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Human Medicines Division

Pharmacovigilance Risk Assessment Committee (PRAC) Minutes of the meeting on 04-07 April 2022

Chair: Sabine Straus – Vice-Chair: Martin Huber

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

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1. Introduction

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

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

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 member(s)/alternate(s) for their contributions to the Committee.

1.2. Agenda of the meeting on 04-07 April 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 07-10 March 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 07-10 March 2022 were published on the EMA website on 22 November 2022 ([EMA/PRAC/856951/2022](#)).

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. Terlipressin¹ (NAP) - EMEA/H/A-31/1514

Applicant(s): various

PRAC Rapporteur: Krööt 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 is ongoing for the review of terlipressin-containing product(s) indicated in the treatment of hepatorenal syndrome (HRS). This procedure was initiated following the assessment of the results from a large clinical trial CONFIRM² involving patients with type 1 HRS within the PSUR single assessment (PSUSA) procedure on terlipressin (PSUSA/00002905/202104) concluded in December 2021³ that raised serious safety concerns 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. For further background, see [PRAC minutes January 2022](#).

Summary of recommendation(s)/conclusions

- PRAC discussed the assessment reports issued by the Rapporteurs.
- PRAC adopted a list of outstanding issues (LoOI) to be addressed by the MAHs for terlipressin-containing product(s) indicated in the treatment of HRS in accordance with a revised timetable ([EMA/PRAC/2205/2022 rev1](#)).
- PRAC agreed on the need to convene an ad-hoc expert group (AHEG). PRAC adopted a list of questions (LoQ) to the AHEG to be held on 13 June 2022.

3.3. Procedures for finalisation

None

¹ Indicated in the treatment of hepatorenal syndrome (HRS)

² 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

³ Held 29 November – 02 December 2021

3.4. Re-examination procedures⁴

None

3.5. Others

None

4. Signals assessment and prioritisation⁵

4.1. New signals detected from EU spontaneous reporting systems

See also Annex I 14.1.

4.1.1. Coronavirus (COVID-19) vaccine (ChAdOx1-S [recombinant]) - VAXZEVRIA (CAP)

Applicant: AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

Scope: Signal of corneal graft rejection

EPITT 19791 – New signal

Lead Member State(s): BE

Background

Coronavirus (COVID-19) vaccine (ChAdOx1-S [recombinant]) is a monovalent vaccine composed of a single recombinant, replication-deficient chimpanzee adenovirus (ChAdOx1) vector encoding the S glycoprotein of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) indicated, as Vaxzevria, a centrally authorised vaccine, for active immunisation to prevent COVID-19 caused by SARS-CoV-2, in individuals 18 years of age and older.

During routine signal detection activities, a signal of corneal graft rejection was identified by EMA, based on fourteen cases from the literature and from EudraVigilance. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by PRAC.

Discussion

Although the absolute number of cases is limited in the context of the total exposure and the information in some cases is scarce, PRAC agreed that following the review of the cases reported in the literature and in EudraVigilance, the signal warrants further investigation considering the seriousness of the condition.

Summary of recommendation(s)

- The MAH for Vaxzevria (COVID-19 vaccine (ChAdOx1-S [recombinant])) should submit to EMA, within 60 days, a detailed review of cases of corneal graft rejection. The MAH should discuss the plausibility and biological mechanism(s) for an association between

⁴ Re-examination of PRAC recommendation under Article 32 of Directive 2001/83/EC

⁵ 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

corneal graft rejection and vaccination with Vaxzevria (COVID-19 vaccine (ChAdOx1-S [recombinant])). In addition, the MAH should include a proposal to update the product information and/or RMP including relevant risk minimisation measures as warranted.

- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.1.2. **Elasomeran - SPIKEVAX (CAP)**

Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Signal of corneal graft rejection

EPITT 19792 – New signal

Lead Member State(s): DK

Background

Elasomeran is a nucleoside-modified messenger ribonucleic acid (mRNA) vaccine (nucleoside-modified) indicated, as Spikevax, for active immunisation to prevent COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 12 years of age and older.

During routine signal detection activities, a signal of corneal graft rejection was identified by EMA, based on twelve cases from the literature and from EudraVigilance. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by PRAC.

Discussion

Having considered the available evidence in the literature and in EudraVigilance, PRAC agreed that the signal warrants further investigation considering the seriousness of the condition.

Summary of recommendation(s)

- The MAH for Spikevax (elasomeran) should submit to EMA, within 60 days, a detailed review of cases of corneal graft rejection. The MAH should discuss the possible mechanism(s) for an association between corneal graft rejection and vaccination with Spikevax (elasomeran). In addition, the MAH should include a proposal to update the product information and/or RMP including relevant risk minimisation measures as warranted.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.1.3. **Tozinameran - COMIRNATY (CAP)**

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Signal of corneal graft rejection

EPITT 19789 – New signal

Lead Member State(s): NL

Background

Tozinameran is a nucleoside-modified messenger ribonucleic acid (mRNA) vaccine indicated, as Comirnaty, for the active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 12 years of age and older.

During routine signal detection activities, a signal of corneal graft rejection was identified by EMA, based on twenty-two cases from the literature and from EudraVigilance. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by PRAC.

Discussion

Having considered the available evidence in the literature and in EudraVigilance, PRAC agreed that the signal warrants further investigation considering the seriousness of the condition.

Summary of recommendation(s)

- The MAH for Comirnaty (tozinameran) should submit to EMA, within 60 days, a detailed review of cases of corneal graft rejection. The MAH should discuss the possible mechanism(s) for an association between corneal graft rejection and vaccination with Comirnaty (tozinameran). In addition, the MAH should include a proposal to update the product information and/or RMP including relevant risk minimisation measures as warranted.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.2. New signals detected from other sources

4.2.1. Gemtuzumab ozogamicin – MYLOTARG (CAP)

Applicant(s): Pfizer Europe MA EEIG

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Signal of atypical haemolytic reactions

EPITT 19788 – New signal

Lead Member State(s): PT

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.

Following the recent publication by Health Canada in 'Health Product InfoWatch' describing five literature cases including four cases of intravascular haemolysis and one case of haemolysis, EMA conducted a search in EudraVigilance that identified eleven cases, including the five cases identified by Health Canada. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by PRAC.

Discussion

Having considered the available evidence in EudraVigilance and in the literature, and considering the biological plausibility for gemtuzumab ozogamicin treatment leading to delayed diagnose of intravascular haemolytic reaction, PRAC agreed that further evaluation on the signal of atypical haemolytic reactions and treatment with gemtuzumab ozogamicin is warranted.

Summary of recommendation(s)

- The MAH for Mylotarg (gemtuzumab ozogamicin) should submit to EMA, within 30 days, a cumulative review of cases of haemolysis, including atypical haemolysis. A discussion on the potential mechanism of gemtuzumab ozogamicin in causing initial haemolysis and/or prolonging/confounding an existing haemolysis should be included. The MAH should also propose to update the product information and/or RMP as warranted.
- A 30 day-timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.3. Signals follow-up and prioritisation

4.3.1. Abatacept - ORENCIA (CAP) - EMEA/H/C/000701/SDA/068

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Kimmo Jaakkola

Scope: Signal of acute respiratory distress syndrome (ARDS)

EPITT 19751 - Follow-up to December 2021

Background

For background information, see [PRAC minutes December 2021](#)⁶.

The MAH replied to the request for information on the signal of acute respiratory distress syndrome (ARDS) and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence from EudraVigilance, the literature, the data provided by the MAH together with the Rapporteur's assessment, PRAC agreed that there is insufficient evidence at present to establish a causal relationship between ARDS/respiratory failure and abatacept.

Summary of recommendation(s)

- The MAH for Orenzia (abatacept) should continue to monitor cases of ARDS as part of routine safety surveillance.

4.3.2. Atezolizumab - TECENTRIQ (CAP) - EMEA/H/C/004143/SDA/022

Applicant: Roche Registration GmbH

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

⁶ Held 29 November – 02 December 2021

Scope: Signal of optic neuritis

EPITT 19747 – Follow-up to December 2021

Background

For background information, see [PRAC minutes December 2021](#)⁷.

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

Discussion

Having considered the available evidence from EudraVigilance, the literature, the cumulative review provided by the MAH together with the Rapporteur's assessment, PRAC agreed that there is insufficient evidence at present to establish a causal relationship between optic neuritis and atezolizumab.

Summary of recommendation(s)

- The MAH for Tecentriq (atezolizumab) should continue to monitor cases of optic neuritis as part of routine safety surveillance.

4.3.3. [Elasomeran - SPIKEVAX \(CAP\) - EMEA/H/C/005791/SDA/054](#)

Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Signal of autoimmune hepatitis

EPITT 19750 – Follow-up to December 2021

Background

For background information, see [PRAC minutes December 2021](#)⁸.

The MAH replied to the request for information on the signal of autoimmune hepatitis (AIH) and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence from EudraVigilance, the literature, the data provided by the MAH together with the Rapporteur's assessment, PRAC agreed that the signal of AIH should be kept under close monitoring.

Summary of recommendation(s)

- In the next PSUR⁹, the MAH for Spikevax (elasomeran) should submit an updated detailed review of cases of AIH, together with a causality assessment. In addition, the MAH should provide a discussion on the underlying mechanism(s) of the occurrence of vaccine associated AIH following administration of Spikevax (elasomeran) and the timing of development of clinical symptoms in relationship to the proposed mechanism of action, and if possible, the type of AIH involved. Finally, the MAH should propose to update the

⁷ Held 29 November – 02 December 2021

⁸ Held 29 November – 02 December 2021

⁹ Data lock point (DLP): 30 June 2022

product information and/or RMP including relevant risk minimisation measures as warranted.

4.3.4. Tocilizumab - ROACTEMRA (CAP) - EMEA/H/C/000955/SDA/060

Applicant: Roche Registration GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Signal of encephalopathy including posterior reversible encephalopathy syndrome (PRES)

EPITT 19731 – Follow-up to November 2021

Background

For background information, see [PRAC minutes November 2021](#)¹⁰.

The MAH replied to the request for information on the signal of encephalopathy including posterior reversible encephalopathy syndrome (PRES) and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence from EudraVigilance, the literature, the data provided by the MAH together with the Rapporteur's assessment, PRAC agreed that further assessment of the signal is warranted.

Summary of recommendation(s)

- The MAH for Roactemra (tocilizumab) should submit to EMA, within 30 days, a detailed review of the cases of PRES as well as additional information regarding the frequency of encephalopathy/PRES in the tocilizumab and placebo arms of the pooled clinical studies in the rheumatoid arthritis population. In addition, the MAH should discuss the potential role of tocilizumab in the development of encephalopathy as suggested in the literature. Finally, the MAH should further review the need for any potential amendment to the product information and/or the RMP, and make proposals as warranted.
- A 30-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.3.5. Tozinameran - COMIRNATY (CAP) - EMEA/H/C/005735/SDA/042

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Signal of autoimmune hepatitis

EPITT 19749 – Follow-up to December 2021¹¹

Background

For background information, see [PRAC minutes December 2021](#)¹².

