate, formoterol fumarate dihydrate, glycopyrronium - TRYDONIS (CAP) - EMEA/H/C/004702/R/0025 (with RMP)

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Jan Neuhauser

Scope: 5-year renewal of the marketing authorisation

18.3.3. Herpes zoster vaccine (recombinant, adjuvanted) - SHINGRIX (CAP) - EMEA/H/C/004336/R/0057 (without RMP)

Applicant: GlaxoSmithkline Biologicals SA

PRAC Rapporteur: Sonja Hrabcik

Scope: 5-year renewal of the marketing authorisation

18.3.4. Infliximab - ZESSLY (CAP) - EMEA/H/C/004647/R/0025 (without RMP)

Applicant: Sandoz GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: 5-year renewal of the marketing authorisation

18.3.5. Insulin glargine - SEMGLEE (CAP) - EMEA/H/C/004280/R/0040 (without RMP)

Applicant: Viatris Limited

PRAC Rapporteur: Menno van der Elst

Scope: 5-year renewal of the marketing authorisation

18.3.6. Sodium zirconium cyclosilicate - LOKELMA (CAP) - EMEA/H/C/004029/R/0027 (without RMP)

Applicant: AstraZeneca AB

PRAC Rapporteur: Kirsti Villikka

Scope: 5-year renewal of the marketing authorisation

18.3.7. Velmanase alfa - LAMZEDE (CAP) - EMEA/H/C/003922/R/0029 (without RMP)

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Jan Neuhauser

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 26-29 September 2022 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	
Jan Neuhauser	Member	Austria	No interests declared	
Sonja Hrabcik	Alternate	Austria	No interests declared	
Jean-Michel Dogné	Member	Belgium	No interests declared	
Jo Robays	Alternate	Belgium	No interests declared	
Maria Popova-Kiradjieva	Member	Bulgaria	No interests declared	
Nikica Mirošević Skvrce	Member	Croatia	No interests declared	
Željana Margan Koletić	Alternate	Croatia	No interests declared	
Panagiotis Psaras	Alternate	Cyprus	No interests declared	
Eva Jirsová	Member	Czechia	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Jana Lukacisinova	Alternate	Czechia	No interests declared	
Anette Kirstine Stark	Member	Denmark	No interests declared	
Marie Louise Schougaard Christiansen	Alternate	Denmark	No interests declared	
Krõõt Aab	Alternate	Estonia	No interests declared	
Kirsti Villikka	Member	Finland	No interests declared	
Kimmo Jaakkola	Alternate	Finland	No interests declared	
Tiphaine Vaillant	Member	France	No interests declared	
Nathalie Gault	Alternate	France	No interests declared	
Martin Huber	Member (Vice-Chair)	Germany	No interests declared	
Brigitte Keller-Stanislawski	Alternate	Germany	No interests declared	
Sofia Trantza	Member	Greece	No interest declared	
Georgia Gkegka	Alternate	Greece	No interest declared	
Julia Pallos	Member	Hungary	No participation in final deliberations and voting on:	14.1.2. Nivolumab – OPDIVO (CAP) 16.1.15. Fedratinib - INREBIC (CAP) - PSUSA/00010909/202202

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				17.1.2. Pomalidomide – IMNOVID (CAP) - EMEA/H/C/PSA/S/0090 17.5.4. Luspatercept - REBLOZYL (CAP) - EMEA/H/C/004444/MEA 002.1
Melinda Palfi	Alternate	Hungary	No interest declared	
Rhea Fitzgerald	Member	Ireland	No interests declared	
Ronan Grimes	Alternate	Ireland	No interests declared	
Amelia Cupelli	Member	Italy	No interests declared	
Valentina Di Giovanni	Alternate	Italy	No interests declared	
Zane Neikena	Member	Latvia	No interests declared	
Zane Stade	Alternate	Latvia	No interests declared	
Rugile Pilviniene	Member	Lithuania	No interests declared	
Lina Seibokiene	Alternate	Lithuania	No participation in discussion, final deliberations and voting on:	4.3.3. Rivaroxaban - RIVAROXABAN ACCORD (CAP), RIVAROXABAN MYLAN (CAP), XARELTO (CAP); NAP - EMEA/H/C/000944/SDA/051
Anne-Cecile Vuillemin	Alternate	Luxembourg	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
John Joseph Borg	Member	Malta	No interests declared	
Benjamin Micallef	Alternate	Malta	No interests declared	
Menno van der Elst	Member	The Netherlands	No interests declared	
Liana Gross-Martirosyan	Alternate	The Netherlands	No interests declared	
David Olsen	Member	Norway	No participation in final deliberations and voting on:	4.3.3. Rivaroxaban - RIVAROXABAN ACCORD (CAP), RIVAROXABAN MYLAN (CAP), XARELTO (CAP); NAP - EMEA/H/C/000944/SDA/051 5.3.1. Aflibercept - EYLEA (CAP) - EMEA/H/C/002392/II/0077/G 6.3.8. Mesterolone (NAP) - PSUSA/00010551/202201 16.3.1. Acetylsalicylic acid (NAP) - PSUSA/00000039/202202 16.3.13. Loratadine (NAP) - PSUSA/00001907/202202 16.3.14. Loratadine, pseudoephedrine (NAP) - PSUSA/00001908/202202 17.6.6. Radium (Ra223) - XOFIGO (CAP) -