¹⁰ Held 25-28 October 2021

¹¹ Held 29 November – 02 December 2021

¹² Held 29 November – 02 December 2021

The MAH replied to the request for information on the signal of autoimmune hepatitis (AIH) and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence from EudraVigilance, the literature, the data provided by the MAH together with the Rapporteur's assessment, PRAC agreed that the signal of AIH should be kept under close monitoring.

Summary of recommendation(s)

- In the next PSUR¹³, the MAH for Comirnaty (tozinameran) should submit an updated detailed review of cases of AIH, including any relevant new data, from all available sources. The cumulative review should include, but not be limited to, data from clinical trials, post-marketing cases and any relevant articles from literature.

4.4. Variation procedure(s) resulting from signal evaluation

See Annex I 14.1.

5. Risk management plans (RMPs)

5.1. Medicines in the pre-authorisation phase

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

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

See also Annex I 14.1.

5.1.1. Asciminib – EMEA/H/C/005605, Orphan

Applicant: Novartis Europharm Limited

Scope: Treatment of Philadelphia chromosome-positive chronic myeloid leukaemia in chronic phase (Ph+ CML-CP)

5.1.2. Coronavirus (COVID-19) vaccine (inactivated, adjuvanted, adsorbed) - EMEA/H/C/006019

Scope: Active immunisation for prevention of coronavirus disease-2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 18 years of age and older

5.1.3. Efgartigimod alfa - EMEA/H/C/005849, Orphan

Applicant: Argenx

¹³ Data lock point (DLP): 18 June 2022

Scope: Treatment of generalised myasthenia gravis (gMG)

5.1.4. Lenacapavir - EMEA/H/C/005638

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

5.1.5. Maribavir - EMEA/H/C/005787, Orphan

Applicant: Takeda Pharmaceuticals International AG Ireland Branch

Scope: Treatment of cytomegalovirus (CMV) infection

5.1.6. Molnupiravir - EMEA/H/C/005789

Scope: Treatment of coronavirus disease 2019 (COVID-19)

5.1.7. Surufatinib - EMEA/H/C/005728

Scope: Treatment of progressive neuroendocrine tumours

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

See Annex I 14.1.

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

See also Annex I 15.3.

5.3.1. Belatacept - NULOJIX (CAP) - EMEA/H/C/002098/II/0079/G

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Grouped variations consisting of: 1) changes to the manufacturing process of the biological active substance belatacept; 2) change to in-process tests or limits applied during the manufacture of the active substance; 3) update of the RMP (version 20.0) to include the new maintenance dose, the new potential risk of medication errors and a direct healthcare professional communication (DHPC) listed as an additional risk minimisation measure (in line with the outcome of CHMP procedure II/0065/G dated November 2021)

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 grouping of variations for Nulojix a centrally authorised medicine containing belatacept, to implement changes relating to the manufacturing process, to update the RMP to include the agreed new maintenance dose and to reflect 'medication errors' as an important potential risk. PRAC is responsible for providing advice to CHMP on the necessary updates to the RMP to support this grouped variation procedure.

Summary of advice

- The RMP (version 20.0) for Nulojix (belatacept) in the context of the grouped variation procedure under evaluation by CHMP is considered acceptable.
- PRAC agreed on the content of a direct healthcare professional communication ([DHPC](#)) along with a communication plan for its distribution.

5.3.2. Deferasirox - EXJADE (CAP) - EMEA/H/C/000670/II/0082/G

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Tiphaine Vaillant

Scope: Grouped variations consisting of: 1) submission of the final report from study C1CL670F2202 (Calypso study) (listed as a category 3 study in the RMP): a randomised, open-label, multicentre, two arm, phase 2 study to evaluate treatment compliance, efficacy and safety of deferasirox (granules) in paediatric patients with iron overload; 2) removal of the risk of 'medication error' from the RMP and of the information related to the discontinuation of the dispersible tablets in the EU. The RMP (version 20.0) 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 grouping of variations, for Exjade a centrally authorised medicine containing deferasirox, consisting of the final study results for study C1CL670F2202 (Calypso study): a randomised, open-label, multicentre, two arm, phase 2 study to evaluate treatment compliance, efficacy and safety of deferasirox (granules) in paediatric patients with iron overload, as well as of the removal of the risk of 'medication error' from the RMP and of the information related to the discontinuation of the dispersible tablets in the EU. PRAC is responsible for providing advice to CHMP on the necessary updates to the RMP to support this grouped variation procedure.

Summary of advice

- The RMP for Exjade (deferasirox) in the context of the variation procedure under evaluation by CHMP could be considered acceptable provided that a satisfactory update to RMP version 20.0 is submitted.
- Although Exjade (deferasirox) dispersible tablets is no longer marketed in the EU, PRAC considered that information regarding the dose adjustment between dispersible tablets and film-coated tablets/granules and information relating to medication errors with dispersible tablets should be maintained in the RMP, as long as dispersible tablet formulations of deferasirox are authorised in the EU as generic medicinal products. The MAH for Exjade (deferasirox) should keep the information in the RMP and Annex II-D on the risk of medication errors unchanged. Furthermore, PRAC supported to update the list of Union reference dates (EURD list) to state that PSURs are required for medicinal products authorised under Articles 10(1), 10a, 14, 16a of Directive 2001/83/EC.

5.3.3. Pneumococcal polysaccharide conjugate vaccine (adsorbed) - VAXNEUVANCE (CAP) - EMEA/H/C/005477/II/0001

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include treatment of infants, children and adolescents from 6 weeks to less than 18 years of age for active immunisation for the prevention of invasive disease, pneumonia and acute otitis media for Vaxneuvance, based on final results from: 1) study V114-008: a phase 2, double-blind, randomised, multicentre trial to evaluate the safety, tolerability, and immunogenicity of V114 (pneumococcal polysaccharide conjugate vaccine (adsorbed)) compared to Prevenar 13 (pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed)) in healthy infants; 2) seven phase 3 studies (V114-023, V114-024, V114-025, V114-027, V114-029, V114-030, V114-031): interventional studies to evaluate the safety, tolerability and immunogenicity of V114 (pneumococcal polysaccharide conjugate vaccine (adsorbed)) in healthy and immunocompromised infants, children and adolescents. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8 and 5.1 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 and to include editorial changes in the product information. The RMP (version 1.1) 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 an extension of the therapeutic indication for Vaxneuvance, a centrally authorised pneumococcal polysaccharide conjugate vaccine (adsorbed), to include treatment of infants, children and adolescents from 6 weeks to less than 18 years of age for active immunisation for the prevention of invasive disease, pneumonia and acute otitis media. PRAC is responsible for providing advice to CHMP on the necessary updates to the RMP to support this extension of indication.

Summary of advice

- The RMP for Vaxneuvance (pneumococcal polysaccharide conjugate vaccine (adsorbed)) in the context of the variation procedure under evaluation by CHMP could be considered acceptable provided that a satisfactory update to RMP version 21.1 is submitted.
- PRAC expressed concerns with regard to the size of the safety database in children of 6 months to 17 years old of age, with a view of an increased reactogenicity of the vaccine, which may lead to fever and febrile convulsions, mostly occurring in children between the ages of 6 months and 5 years. The MAH should provide a detailed discussion on the expected safety profile of the vaccine in the paediatric population and the need for post-marketing activities to address the limited safety information available in this population.

6. Periodic safety update reports (PSURs)

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

See also Annex I 14.1.

6.1.1. Alemtuzumab - LEMTRADA (CAP) - PSUSA/00010055/202109

Applicant: Sanofi Belgium

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 PSUR, PRAC reviewed the benefit-risk balance of Lemtrada, a centrally authorised medicine containing alemtuzumab 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 Lemtrada (alemtuzumab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include autoimmune encephalitis as a warning and as an undesirable effect with a frequency 'uncommon'. Therefore, the current terms of the marketing authorisation(s) should be varied¹⁴.
- In the next PSUR, the MAH should provide an updated review on cases of cardiomyopathy.

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. Cabotegravir - VOCABRIA (CAP) - PSUSA/00010900/202109

Applicant: ViiV Healthcare B.V.

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.

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

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Vocabria, a centrally authorised medicine containing cabotegravir 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 Vocabria (cabotegravir) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add type I hypersensitivity, urticaria and angioedema as undesirable effects with a frequency 'uncommon'. In addition, the existing warning on hypersensitivity reactions is refined accordingly. Therefore, the current terms of the marketing authorisation(s) should be varied¹⁵.
- In the next PSUR, the MAH should closely monitor cases of weight gain, sleep disorders, anxiety, depression, suicidal ideation and behaviour, bipolar disorder, psychosis, mood disorders, injection site reactions, rash, rhabdomyolysis, seizure, hyperglycaemia as well as severe cutaneous adverse reactions (SCARs).

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC. The frequency of submission of the subsequent PSURs should be changed from 6-monthly to yearly and the list of Union reference dates (EURD list) will be updated accordingly.

6.1.3. Crizotinib - XALKORI (CAP) - PSUSA/00010042/202108

Applicant: Pfizer Europe MA EEIG

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 Xalkori, a centrally authorised medicine containing crizotinib 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 Xalkori (crizotinib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add photosensitivity as a warning and as an undesirable effect with a frequency 'uncommon'. In addition, blood creatine phosphokinase increased should be added as an undesirable effect with a

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

frequency 'uncommon'. Therefore, the current terms of the marketing authorisation(s) should be varied¹⁶.

- In the next PSUR, the MAH should provide detailed reviews of cases of cholestasis/cholangitis and thyroid dysfunction together with a discussion on the need to update the product information and/or RMP 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.

6.1.4. [Influenza vaccine \(intranasal, live attenuated\) - FLUENZ TETRA \(CAP\) - PSUSA/00001742/202108](#)

Applicant: AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

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 Fluenz Tetra, a centrally authorised influenza vaccine (intranasal, live attenuated) 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 Fluenz Tetra (influenza vaccine (intranasal, live attenuated)) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- The MAH should submit to EMA, within 60 days, a variation to update the requirements related to study MA-VA-MEDI3250-1116¹⁷ together with data on the three completed seasons supplemented with effectiveness data from other sources.

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. [Isavuconazole - CRESEMBA \(CAP\) - PSUSA/00010426/202109](#)

Applicant: Basilea Pharmaceutica Deutschland GmbH

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

¹⁶ 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

¹⁷ A case-control study of the effectiveness of quadrivalent live attenuated influenza vaccine (Q/LAIV) versus inactivated influenza vaccine and no vaccine in subjects 2-17 years of age

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 Cresemba, a centrally authorised medicine containing isavuconazole 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 Cresemba (isavuconazole) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add anaphylactic reaction as a warning and as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied¹⁸.

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.

6.1.6. Lacosamide - LACOSAMIDE UCB (CAP); VIMPAT (CAP) - PSUSA/00001816/202108

Applicant(s): UCB Pharma S.A.

PRAC Rapporteur: Ulla Wändel Liminga

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 Lacosamide UCB and Vimpat, centrally authorised medicines containing lacosamide 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 Lacosamide UCB and Vimpat (lacosamide) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add information that lacosamide is excreted in breast milk. Therefore, the current terms of the marketing authorisation(s) should be varied¹⁹.

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

¹⁹ Update of SmPC section 4.6. 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 detailed review on pregnancy and breastfeeding.

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. Linaclotide - CONSTELLA (CAP) - PSUSA/00010025/202108

Applicant: Allergan Pharmaceuticals International Limited

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.

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Constella, a centrally authorised medicine containing linaclotide 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 Constella (linaclotide) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAH should provide a detailed review of cases of urinary retention.

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

6.1.8. Naltrexone, bupropion - MYSIMBA (CAP) - PSUSA/00010366/202109

Applicant: Orexigen Therapeutics Ireland Limited

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.

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Mysimba, a centrally authorised medicine containing naltrexone/bupropion 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 Mysimba (naltrexone/bupropion) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add panic attack as a warning as part of the existing warning on neuropsychiatric symptoms and as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied²⁰.
- In the next PSUR, the MAH should provide an updated analysis of cases of incorrect dosing patterns/treatment withdrawals in order to evaluate intentional dose reductions, delayed up-titrations and treatment withdrawals due to intolerance, as well as other patterns of intentional treatment modifications, off-label use and misuse.

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

6.1.9. Pembrolizumab - KEYTRUDA (CAP) - PSUSA/00010403/202109

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

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 Keytruda, a centrally authorised medicine containing pembrolizumab 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 Keytruda (pembrolizumab) in the approved indication(s) remains unchanged.
- Nevertheless, the package leaflet should be updated in line with the summary of product characteristics (SmPC) to ensure that patients are fully informed about diabetic ketoacidosis (DKA), the particular signs to be aware of and relevant symptoms. Therefore, the current terms of the marketing authorisation(s) should be varied²¹.
- In the next PSUR, the MAH should provide an updated detailed review of cases of systemic lupus erythematosus with 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.

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 the package leaflet. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion

6.1.10. Tildrakizumab - ILUMETRI (CAP) - PSUSA/00010720/202109

Applicant: Almirall S.A

PRAC Rapporteur: Adam Przybylkowski

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 Ilumetri, a centrally authorised medicine containing tildrakizumab 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 Ilumetri (tildrakizumab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the existing information on immunogenicity and neutralising antibodies (NAb). Therefore, the current terms of the marketing authorisation(s) should be varied²².
- In the next PSUR, the MAH should continue collecting data from ongoing trials regarding the clinical significance of anti-drug antibodies, especially NAb against tildrakizumab during shorter courses of therapy up to 12 weeks of drug use and during more prolonged treatment, > 12 weeks of drug use.

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

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

See also Annex I 16.2.

6.2.1. Brinzolamide - AZOPT (CAP); NAP - PSUSA/00000432/202108

Applicants: Novartis Europharm Limited (Azopt), various

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

Background

Brinzolamide is a carbonic anhydrase inhibitor indicated to decrease elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma, as monotherapy in

²² Update of SmPC section 4.8. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion

adult patients unresponsive to beta-blockers or in adult patients in whom beta-blockers are contraindicated, or as adjunctive therapy to beta-blockers or prostaglandin analogues.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of Azopt, a centrally authorised medicine containing brinzolamide, and nationally authorised medicine(s) containing brinzolamide 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 brinzolamide-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) as a warning and as undesirable effects with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied²³.
- In the next PSUR, the MAHs should provide an updated detailed review of cases of corneal decompensation.

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 considered that the risk of SJS and TEN is also relevant for medicinal products containing brinzolamide in fixed-dose combinations. Further consideration is to be given at CHMP and CMDh. PRAC also considered that MAH(s) with an RMP in place should update it in line with the outcome of the current procedure at the next regulatory opportunities affecting the RMP or within 180 days following finalisation of the current procedure.

6.2.2. Mercaptopurine - XALUPRINE (CAP); NAP - PSUSA/00001988/202109

Applicants: Nova Laboratories Ireland Limited (Xaluprine), various

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

Background

6-mercaptopurine is an inactive pro-drug which acts as a purine antagonist but requires cellular uptake and intracellular anabolism to thioguanine nucleotides (TGNs). It is indicated for the treatment of acute lymphoblastic leukaemia (ALL) in adults, adolescents and children.

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

²³ 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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of mercaptopurine-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add erythema nodosum as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied²⁴.
- In the next PSUR, the MAHs should provide a detailed review of cases of coagulation disorders together with a proposal to update the product information as warranted. In addition, the MAH Nova Laboratories Ireland Limited should provide a detailed review of cases of medication errors related to conversion errors reported with Xaluprine (mercaptopurine). The MAH Aspen should provide a cumulative review on veno-occlusive liver disease together with a proposal to update the product information as warranted.

The frequency of PSUR submission should be revised from five-yearly to two-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. PSUR single assessment (PSUSA) procedures including nationally authorised products (NAPs) only

See also Annex I 14.1.

6.3.1. Dexamfetamine (NAP) - PSUSA/00000986/202109

Applicant(s): various

PRAC Lead: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

Background

Dexamfetamine is a non-catecholamine indicated for the treatment of attention-deficit/hyperactivity disorder (ADHD) in children and adolescents aged 6 to 17 years when response to previous methylphenidate treatment is considered clinically inadequate. In some Member States, it is indicated for the treatment of refractory hyperkinetic states and of narcolepsy.

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

²⁴ 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

- Nevertheless, the product information should be updated to add that amphetamines can cause an increased cortisol level. Therefore, the current terms of the marketing authorisation(s) should be varied²⁵.
- In the next PSUR, the MAH(s) should provide analyses of cases of azoospermia and of artery dissection.

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

6.3.2. Estradiol²⁶ (NAP) - PSUSA/00010440/202108

Applicant(s): various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

Background

Estradiol is a steroid, an estrogen and the primary female sex hormone. It is indicated, as oral tablets, transdermal patches, topical/transdermal gel and transdermal spray, for the treatment of signs and symptoms of estrogen deficiency due to natural menopause or castration as treatment of hormone replacement therapy (HRT) as well as for the prevention of post-menopausal osteoporosis. As vaginal rings and vaginal tablets, estradiol is indicated for the treatment of vaginal atrophy due to estrogen deficiency in postmenopausal women.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing estradiol²⁷ 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 estradiol²⁸-containing product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information of estradiol-containing spray/gel product(s) for transdermal use should be updated to add information on the risk of estradiol transfer to children and pets from patients using estradiol as spray or gel for transdermal use. Therefore, the current terms of the marketing authorisation(s) should be varied²⁹.
- The current terms of the marketing authorisation(s) for estradiol oral tablets, transdermal patches, vaginal rings and vaginal tablets should be maintained.
- In the next PSUR, the MAH(s) of estradiol transdermal patches should provide a detailed review on the risk of estradiol transfer together with a proposal to update the product information as warranted.

²⁵ Update of SmPC section 4.5. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position

²⁶ Except cream, balm, emulsion for application in female genital area

Except cream, balm, emulsion for application in female genital area

²⁸ Except cream, balm, emulsion for application in female genital area

²⁹ Update of SmPC sections 4.2 and 4.4. 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.

6.3.3. Etonogestrel (NAP) - PSUSA/00001331/202109

Applicant(s): various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

Background

Etonogestrel is a synthetic progestogen indicated as a long-acting contraceptive implant.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing etonogestrel 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 etonogestrel-containing product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add vasovagal reactions as an undesirable effect in connection with the insertion of the implant. Therefore, the current terms of the marketing authorisation(s) should be varied³⁰.
- In the next PSUR, the MAH(s) should provide reviews of cases of arterial thrombotic events, nerve injury, meningioma and inappropriate product administration duration. In addition, the MAH(s) should provide a cumulative review of cases of breast hyperplasia/pseudoangiomatous stromal hyperplasia (PASH).

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

6.3.4. Gadobenic acid (NAP) - PSUSA/00001500/202108

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

Gadobenic acid is a linear gadolinium-based contrast agent (GdCA) indicated for use in diagnostic magnetic resonance imaging (MRI) of the liver, only when diagnostic information is essential and not available with unenhanced MRI and when delayed phase imaging is required.

³⁰ Update of SmPC section 4.8. 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 gadobenic acid and issued a recommendation on their marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of gadobenic acid-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 MAH(s) should provide a detailed review of cases of persistent symptoms in patients who retain gadolinium after receiving GdCAs together with a proposal for further assessment and to update the product information as warranted with relevant communication as applicable. The review should also include all cases in which laboratory tests are performed to assess gadolinium levels in tissues/body fluids as well as all cases in which patients are treated with chelating agents or other treatments for gadolinium retention or gadolinium deposition disease. The MAH(s) should search for cases identified as 'gadolinium deposition disease'. In addition, the MAH(s) should provide the protocol of study ODYSSEY³¹, with a status update and preliminary results. Moreover, the MAH(s) should provide reviews on the potential risk of congenital abnormalities, stillbirth and neonatal death with the use of GdCAs during pregnancy and when administered intrathecally.

The frequency of PSUR submission should be revised from yearly to two-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 considered that follow-up questionnaires for cases of potential persistent symptoms should be implemented in RMPs of medicinal product(s) that have one in place. Further consideration is to be given at the level of CMDh.

6.3.5. Gadobutrol (NAP) - PSUSA/00001502/202108

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

Gadobutrol is a macrocyclic gadolinium-based contrast agent (GdCA) indicated for diagnostic magnetic resonance imaging (MRI) of the whole body, including cranial and spinal MRI, head and neck, thoracic space, breast, abdomen, pelvis, retroperitoneal space, musculoskeletal system, magnetic resonance angiography and cardiac MRI.

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

Summary of recommendation(s) and conclusions

³¹ A prospective evaluation of potential effects of repeated GdCA administrations of the same GdCA on motor and cognitive functions in neurologically normal adults in comparison to a non-GdCA exposed control group

- Based on the review of the data on safety and efficacy, the benefit-risk balance of gadobutrol-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 MAH(s) should provide a detailed review of cases of persistent symptoms in patients who retain gadolinium after receiving GdCAs together with a proposal for further assessment and to update the product information as warranted with relevant communication as applicable. The review should also include all cases in which laboratory tests are performed to assess gadolinium levels in tissues/body fluids as well as all cases in which patients are treated with chelating agents or other treatments for gadolinium retention or gadolinium deposition disease. In addition, the MAH(s) should provide an overview of the implementation of the targeted follow-up questionnaire in this respect. The MAH(s) should search for cases identified as 'gadolinium deposition disease'. In addition, the MAH(s) should provide the protocol of study ODYSSEY³², with a status update and preliminary results. Moreover, the MAH(s) should provide reviews on the potential risk of congenital abnormalities, stillbirth and neonatal death with the use of GdCAs during pregnancy and when administered intrathecally.

The frequency of PSUR submission should be revised from yearly to two-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 considered that follow-up questionnaires for cases of potential persistent symptoms should be implemented in RMPs of medicinal product(s) that have one in place. Further consideration is to be given at the level of CMDh.

6.3.6. Gadopentetic acid (NAP) - PSUSA/00001504/202108

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

Gadopentetic acid is a linear gadolinium-contrast agent (GdCA) indicated for diagnostic magnetic resonance imaging (MRI) of the whole body, as well as cranial and spinal MRI. It is also indicated for contrast enhancement in magnetic resonance arthrography and for the demonstration and demarcation of the digestive tract from adjacent normal and pathological tissue structures in MRI, under certain conditions.