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				EMEA/H/C/002653/ANX 013.2
Karen Pernille Harg	Alternate	Norway	No interests declared	
Adam Przybylkowski	Member	Poland	No interests declared	
Katarzyna Ziolkowska	Alternate	Poland	No interests declared	
Ana Diniz Martins	Member	Portugal	No interests declared	
Marcia Sofia Sanches de Castro Lopes Silva	Alternate	Portugal	No interests declared	
Roxana Dondera	Member	Romania	No interests declared	
Alexandra - Maria Spurni	Alternate	Romania	No interests declared	
Anna Mareková	Member	Slovakia	No interests declared	
Lucia Kuráková	Alternate	Slovakia	No interests declared	
Milena Radoha-Bergoc	Alternate	Slovenia	No participation in final deliberations and voting on:	4.3.4. Selective serotonin reuptake transporter inhibitors (SSRIs): citalopram (NAP); escitalopram (NAP); fluoxetine (NAP); fluvoxamine (NAP); paroxetine (NAP); sertraline (NAP) serotonin-norepinephrine reuptake

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				inhibitor (SNRIs): desvenlafaxine (NAP); duloxetine – CYMBALTA (CAP) - EMEA/H/C/000572/SDA/050, DULOXETINE LILLY (CAP), DULOXETINE MYLAN (CAP), DULOXETINE ZENTIVA (CAP), YENTREVE (CAP) - EMEA/H/C/000545/SDA/046; NAP; milnacipran (NAP); venlafaxine (NAP); mirtazapine (NAP); vortioxetine - BRINTELLIX (CAP) - EMEA/H/C/002717/SDA/008
Maria del Pilar Rayon	Alternate	Spain	No interests declared	
Ulla Wändel Liminga	Member	Sweden	No interests declared	
Mari Thorn	Alternate	Sweden	No restrictions applicable to the meeting	
Annalisa Capuano	Member	Independent scientific expert	No interests declared	
Milou Daniel Drici	Member	Independent scientific expert	No interests declared	
Maria Teresa Herdeiro	Member	Independent scientific expert	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Patricia McGettigan	Member	Independent scientific expert	No interests declared	
Hedvig Nordeng	Member	Independent scientific expert	No interests declared	
Roberto Frontini	Member	Healthcare Professionals' Representative	No restrictions applicable to the meeting	
Salvatore Antonio Giuseppe Messana	Alternate	Healthcare Professionals' Representative	No interests declared	
Declan Noone	Member	Patients' Organisation Representative	No interests declared	
Marko Korenjak	Alternate	Patients' Organisation Representative	No restrictions applicable to this meeting	
Andrea Laslop	Expert	Austria	No interests declared	
Laurence de Fays	Expert	Belgium	No interests declared	
Flora Musuamba Tshinanu	Expert	Belgium	No restrictions applicable to this meeting	
Ivana Ljubicic	Expert	Croatia	No interests declared	
Lara Miletić	Expert	Croatia	No restrictions applicable to this meeting	
Petra Kaftanová	Expert	Czechia	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Anna Kroupová	Expert	Czechia	No interests declared	
Marian Hjortlund Allon	Expert	Denmark	No interests declared	
Alexander Braathen	Expert	Denmark	No interests declared	
Marianne Hald Clemmensen	Expert	Denmark	No restrictions applicable to this meeting	
Annette Cleveland Nielsen	Expert	Denmark	No restrictions applicable to this meeting	
Helle Gerda Olsen	Expert	Denmark	No interests declared	
Ane Blicher Schelde	Expert	Denmark	No restrictions applicable to this meeting	
Aynur Sert	Expert	Denmark	No interests declared	
Per Sindahl	Expert	Denmark	No interests declared	
Ditte Søgaard	Expert	Denmark	No restrictions applicable to this meeting	
Chau Minh Tran	Expert	Denmark	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Vincent Gazin	Expert	France	No interests declared	
Stephanie Hueber	Expert	France	No interests declared	
Leo Lambart	Expert	France	No restrictions applicable to this meeting	
Ludivine Martin	Expert	France	No restrictions applicable to this meeting	
Marie-Caroline Pesquidous	Expert	France	No restrictions applicable to this meeting	
Dina Sanctussy	Expert	France	No interests declared	
Youssef Shaim	Expert	France	No restrictions applicable to this meeting	
Marie Tardieu	Expert	France	No interests declared	
Maxim Frizler	Expert	Germany	No interests declared	
Dennis Lex	Expert	Germany	No interests declared	
Kerstin Löschcke	Expert	Germany	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Elmer Schabel	Expert	Germany	No interests declared	
Gabriele Schwarz	Expert	Germany	No interests declared	
Karin Seifert	Expert	Germany	No interests declared	
Natalie Welter	Expert	Germany	No restrictions applicable to this meeting	
Sheena Kennedy	Expert	Ireland	No restrictions applicable to this meeting	
Ruchika Sharma	Expert	Ireland	No restrictions applicable to this meeting	
Anthony Gerry Wilson	Expert	Ireland	No restrictions applicable to this meeting	
Cinzia Ciceroni	Expert	Italy	No interests declared	
Valentina Conti	Expert	Italy	No interests declared	
Sara Galluzzo	Expert	Italy	No interests declared	
Armando Genazzani	Expert	Italy	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Peter Mol	Expert	The Netherlands	No interests declared	
Evelyn Olthof	Expert	The Netherlands	No interests declared	
Carmen Gallego López Jurado	Expert	Spain	No interests declared	
Monica Martinez Redondo	Expert	Spain	No restrictions applicable to this meeting	
Fernanda Inês Carvalho Pereira Ribeiro Vaz (Inês Vaz)	Expert	Portugal	No interests declared	
Charlotte Backman	Expert	Sweden	No interests declared	
Kristina Dunder	Expert	Sweden	No interests declared	
Hanna Kastman	Expert	Sweden	No interests declared	
Kristina Magnusson Lundqvist	Expert	Sweden	No interests declared	
A representative from the European Commission attended the meeting				
Meeting run with support from relevant EMA staff				

Experts were 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, 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