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

³² A prospective evaluation of potential effects of repeated GdCA administrations of the same GdCA on motor and cognitive functions in neurologically normal adults in comparison to a non-GdCA exposed control group

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of gadopentetic acid-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 MAH(s) should provide a detailed review of cases of persistent symptoms in patients who retain gadolinium after receiving GdCAs together with a proposal for further assessment and to update the product information as warranted with relevant communication as applicable. The review should also include all cases in which laboratory tests are performed to assess gadolinium levels in tissues/body fluids as well as all cases in which patients are treated with chelating agents or other treatments for gadolinium retention or gadolinium deposition disease. In addition, the MAH(s) should provide an overview of the implementation of the targeted follow-up questionnaire in this respect. The MAH(s) should search for cases identified as 'gadolinium deposition disease'. In addition, the MAH(s) should provide the protocol of study ODYSSEY³³, with a status update and preliminary results. Moreover, the MAH(s) should provide reviews on the potential risk of congenital abnormalities, stillbirth and neonatal death with the use of GdCAs during pregnancy and when administered intrathecally.

The frequency of PSUR submission should be revised from yearly to two-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 considered that follow-up questionnaires for cases of potential persistent symptoms should be implemented in RMPs of medicinal product(s) that have one in place. Further consideration is to be given at the level of CMDh.

6.3.7. Gadoteric acid³⁴ (NAP) - PSUSA/00001506/202108

Applicant(s): various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

Background

Gadoteric acid is a macrocyclic gadolinium-based contrast agent (GdCA) indicated as intravenous and intravascular formulations for intensification of the contrast in magnetic resonance imaging (MRI) for a better visualisation/delineation of lesions of the brain, spine, and surrounding tissues, lesions of the liver, kidneys, pancreas, pelvis, lungs, heart, breast, and musculoskeletal system in adults and paediatrics. It is also indicated for a better visualisation/delineation of lesions or stenoses of the non-coronary arteries in adults.

³³ A prospective evaluation of potential effects of repeated GdCA administrations of the same GdCA on motor and cognitive functions in neurologically normal adults in comparison to a non-GdCA exposed control group

³⁴ Intravenous (IV) and intravascular formulation(s) only

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing gadoteric acid³⁵ 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 gadoteric acid-containing product(s) as intravenous and intravascular formulations in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAH(s) should provide a detailed review of cases of persistent symptoms in patients who retain gadolinium after receiving GdCAs together with a proposal for further assessment and to update the product information as warranted with relevant communication as applicable. The review should also include all cases in which laboratory tests are performed to assess gadolinium levels in tissues/body fluids as well as all cases in which patients are treated with chelating agents or other treatments for gadolinium retention or gadolinium deposition disease. In addition, the MAH(s) should provide an overview of the implementation of the targeted follow-up questionnaire in this respect. The MAH(s) should search for cases identified as 'gadolinium deposition disease'. In addition, the MAH(s) should provide the protocol of study ODYSSEY³⁶, with a status update and preliminary results. Moreover, the MAH(s) should provide a review of cases of throat irritation.

The frequency of PSUR submission should be revised from yearly to two-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 considered that follow-up questionnaires for cases of potential persistent symptoms should be implemented in RMPs of medicinal product(s) that have one in place. Further consideration is to be given at the level of CMDh.

6.3.8. Gadoteridol (NAP) - PSUSA/00001507/202108

Applicant(s): various

PRAC Lead: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

Background

Gadoteridol is a macrocyclic gadolinium-contrast agent (GdCA) indicated for diagnostic magnetic resonance imaging (MRI) of the whole body, including head, neck, liver, breast, musculoskeletal system and soft tissue pathologies, as well as cranial and spinal MRI.

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

³⁵ IV and intravascular formulation(s) only

³⁶ A prospective evaluation of potential effects of repeated GdCA administrations of the same GdCA on motor and cognitive functions in neurologically normal adults in comparison to a non-GdCA exposed control group

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of gadoteridol-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 MAH(s) should provide a detailed review of cases of persistent symptoms in patients who retain gadolinium after receiving GdCAs together with a proposal for further assessment and to update the product information as warranted with relevant communication as applicable. The review should also include all cases in which laboratory tests are performed to assess gadolinium levels in tissues/body fluids as well as all cases in which patients are treated with chelating agents or other treatments for gadolinium retention or gadolinium deposition disease. In addition, the MAH(s) should provide an overview of the implementation of the targeted follow-up questionnaire in this respect. The MAH(s) should search for cases identified as 'gadolinium deposition disease'. In addition, the MAH(s) should provide the protocol of study ODYSSEY³⁷, with a status update and preliminary results. Moreover, the MAH(s) should discuss the article by *Patel et al*³⁸ concerning the safety of intrathecal administration of GdCAs (off-label to gadoteridol) and comment whether the current product information on gadoteridol in relation to off-label use is adequate.

The frequency of PSUR submission should be revised from yearly to two-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 considered that follow-up questionnaires for cases of potential persistent symptoms should be implemented in RMPs of medicinal product(s) that have one in place. Further consideration is to be given at the level of CMDh.

6.3.9. Gadoxetic acid disodium (NAP) - PSUSA/00001509/202108

Applicant(s): various

PRAC Lead: Annika Folin

Scope: Evaluation of a PSUSA procedure

Background

Gadoxetic acid disodium is a linear gadolinium-based contrast agent (GdCA) indicated for diagnostic magnetic resonance imaging (MRI) of the liver.

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

Summary of recommendation(s) and conclusions

³⁷ A prospective evaluation of potential effects of repeated GdCA administrations of the same GdCA on motor and cognitive functions in neurologically normal adults in comparison to a non-GdCA exposed control group

³⁸ Patel et al. Safety of intrathecal administration of gadolinium-based contrast agents: a systematic review and meta-analysis. *Radiology*. 2020 Oct;297(1):75-83. doi: 10.1148/radiol.2020191373. Epub 2020 Jul 28

- Based on the review of the data on safety and efficacy, the benefit-risk balance of gadoxetic acid disodium-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 MAH(s) should provide a detailed review of cases of persistent symptoms in patients who retain gadolinium after receiving GdCAs together with a proposal for further assessment and to update the product information as warranted with relevant communication as applicable. The review should also include all cases in which laboratory tests are performed to assess gadolinium levels in tissues/body fluids as well as all cases in which patients are treated with chelating agents or other treatments for gadolinium retention or gadolinium deposition disease. In addition, the MAH(s) should provide an overview of the implementation of the targeted follow-up questionnaire in this respect. The MAH(s) should search for cases identified as 'gadolinium deposition disease'. In addition, the MAH(s) should provide the protocol of study ODYSSEY³⁹, with a status update and preliminary results.

The frequency of PSUR submission should be revised from yearly to two-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 considered that follow-up questionnaires for cases of potential persistent symptoms should be implemented in RMPs of medicinal product(s) that have one in place. Further consideration is to be given at the level of CMDh.

6.3.10. Modafinil (NAP) - PSUSA/00010242/202108

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

Modafinil is a psychostimulant indicated for the treatment of excessive sleepiness associated with narcolepsy with or without cataplexy in adults.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing modafinil 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 modafinil-containing product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the existing warning on abuse, misuse and diversion to include patients with a history of psychiatric

³⁹ A prospective evaluation of potential effects of repeated GdCA administrations of the same GdCA on motor and cognitive functions in neurologically normal adults in comparison to a non-GdCA exposed control group

disorders. Therefore, the current terms of the marketing authorisation(s) should be varied⁴⁰.

- In the next PSUR, the MAH(s) should provide a detailed review of cases of 'ischaemic cerebrovascular events' together with a proposal to update the product information as applicable.

The frequency of PSUR submission should be revised from yearly to two-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 considered that targeted follow-up questionnaire(s) should be implemented to aid data capture from cases on 'drug abuse, misuse, dependence and diversion'. Further consideration is to be given at the level of CMDh.

6.3.11. Nifuroxazide (NAP) - PSUSA/00002160/202108

Applicant(s): various

PRAC Lead: Jana Lukačičšinová

Scope: Evaluation of a PSUSA procedure

Background

Nifuroxazide is a nitrofurantoin indicated for the treatment of acute diarrhoea presumably from bacterial origin, in the absence of suspected invasive phenomena.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing nifuroxazide 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 nifuroxazide-containing product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the information regarding use during pregnancy, while breastfeeding and use in patients with childbearing potential. In addition, the product information should be updated to include information regarding nifuroxazide bioavailability, potential mutagenicity, absence of carcinogenicity and non-clinical investigations. Therefore, the current terms of the marketing authorisation(s) should be varied⁴¹.
- In the next PSUR, the MAH(s) should provide a detailed review of cases of haemolytic uremic syndrome.

The frequency of PSUR submission should be revised from two-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.

⁴⁰ 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

⁴¹ Update of SmPC sections 4.6, 5.2 and 5.3. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position

6.3.12. Oxcarbazepine (NAP) - PSUSA/00002235/202108

Applicant(s): various

PRAC Lead: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

Background

Oxcarbazepine is an antiepileptic, a derivate of carbamazepine. It is indicated in adults and in children aged one month and above for the treatment of partial seizures, including seizure subtypes of simple, complex and partial seizures evolving to secondarily generalised seizures as well as for the treatment of generalised tonic-clonic seizure.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing oxcarbazepine 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 oxcarbazepine-containing product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the information on breastfeeding and to add information on neurodevelopmental disorders. In addition, information on congenital malformations should be added to the package leaflet in line with the summary of product characteristics (SmPC). Therefore, the current terms of the marketing authorisation(s) should be varied⁴².
- In the next PSUR, the MAH(s) should provide a review of any safety information on breastfeeding including data supporting breastfeeding of infants by mothers using oxcarbazepine, together with a proposal to update the product information as warranted. The MAH Novartis should provide an analysis of cases of major malformations.

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.

6.4. Follow-up to PSUR/PSUSA procedures

See also Annex I 14.1.

6.4.1. Tolvaptan - JINARC (CAP) - EMEA/H/C/002788/LEG 008.2

Applicant: Otsuka Pharmaceutical Netherlands B.V.

PRAC Rapporteur: Amelia Cupelli

Scope: MAH's response to LEG 008.1 [review of cases of rapid correction of hyponatremia and neurological sequelae as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00010395/202005) adopted in January 2021] as per the

⁴² Update of SmPC section 4.6. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position

request for supplementary information (RSI) adopted in December 2021⁴³

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.

Following the evaluation of the most recently submitted PSUR(s) for the above-mentioned medicine(s), PRAC requested the MAH for Jinarc (tolvaptan) to submit further data on cases of rapid correction of hyponatremia and neurological sequelae. For further background, see [PRAC minutes January 2021](#), [PRAC minutes June 2021](#) and [PRAC minutes December 2021](#)⁴⁴. The responses were assessed by the Rapporteur for further PRAC advice.

Summary of advice/conclusion(s)

- Based on the available data and the Rapporteur's assessment, PRAC supported the implementation of a targeted follow-up questionnaire (FUQ) as a tool to gather additional clinical and laboratory information on sodium levels at baseline and at the time of occurrence of neurological or emotional events potentially related to suspected rapid correction of hyponatremia (RCHN) and neurological sequelae, including osmotic demyelination syndrome (ODS).

6.5. Variation procedure(s) resulting from PSUSA evaluation

See also Annex I 14.1.

6.5.1. Pregabalin - LYRICA (CAP) - EMEA/H/C/000546/WS2168/0114; PREGABALIN PFIZER (CAP) - EMEA/H/C/003880/WS2168/0043

Applicant: Upjohn EESV

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Update of sections 4.4 and 4.8 of the SmPC to reflect new data on suicidal ideation as requested in the outcome of the review assessed in LEG 0054 (Lyrica) and LEG 007 (Pregabalin Pfizer) adopted in April 2021 and requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00002511/202001) adopted in September 2020

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.

Following the evaluation of the most recently submitted PSUR(s) for the above-mentioned medicine(s), the MAH for Lyrica and Pregabalin Pfizer (pregabalin) submitted a variation to EMA to update the product information to reflect new data on suicidal ideation and behaviour. 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

⁴³ Held 29 November - 02 December 2021

⁴⁴ Held 29 November - 02 December 2021

adopting an opinion on this variation. For further background, see [PRAC minutes September 2020](#)⁴⁵ and [PRAC minutes April 2021](#).

Summary of recommendation(s)

- Based on the available data and the Rapporteur's assessment, PRAC agreed to amend⁴⁶ the existing warning of the product information on suicidal ideation and behaviour, and to add these as undesirable effects with a frequency 'rare'.

6.6. Expedited summary safety reviews⁴⁷

See Annex I 14.1.

7. Post-authorisation safety studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)⁴⁸

See Annex I 14.1.

7.2. Protocols of PASS non-imposed in the marketing authorisation(s)⁴⁹

See Annex I 14.1.

7.3. Results of PASS imposed in the marketing authorisation(s)⁵⁰

7.3.1. Dexketoprofen, tramadol (NAP) - EMEA/H/N/PSR/S/0035

Applicant: Menarini International Operations Luxembourg S.A. (Dextradol, Enanplus, Skudexa, Takudex)

PRAC Rapporteur: Eva Segovia

Scope: MAH's response to PSR/S/0035 [results of a drug utilisation study (DUS) and PASS on tramadol-dexketoprofen (DKP-TRAM) fixed combination to evaluate pattern of prescriptions of DKP-TRAM and assess the risk of adverse events (AE) (e.g. nausea, vomiting, diarrhoea, vertigo) in DKP-TRAM vs. tramadol monotherapy (including tramadol-paracetamol combinations) users, with a special focus on patients 75 years old and over] as per the request for supplementary information (RSI) adopted in November 2021⁵¹

Background

Dexketoprofen is a nonsteroidal anti-inflammatory drug (NSAID) and tramadol an opioid. In combination, dexketoprofen/tramadol is indicated for the symptomatic short-term treatment of moderate to severe acute pain in adult patients whose pain is considered to require a combination of dexketoprofen and tramadol.

⁴⁵ Held 31 August – 3 September 2020

⁴⁶ Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly

⁴⁷ 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

⁴⁸ In accordance with Article 107n of Directive 2001/83/EC

⁴⁹ 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

⁵⁰ In accordance with Article 107p-q of Directive 2001/83/EC

⁵¹ Held 25-28 October 2021

In line with the conditions of the marketing authorisation(s) imposed as an outcome of the assessment of the marketing authorisation application (ES/H/O317-0318/001/DC), the MAH Menarini International Operations Luxembourg SA (MIOL) - Laboratorios Menarini S.A. conducted a study to evaluate the pattern of prescriptions of dexketoprofen/tramadol as a fixed dose combination in the primary care setting with a special focus on patients aged 75 years and over.

The MAH Menarini International Operations Luxembourg SA (MIOL) - Laboratorios Menarini S.A. submitted to EMA the final results version 03 of the 'drug utilisation study (DUS) and post authorisation safety study (PASS) on the fixed combination dexketoprofen/tramadol'. PRAC discussed the final study results. PRAC is responsible for evaluating the PASS final results. For further background, see [PRAC minutes November 2021](#)⁵².

Summary of recommendation(s) and conclusions

- Based on the review of the final report of the study and the assessment from the Rapporteur, PRAC considered that the obligation to perform the PASS is fulfilled.
- Despite some study limitations, PRAC agreed that no new relevant concerns have emerged in relation to the safety profile or the pattern of use of dexketoprofen/tramadol.
- The benefit-risk balance of dexketoprofen/tramadol-containing product(s) concerned by this study final report remains unchanged. PRAC agreed that changes to the product information⁵³ are not warranted, and the medicinal product(s) should be removed from the list of medicinal products subject to additional monitoring. The RMP should be updated at the next regulatory opportunity to remove the study from all relevant sections.

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

See Annex I 14.1.

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

See Annex I 14.1.

7.6. Others

See Annex I 14.1.

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.

⁵² Held 25-28 October 2021

⁵³ SmPC and package leaflet

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

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

10.1.1. Rucaparib - RUBRACA (CAP) - EMEA/H/C/004272/II/0029

Applicant: Clovis Oncology Ireland Limited

PRAC Rapporteur: Annika Folin

Scope: PRAC consultation in a variation to update sections 4.4, 4.8 and 5.1 of the SmPC based on final results from study CO-338-043 (ARIEL4) (listed as a specific obligation in Annex II): a phase 3, multicentre, open-label, randomised study evaluating the efficacy and safety of rucaparib versus chemotherapy for treatment of relapsed ovarian cancer. The package leaflet and the RMP (version 6.1) are updated accordingly. In addition, the MAH took the opportunity to make minor editorial changes and bring the product information in line with the latest bring the product information in line with the latest quality review of documents (QRD) template (version 10.2 Rev.1)

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.

A type II variation proposing to update the product information of Rubraca (rucaparib) based on results from study CO-338-043 (ARIEL4), a phase 3, multicentre, open-label, randomised study evaluating the efficacy and safety of rucaparib versus chemotherapy for treatment of relapsed ovarian cancer is under evaluation at CHMP. PRAC was requested to provide advice on this variation. For further background, see [PRAC minutes November 2021](#)⁵⁵.

Summary of advice

- Based on the review of the available information and assessment, PRAC agreed with CHMP that the interim analysis of overall survival data is suggestive of a detrimental effect. PRAC supported to make available those data with key messages to healthcare professionals in a timely manner via a direct healthcare professional communication (DHPC). This is without prejudice to further assessment and regulatory actions.

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.

⁵⁵ Held 25-28 October 2021

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

11.1. Safety related variations of the marketing authorisation

11.1.1. Ibuprofen (NAP) - DE/H/0392/II/032/G

Applicant: Johnson & Johnson GmbH (Dolormin für Kinder Ibuprofensaft 20 mg/mL)

PRAC Lead: Martin Huber

Scope: PRAC consultation on a grouped type II variation (DE/H/0392/II/032/G) on the use of ibuprofen during pregnancy, on request of Germany

Background

Ibuprofen is a nonsteroidal anti-inflammatory drug (NSAID) indicated in the treatment of pain, fever and inflammation under certain conditions.

In the context of the evaluation of a grouped variation procedure for Dolormin für Kinder Ibuprofensaft 20 mg/mL (ibuprofen) on the use of ibuprofen during pregnancy, Germany as reference Member State (RMS) for the medicinal product, requested PRAC advice on its assessment.

Summary of advice

- Based on the review of the available information, PRAC agreed that further consideration is needed regarding the suggested wording on the use of ibuprofen in pregnancy before any final advice can be issued.
- The RMS agreed to consult PRAC again for further PRAC advice.

11.2. Other requests

None

12. Organisational, regulatory and methodological matters

12.1. Mandate and organisation of PRAC

12.1.1. PRAC membership

The PRAC Chair welcomed Lina Šeibokienė as the new alternate for Lithuania (mandate started on 25 March 2022).

12.1.2. Vote by proxy

None

12.1.3. Relaunch of face-to-face scientific Committee meetings - pilot

Following the previous discussion on the relaunch of face-to-face scientific Committee meetings at EMA (for background, see [PRAC minutes September 2021](#)⁵⁶), the EMA Secretariat presented to PRAC the revised pilot including a practical guidance for hybrid meetings (including remote and physical participants) to start from May 2022.

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, 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.

12.5. Cooperation with International Regulators

None

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 Q1 2022

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

⁵⁶ Held 30 August – 02 September 2021

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)

None

12.10.3. PSURs repository

None

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

PRAC endorsed the draft revised EURD list, version April 2022, reflecting 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 PRAC (see [PRAC minutes April 2013](#)).

Post-meeting note: following the PRAC meeting of April 2022, the updated EURD list was adopted by CHMP and CMDh at their April 2022 meetings and published on the EMA website, see: [Home > Human Regulatory > Pharmacovigilance > Periodic safety update reports > EURD list > List of Union reference dates and frequency of submission of periodic safety update reports \(PSURs\)](#)

12.11. Signal management

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

PRAC lead: Menno van der Elst

PRAC was updated on the progress from the SMART Working Group meeting on processes

held on 14 March 2022. The meeting focused on best practices to frame the scope of PRAC recommendations for signal procedures, in particular when it refers to a class of substances. Follow-up discussion will take place as appropriate.

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

12.16.2. Renewals, conditional renewals, annual reassessments

None

12.17. Risk communication and transparency

12.17.1. Public participation in pharmacovigilance

None

12.17.2. Safety communication

None

12.17.3. Direct healthcare professional communication (DHPC) review process - proposal for improvement

PRAC held a discussion on the review process of DHPC for safety issues to ensure the Committee is systematically involved for any procedures handled at CHMP level with a need for a DHPC. PRAC also discussed scenarios where several medicinal products are involved for a given substance or combination of substances, with different types of marketing authorisations, and possibilities to encourage joint DHPCs. Further discussion will follow in due course.

12.18. Continuous pharmacovigilance

12.18.1. Incident management

None

12.19. Impact of pharmacovigilance activities

12.19.1. Strategy on measuring the impact of pharmacovigilance activities revision 2 – PRAC interest group (IG) Impact

In line with the PRAC interest group (IG) work plan, on behalf of the PRAC IG Impact, the EMA Secretariat presented to PRAC the proposed revised PRAC impact strategy document that includes achievements of the past 5 years. PRAC endorsed the document.

Post-meeting note: On 6 April 2022, the 'PRAC Strategy on Measuring the Impact of Pharmacovigilance Activities revision 2' ([EMA/590673/2020 Rev2](https://www.ema.europa.eu/en/press/news/2022/04/06/prac-strategy-on-measuring-the-impact-of-pharmacovigilance-activities-revision-2)) was published on the EMA website.

12.19.2. [Strategy on measuring the impact of pharmacovigilance – PRAC interest group \(IG\) Impact – revision of the process for prioritisation and follow-up of impact research](#)

In the context of the adoption of the revised 'PRAC strategy on measuring the impact of pharmacovigilance activities' (see 12.20.1.), on behalf of the PRAC interest group (IG) Impact, the EMA Secretariat presented to PRAC the proposed revised process for prioritisation and regulatory follow-up on EMA commissioned and collaborative impact research to ensure the results of impact studies are integrated in PRAC regulatory decision-making. PRAC endorsed the document.

12.19.3. [Strategy on measuring the impact of pharmacovigilance – PRAC interest group \(IG\) Impact – pilot for enhancing PRAC stakeholder engagement](#)

PRAC lead: Daniel Morales

In line with the PRAC Impact strategy objectives and following previous discussion (for background, see [PRAC minutes October 2021](#)⁵⁷), the EMA Secretariat presented to PRAC, on behalf of the PRAC interest group (IG) Impact, a more detailed plan for a pilot for a working group for enhancing PRAC engagement with patients and healthcare professionals in relation to risk minimisation measures (RMM). The pilot working group will be established to provide support for preparing and discussing input to PRAC decisions on the implementability of potential additional risk minimisation measures (aRMM). The modus operandi of the pilot working group called 'PRAC Risk Minimisation Alliance (PRISMA)' was presented to PRAC. The committee agreed with the document. The pilot will be continuously evaluated until 2023 to inform future operations. Further update will be provided in due course.

12.20. Others

12.20.1. [EMA-funded study on thrombosis and thrombocytopenia syndrome \(TTS\) after vaccination against severe acute respiratory syndrome coronavirus 2 \(SARS-CoV-2\) – study results](#)

The EMA Secretariat presented to PRAC the key results of the EMA-funded study on thrombosis and thrombocytopenia syndrome (TTS) or thromboembolic events after vaccination against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). PRAC noted the results.

Post-meeting note: In October 2022, the 'Comparative risk of thrombosis with thrombocytopenia syndrome or thromboembolic events associated with different covid-19 vaccines: international network cohort study from five European countries and the US' was published in BMJ⁵⁸.

12.20.2. [EMA-funded study on early safety monitoring of coronavirus 2019 \(COVID-19\) vaccines in EU Member States – study results](#)

The key results of the EMA-funded study on early safety monitoring of coronavirus 2019 (COVID-19) vaccines in EU Member States, including adverse events of special interest (AESIs) were presented to PRAC. PRAC noted the results.

⁵⁷ Held 27-30 September 2021

⁵⁸ BMJ. 2022 Oct 26;379:e071594. doi: 10.1136/bmj-2022-071594

12.20.3. Questions and answers (Q&A) document on 'complex clinical trials' - draft

The EMA Secretariat presented to PRAC the draft questions and answers (Q&A) document on 'complex clinical trials', a joint European Commission (EC)- Clinical Trials Coordination Group (CTCG)-EMA document. PRAC members were invited to provide written comments by 28 April 2022.

Post-meeting note: On 23 May 2022, the final Q&A on 'complex clinical trials' ([EMA/298712/2022](https://www.ema.europa.eu/en/press-room/2022/05/wcms_748112)) was published on the EC website.

13. Any other business

None

14. Annex I – Signals assessment and prioritisation⁵⁹

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 timetables⁶⁰.

14.1.1. Rivaroxaban - RIVAROXABAN ACCORD (CAP), RIVAROXABAN MYLAN (CAP), XARELTO (CAP); NAP

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 – New signal

Lead Member State(s): SE

14.2. New signals detected from other sources

None

14.3. Signals follow-up and prioritisation

None

⁵⁹ Each signal refers to a substance or therapeutic class. The route of marketing authorisation is indicated in brackets (CAP for Centrally Authorised Products; NAP for Nationally Authorised Products including products authorised via Mutual Recognition Procedures and Decentralised Procedure). Product names are listed for reference Centrally Authorised Products (CAP) only. PRAC recommendations will specify the products concerned in case of any regulatory action required

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

14.4. Variation procedure(s) resulting from signal evaluation

14.4.1. Lenvatinib - KISPLYX (CAP) - EMEA/H/C/004224/WS2235/0050; LENVIMA (CAP) - EMEA/H/C/003727/WS2235/0046

Applicant: Eisai GmbH

PRAC Rapporteur: Annika Folin

Scope: Update of section 4.8 of the SmPC in order to add colitis as an adverse drug reaction with a frequency 'uncommon' following the outcome of the signal procedure (EPITT 19691) adopted in November 2021. The package leaflets are updated accordingly

14.4.2. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/II/0044

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Update of sections 4.4, 4.8 and 5.1 to add warnings and safety data on serious infections, viral reactivation, non-melanoma skin cancer and fractures. This is based on the final results from study A3921133 (listed as a category 3 study in the RMP): a PASS conducted to evaluate the safety of tofacitinib 5 mg and 10 mg compared to tumour necrosis factor inhibitor (TNFi) in adult subjects aged ≥ 50 years with moderately or severely active rheumatoid arthritis (RA) and with at least 1 additional cardiovascular (CV) risk factor, as requested in the outcome of the signal procedure (EPITT 19382) adopted in June 2021 (SDA 016). The package leaflet is updated accordingly. The RMP (version 21.1) is also updated in accordance. In addition, the MAH took the opportunity to update the outer carton (section 4 for oral solution) to include a total volume of 240 mL as requested in the conclusions of procedure X/0024/G adopted in June 2021

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/005963

Generic

Scope: Treatment of multiple sclerosis

15.1.2. Ranibizumab - EMEA/H/C/005019

Scope: Treatment of neovascular (wet) age-related macular degeneration (AMD), visual impairment due to diabetic macular oedema (DME), proliferative diabetic retinopathy (PDR), visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO)

or central RVO) and visual impairment due to choroidal neovascularisation (CNV)

15.1.3. Sorafenib - EMEA/H/C/005921

Scope: Treatment of hepatocellular carcinoma and renal cell carcinoma

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. Bulevirtide - HEPCLUDEX (CAP) - EMEA/H/C/004854/II/0012, Orphan

Applicant: Gilead Sciences Ireland Unlimited Company

PRAC Rapporteur: Adam Przybylkowski

Scope: Submission of an updated RMP (version 1.2) in order to replace non-interventional study MYR-HDV (listed as a category 3 study in the RMP): a long-term safety and efficacy registry, with interventional registry study GS-US-589-6206: a registry study of treatment with bulevirtide in participants with chronic hepatitis D infection. In addition, the MAH took the opportunity to update the information in the RMP on epidemiology, clinical trial exposure and post-authorisation experience

15.2.2. Fremanezumab - AJOVY (CAP) - EMEA/H/C/004833/II/0029

Applicant: Teva GmbH

PRAC Rapporteur: Kirsti Villikka

Scope: Submission of an updated RMP (version 3.0) in line with the product information changes implemented following the assessment of PSUR single assessment (PSUSA) procedure (PSUSA/00010758/202103) adopted in October 2021 with regards to severe hypersensitivity reactions. The MAH took the opportunity to update PASS details according to the latest approved PASS protocols, namely the study on the 'assessment of pregnancy outcomes in patients treated with Ajovy (fremanezumab): pregnancy registry' and the study on the 'assessment of pregnancy outcomes in patients treated with Ajovy (fremanezumab): pregnancy database study'

15.2.3. Mepolizumab - NUCALA (CAP) - EMEA/H/C/003860/II/0048

Applicant: GlaxoSmithKline Trading Services Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Submission of an updated RMP (version 9) to reflect the proposal to stop the enrolment and to close the pregnancy registry known as mepolizumab pregnancy exposure study 200870 (listed as category 3 study in the RMP): a phase 4, prospective, observational, exposure cohort study of pregnancy outcomes in women. The application also includes details of the proposed enhanced data collection for all pregnancies reported as an alternative

15.2.4. [Mercaptamine - CYSTADROPS \(CAP\) - EMEA/H/C/003769/II/0023, Orphan](#)

Applicant: Recordati Rare Diseases

PRAC Rapporteur: Eva Segovia

Scope: Submission of an updated RMP (version 1.4) in order to bring it in line with revision 2 of GVP module V on 'Risk management systems' and to remove 'patients with other ocular co-morbidities' and 'patients receiving concomitant treatment with ophthalmic products containing benzalkonium chloride' as missing information from the list of safety concerns

15.2.5. [Nintedanib - OFEV \(CAP\) - EMEA/H/C/003821/II/0046](#)

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Submission of an updated RMP (version 11.0) in line with the outcome of the renewal procedure R/0025 finalised in May 2019 to remove the following safety concerns: 1) important identified risks: diarrhoea, liver enzyme and bilirubin elevations including drug-induced liver injury (DILI), bleeding, myocardial infarction; 2) important potential risks: venous thromboembolism, arterial thromboembolism excluding myocardial infarction, perforation, hepatic failure, treatment of pregnant women and teratogenicity, cardiac failure; 3) missing information: treatment of patients with moderate or severe hepatic impairment (Child Pugh B/C), treatment of black patients, treatment of patients with healing wounds, treatment of patients with severe renal impairment or end-stage renal disease, treatment of patients receiving full-dose therapeutic anticoagulation and treatment of breastfeeding women. In addition, the anatomical therapeutic chemical (ATC) code and post-marketing exposure are updated

15.2.6. [Romosozumab - EVENITY \(CAP\) - EMEA/H/C/004465/II/0010](#)

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Tiphaine Vaillant

Scope: Submission of an updated RMP (version 2.0) in order to remove 'immunogenicity' as an important identified risk revision 2 of GVP module V on 'Risk management systems', EMA guidance on immunogenicity assessment, and the available non-clinical, clinical and post-marketing data. In addition, the MAH took the opportunity to add 'cardiac arrhythmia' as an important potential risk to the RMP and to update the protocol for the ongoing study OP0004: a European non-interventional PASS related to serious cardiovascular events of myocardial infarction and stroke, and all-cause mortality for romosozumab by the EU-ADR Alliance to include cardiac arrhythmias as specific events to monitor, and include a targeted follow-up questionnaire (FUQ) related to cardiac arrhythmias, in line with the outcome of the signal procedure on cardiac arrhythmia (EPITT 19629) adopted in May 2021. The MAH took also the opportunity to introduce minor changes in the PASS protocols of studies OP0004, OP0005: a European non-interventional PASS related to adherence to the risk minimisation measures for romosozumab by the EU-ADR Alliance, and OP0006: European non-interventional PASS related to serious infections for romosozumab by the EU-ADR Alliance

15.2.7. Sacubitril, valsartan - ENTRESTO (CAP) - EMEA/H/C/004062/WS2185/0041; NEPARVIS (CAP) - EMEA/H/C/004343/WS2185/0039

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Anette Kirstine Stark

Scope: Submission of an updated RMP (version 3.0) as requested in the outcome of variation WS1830 completed in November 2020. In addition, the following changes have been introduced: 1) change to the agreed milestone for study CLCZ696B2320 (listed as a category 3 study in the RMP): a multicentre, randomized, double-blind, active-controlled study to evaluate the effects of sacubitril/valsartan (LCZ696) compared to valsartan on cognitive function as assessed by comprehensive neurocognitive battery and brain amyloid plaque deposition as assessed by positron emission tomography (PET) imaging in patients with chronic heart failure with preserved ejection fraction; 2) update to the date for the submission of the final report for study CLCZ696B2320 from 'Q1 2022' to 'Q1 2023', 3) update of the presentation of important identified risks and important potential risks; 4) update to exposure and post-marketing data provided for the data lock point (DLP) of PSUR#9 (31 July 2021)

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. Abrocitinib - CIBINQO (CAP) - EMEA/H/C/005452/II/0001

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Update of sections 4.4 and 4.8 of the SmPC based on updated safety data from the full cumulative pool from ongoing long-term extension study B7451015: a phase 3 multicentre, long-term extension study investigating the efficacy and safety of abrocitinib, with or without topical medications, administered to subjects aged 12 years and older with moderate to severe atopic dermatitis. The RMP (version 1.0) is updated accordingly. In addition, MAH took the opportunity to implement editorial changes in the SmPC and to update the contact details of the local representatives in the package leaflet

15.3.2. Adalimumab - IMRALDI (CAP) - EMEA/H/C/004279/II/0048/G

Applicant: Samsung Bioepis NL B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Grouped variations consisting of: 1) introduction of an additional concentration of 40 mg/0.4 mL for the solution for subcutaneous injection in pre-filled syringe (PFS) and pre-filled pen (PFP); 2) Change in the composition of excipients for the proposed 40 mg/0.4 mL solution for injection in PFS and PFP; 3) variations to introduce a change in the number of units in a pack within the range of the currently approved pack sizes. The RMP (version 7.1) is updated accordingly. The applicant took the opportunity to change the registration mark '®', which is adjacent to the brand name Imraldi, to the trademark '™'

15.3.3. Baloxavir marboxil - XOFLUZA (CAP) - EMEA/H/C/004974/X/0008/G

Applicant: Roche Registration GmbH

PRAC Rapporteur: Sonja Hrabcik

Scope: Grouped variations consisting of: 1) extension application to introduce a new pharmaceutical form associated with new strength (2 mg/mL granules for oral suspension); 2) extension of indication to add a paediatric indication applicable to the new presentation, as well as to all approved presentations (EU/1/20/1500/001 and 002). The RMP (version 2.0) is updated in accordance

15.3.4. Baricitinib - OLUMIANT (CAP) - EMEA/H/C/004085/II/0029/G

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Grouped variations consisting of: 1) extension of indication to include treatment of severe alopecia areata in adult patients. As a consequence, sections 4.1, 4.2, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 12.1) are updated in accordance; 2) update of the RMP (version 12.1) regarding study I4V-MC-B011 (listed as a category 3 study in the RMP): a retrospective cohort study to assess the safety of baricitinib compared with other therapies used in the treatment of rheumatoid arthritis in Nordic countries to change the end of data collection for the atopic dermatitis cohort from 'December 2026' to 'December 2027' and the subsequent final study report milestone from 'December 2027' to 'December 2028'

15.3.5. Burosumab - CRYSVITA (CAP) - EMEA/H/C/004275/II/0028, Orphan

Applicant: Kyowa Kirin Holdings B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of sections 4.8 and 5.1 of the SmPC in order to update the frequency of adverse drug reactions, to split immunogenicity data into paediatric and adult populations and to update clinical efficacy in paediatric patients upon request by the CHMP, following procedures P46/006, P46/007 and variations II/04 and II/10/G finalised in October 2019 and July 2020 respectively, based on the final results from: 1) study UX023-CL201: a randomised, open-label, dose finding, phase 2 study to assess the pharmacodynamics and safety of KRN23 (burosumab) in paediatric patients with X-linked hypophosphatemia (XLH); 2) study UX023-CL205: an open-label, phase 2 study to assess the safety, pharmacodynamics, and efficacy of KRN23 in children from 1 to 4 years old with XLH; 3) study UX023-CL301: randomised, open-label, phase 3 study to assess the efficacy and safety of krn23 versus oral phosphate and active vitamin D treatment in paediatric patients with XLH. In addition, the MAH proposed to delete the remaining specific obligation (SO) for study UX023-CL205 from Annex II, and to request a switch from a conditional marketing authorisation (MA) to standard MA. The package leaflet and the RMP (version 5.0) are updated accordingly

15.3.6. [Caplacizumab - CABLIVI \(CAP\) - EMEA/H/C/004426/II/0035, Orphan](#)

Applicant: Ablynx NV

PRAC Rapporteur: Jan Neuhauser

Scope: Update of sections 4.4 and 4.8 of the SmPC in order to amend an existing warning on increased risk of bleeding and to add blood and lymphatic system disorders to the list of adverse drug reactions (ADRs) with a frequency not known based on a safety evaluation report. The package leaflet and the RMP (version 2.0) are updated accordingly

15.3.7. [Cemiplimab - LIBTAYO \(CAP\) - EMEA/H/C/004844/II/0028](#)

Applicant: Regeneron Ireland Designated Activity Company (DAC)

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication to include cemiplimab in combination with platinum-based chemotherapy for the first-line treatment of adult patients with locally advanced non-small-cell lung carcinoma (NSCLC) who are not candidates for definitive chemoradiation or metastatic NSCLC with no epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK) or c-Ros oncogene 1 receptor tyrosine kinase (ROS1) aberrations. As a consequence, sections 4.1, 4.4, 4.8, and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 4.0) are updated accordingly

15.3.8. [Corifollitropin alfa - ELONVA \(CAP\) - EMEA/H/C/001106/II/0061](#)

Applicant: Organon N.V.

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication to include treatment of adolescent males (14 to less than 18 years) with hypogonadotropic hypogonadism in combination with human chorionic gonadotropin (hCG) based on final results of paediatric study P043: an open-label, non-comparative, multicentre safety and efficacy study of corifollitropin in association with hCG in male adolescents with hypogonadotropic hypogonadism, part of the paediatric investigation plan (PIP). As a consequence, sections 4.1, 4.2, 4.4, 4.6, 4.8, 4.9, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 9.2) are updated in accordance. In addition, the MAH took the opportunity to implement some minor editorial and formatting changes throughout the product information

15.3.9. [Dapivirine - DAPIVIRINE VAGINAL RING 25 MG \(Art 58⁶¹\) - EMEA/H/W/002168/II/0015/G](#)

Applicant: International Partnership for Microbicides Belgium AISBL

PRAC Rapporteur: Jan Neuhauser

Scope: Grouped variations consisting of submission of four addenda from studies (listed as category 3 studies in the RMP): 1) IPM 007 (RING study): a phase 3, randomised study exploring dapivirine ring long-term safety and efficacy; 2) study MTN-015: a multisite,

⁶¹ 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)

prospective, observational cohort study of women following human immunodeficiency virus type 1 (HIV-1) seroconversion in microbicide trials of antiretroviral (ARV)-based microbicides or oral pre-exposure prophylaxis (PrEP); 3) studies IPM 032 and MTN-025: phase 3b open-label extension (OLE) dapivirine ring trials. The data presented in the addenda are the results of retrospective next generation sequencing (NGS) and phenotype susceptibility testing on blood samples to further assess the potential development of non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance in women with unrecognised or acute HIV-1 infection. The RMP (version 0.9) is updated accordingly. Additionally, the MAH took the opportunity to update the EMA on other commitments outlined in the RMP as additional risk minimisation measures. These include the development of a healthcare professional guide (HCP guide) and a user guide with agreed objectives and key messages

15.3.10. [Dapivirine - DAPIVIRINE VAGINAL RING 25 MG \(Art 58⁶²\) - EMEA/H/W/002168/II/0016](#)

Applicant: International Partnership for Microbicides Belgium AISBL

PRAC Rapporteur: Jan Neuhauser

Scope: Update of Annex II in order to replace the current post-authorisation efficacy study (PAES) IPM 055 (listed as a category 1 study in the RMP): a phase 4, open label, multicentre efficacy trial in healthy human immunodeficiency virus (HIV)-negative young women aged 18-25 years, with the implementation study: 'dapivirine vaginal ring implementation in a real-world setting in young women. The RMP (version 0.9) is updated accordingly

15.3.11. [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

⁶² 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)

15.3.12. Elbasvir, grazoprevir - ZEPATIER (CAP) - EMEA/H/C/004126/II/0034

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Submission of the final report from study MK-5172-017 (listed as a category 3 study in the RMP): a long-term follow-up study to evaluate the durability of virologic response and/or viral resistance patterns of subjects with chronic hepatitis C who have been previously treated with Zepatier (elbasvir/grazoprevir) in a prior clinical trial (in fulfilment of MEA 002.1). The RMP (version 5.1) is updated accordingly

15.3.13. Eltrombopag - REVOLADE (CAP) - EMEA/H/C/001110/II/0068

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Eva Segovia

Scope: Extension of indication to include treatment of adult patients with primary immune thrombocytopenia (ITP) who are refractory to other treatments (e.g. corticosteroids, immunoglobulins) irrespective of time since initial diagnosis, based on an ad-hoc analysis of study TAPER (CETB115J2411): an ongoing phase 2, open-label, prospective, single-arm study in adult ITP patients who are refractory or relapsed after first-line steroids. As a consequence, sections 4.1 and 5.1 of the SmPC have been updated. In addition, the MAH took the opportunity to make some minor amendments in section 4.8 of the SmPC for increased consistency. The RMP (version 54.0) is updated accordingly

15.3.14. Emtricitabine, tenofovir alafenamide - DESCOVY (CAP) - EMEA/H/C/004094/II/0057

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Submission of the clinical study report and supporting modular summaries for study GS-US-311-1269: a phase 2/3, open label, multi-cohort switch study to evaluate emtricitabine/tenofovir alafenamide (F/TAF) in human immunodeficiency virus type 1 (HIV-1) infected children and adolescents virologically suppressed on a two nucleoside reverse transcriptase inhibitors (NRTI) containing regimen in fulfilment of the milestone for the category 3 additional pharmacovigilance activity to address long-term safety information in adolescents as missing information. The RMP (version 6.1) is updated accordingly

15.3.15. Eptacog alfa (activated) - NOVOSEVEN (CAP) - EMEA/H/C/000074/II/0116

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication to include treatment of severe postpartum haemorrhage for NovoSeven (eptacog alfa). As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 8.0) are updated accordingly

15.3.16. Exenatide - BYDUREON (CAP) - EMEA/H/C/002020/II/0073

Applicant: AstraZeneca AB

PRAC Rapporteur: Annika Folin

Scope: Extension of indication to include the treatment of adolescents and children aged 10 years and above based on the results from study BCB114 (D5551C00002): a phase 3, double-blind, placebo-controlled, randomised, multicentre study to assess the safety and efficacy of exenatide once weekly in adolescents with type 2 diabetes (T2DM), which was initially submitted and assessed by the CHMP as part of post-authorisation measure (PAM) P46 028. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 35s1) are updated in accordance

15.3.17. 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

15.3.18. Insulin lispro - LYUMJEV (CAP) - EMEA/H/C/005037/II/0014

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Annika Folin

Scope: Extension of indication to include the treatment of diabetes mellitus in adolescents and children aged 1 year and above, based on the final results from study I8B-MC-ITSB: a pivotal phase 3 study designed to evaluate the safety and efficacy of Lyumjev (insulin lispro) compared to Humalog (insulin lispro) in combination with basal insulin in children and adolescent patients with type 1 diabetes mellitus (T1DM). As a consequence, sections 4.1, 4.2, 4.8, 5.1, and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 12.1) are updated in accordance. In addition, the MAH took the opportunity to implement minor editorial and linguistic changes in the product information. As part of the application, the MAH is also requesting one additional year of market protection

15.3.19. Mercaptamine - PROCYSBI (CAP) - EMEA/H/C/002465/X/0035, Orphan

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension application to introduce a new pharmaceutical form associated with two new strengths (75 and 300 mg gastro-resistant granules). The RMP (version 7.2) is updated in accordance

15.3.20. [Mirabegron - BETMIGA \(CAP\) - EMEA/H/C/002388/X/0039/G](#)

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Grouped variations consisting of: 1) extension application to introduce a new pharmaceutical form associated with new strength (8 mg/mL prolonged-release granules for oral suspension); 2) extension of indication to include treatment of neurogenic detrusor overactivity (NDO) in paediatric patients aged 3 to less than 18 years. The RMP (version 9.0) is updated in accordance

15.3.21. [Octocog alfa - KOVALTRY \(CAP\) - EMEA/H/C/003825/II/0038](#)

Applicant: Bayer AG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of sections 4.8 and 5.1 of the SmPC to include data from LEOPOLD kids part B: a long-term efficacy open-label programme in severe haemophilia A disease (previously submitted as an Art 46; an addendum on biomarker data is included in this submission) and extension study results. In addition, an editorial revision in section 4.2 and a clarification in section 6.5 of the SmPC are proposed. The package leaflet is updated accordingly. The MAH took the opportunity to correct a typo in the Greek product information. The RMP (version 4.1) is updated and brought in line with revision 2.0.1 of the guidance on the format of RMP in the EU (template)

15.3.22. [Olaparib - LYNPARZA \(CAP\) - EMEA/H/C/003726/II/0051/G](#)

Applicant: AstraZeneca AB

PRAC Rapporteur: Amelia Cupelli

Scope: Extension of indication to include adjuvant treatment of breast cancer for Lynparza (olaparib) tablets. As a consequence, sections 4.1, 4.2, 4.5, 4.8 and 5.1 of the SmPC are updated. In addition, section 4.8 of the SmPC for Lynparza (olaparib) hard capsules is revised based on the updated safety data analysis. The package leaflet and the RMP (version 23) are updated accordingly

15.3.23. [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

15.3.24. Palbociclib - IBRANCE (CAP) - EMEA/H/C/003853/II/0037

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Submission of the final report from study A5481027 (listed as a category 3 study in the RMP): a multicentre, randomized, double-blind, phase 3 study of palbociclib plus letrozole versus placebo plus letrozole for the treatment of previously untreated Asian postmenopausal women with estrogen receptor (ER)-positive, human epidermal growth factor receptor-2 (HER2)-negative advanced breast cancer to evaluate the effect of palbociclib on hyperglycaemia (in fulfilment of MEA 001). The RMP (version 1.8) is updated accordingly

15.3.25. Pandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) - ADJUPANRIX (CAP) - EMEA/H/C/001206/II/0074

Applicant: GlaxoSmithkline Biologicals SA

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication to include use in children from 6 months to <18 years for Adjuvanrix (pandemic influenza vaccine (H5N1)) based on the results of the following studies: 1) study H5N1-013: a phase 2, non-randomised, open-label study to evaluate the safety and immunogenicity in children aged 6 to 35 months; 2) study H5N1-032: a phase 3, randomised, open, active-controlled study to evaluate the safety and immunogenicity in children aged 3 to 17 years. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 6.6 of the SmPC are updated. The package leaflet and the RMP (version 13) are updated in accordance. Further, the MAH proposed to update section 4.4 with information on sodium and potassium content in line with the excipient guideline, as well as to add some wording on traceability. 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). Finally, the MAH introduced minor editorial changes throughout the product information

15.3.26. Remdesivir - VEKLURY (CAP) - EMEA/H/C/005622/II/0034/G

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Eva Jirsová

Scope: Grouped variations consisting of: 1) update sections 5.1 and 5.2 of the SmPC as a consequence of the submission of the final component of specific obligation (SO) 012 agreed in the renewal procedure of the conditional marketing authorisation (CMA) (R/0015) finalised in April 2021 and listed in Annex II of the product information. This submission includes the adaptive COVID-19 treatment trial (ACTT-1) final sequencing and phenotyping analysis and the full virology report including activity against variants. The package leaflet and the RMP (version 3.1) are updated accordingly

15.3.27. Ribociclib - KISQALI (CAP) - EMEA/H/C/004213/II/0035

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Update of sections 4.4, 4.8 and 5.1 of the SmPC based on the final overall survival (OS) analysis from study A2301 (MONALEESA-2) (listed as a category 3 study in the RMP): a phase 3, randomised, double-blind, placebo-controlled, multicentre study of ribociclib in combination with letrozole in postmenopausal women with hormonal receptor + (HR+), human epidermal growth factor receptor-2 negative (HER2-), locoregionally recurrent or metastatic breast cancer who had not received previous systemic therapy for advanced disease, and based on an updated pooled safety dataset including 1) study MONALEESA-2; 2) study MONALEESA-3: a randomised double-blind, placebo-controlled study of ribociclib in combination with fulvestrant for the treatment of men and postmenopausal women with hormone receptor positive, HER2-negative, advanced breast cancer who have received no or only one line of prior endocrine treatment; 3) study MONALEESA-7: a phase 3 randomised, double-blind, placebo-controlled study of LEE011 or placebo in combination with tamoxifen and goserelin or a non-steroidal aromatase inhibitor (NSAI) and goserelin for the treatment of premenopausal women with hormone receptor positive, HER2-negative, advanced breast cancer (in fulfilment of MEA 004). The package leaflet and the RMP (version 6.0) is updated accordingly

15.3.28. Risankizumab - SKYRIZI (CAP) - EMEA/H/C/004759/X/0020/G

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Grouped variations consisting of: 1) extension application to introduce a new pharmaceutical form (concentrate for solution for infusion), a new strength (600 mg) and a new route of administration (intravenous use); 2) extension of application to add a new strength of 360 mg (150 mg/mL) for risankizumab solution for injection (in cartridge) for subcutaneous use. The new presentations are indicated for the treatment of patients aged 16 years and older with moderately to severely active Crohn's disease who have had an inadequate response to, lost response to, or were intolerant to conventional therapy or a biologic therapy, or if such therapies are not advisable. The RMP (version 4.0) is updated in accordance

15.3.29. 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

15.3.30. Selpercatinib - RETSEVMO (CAP) - EMEA/H/C/005375/II/0011

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication to include first-line treatment of rearranged during transfection (RET) fusion-positive non-small cell lung cancer (NSCLC) based on results from study LIBRETTO-001: an open-label, multicentre, global phase 1/2 study of selpercatinib in patients with RET-altered advanced solid tumours. As a consequence, sections 4.1, 4.5, 4.8 and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 1.1) are updated in accordance

15.3.31. Semaglutide - OZEMPIC (CAP) - EMEA/H/C/004174/WS2141/0024; RYBELSUS (CAP) - EMEA/H/C/004953/WS2141/0018

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Annika Folin

Scope: Submission of the final report from study NN9535-4386 (SUSTAIN-11) (listed as a category 3 study in the RMP): a 52-week, multicentre, multinational, open-label, active controlled, two armed, parallel, randomised trial undertaken to investigate the effect on glycaemic control, body weight, safety and health-related quality of life of once-weekly semaglutide subcutaneous (sc) vs insulin aspart three times daily, both as add-on to metformin and optimised insulin glargine U100 treatment in subjects with inadequately controlled type 2 diabetes mellitus (T2DM). The RMP (version 7.0) is updated accordingly

15.3.32. Setmelanotide - IMCIVREE (CAP) - EMEA/H/C/005089/II/0002/G, Orphan

Applicant: Rhythm Pharmaceuticals Netherlands B.V.

PRAC Rapporteur: Marek Juracka

Scope: Grouped variations consisting of: 1) addition of a new therapeutic indication for the treatment of obesity and the control of hunger associated with genetically confirmed Bardet-Biedl syndrome (BBS). As a consequence, sections 4.1, 4.2, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The package leaflet and the RMP (version 1.0) are updated accordingly; 2) addition of a new therapeutic indication for the treatment of obesity and the control of hunger associated with genetically confirmed Alström syndrome (AS). As a consequence, sections 4.1, 4.2, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated accordingly. The package leaflet and the RMP (version 1.0) are updated in accordance

15.3.33. Tagraxofusp - ELZONRIS (CAP) - EMEA/H/C/005031/II/0009, Orphan

Applicant: Stemline Therapeutics B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Submission of the final report from study 20255431 (CRL-263114) (listed as a category 3 study in the RMP): a non-interventional, post-authorisation study on blood brain barrier (BBB) models in order to determine a potential toxicity biomarker to further investigate the risk of choroid plexus lesions - a characterisation of fixed choroid plexus samples from primate study MPI-2231-007 by immunohistochemistry with diphtheria toxin (DT), interleukin-3 receptor (CD123), interleukin-3 (IL-3) and immunoglobulin G (IgG) (in fulfilment of MEA 002). The RMP (version 2.0) is updated accordingly

15.3.34. Teduglutide - REVESTIVE (CAP) - EMEA/H/C/002345/II/0054/G, Orphan

Applicant: Shire Pharmaceuticals Ireland Limited

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Grouped variations consisting of: 1) extension of indication to include patients from 4 months corrected gestational aged 1 year and above. Consequently, sections 4.1, 4.2, 4.8, 5.1 and 5.2 are updated. The package leaflet and the RMP (version 9.1) are updated accordingly; 2) update of Annex II-D on 'Conditions or restrictions with regards to the safe and effective use of the medicinal product' to amend the date of completion of the imposed post authorisation study: an international short bowel syndrome registry, from Q3 2031 to Q2 2032. In addition, the MAH took the opportunity to amend the list of local representatives

15.3.35. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/II/0046

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Update of section 5.3 of the SmPC in order to update safety information on reproductive and developmental toxicity based on final study results from study 00655256 (20GR261) (listed as a category 3 study in the RMP): an oral (gavage) juvenile toxicity study of CP-690550 (tofacitinib) in Sprague Dawley rats (in fulfilment of MEA 022). In addition, the MAH took the opportunity to update the contact details of the local representatives in the package leaflet. The RMP (version 23.1) is updated accordingly

15.3.36. Upadacitinib - RINVOQ (CAP) - EMEA/H/C/004760/II/0016

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Extension of indication to include the treatment of active non-radiographic axial spondyloarthritis (nr-axSpA) in adult patients with objective signs of inflammation who have responded inadequately to non-steroidal anti-inflammatory drugs (NSAIDs) or other conventional therapy based on the final clinical study report from pivotal study M19-944 study 2 (nr-axSpA): a randomised, double-blind, phase 3 study evaluating the long-term safety, tolerability, and efficacy of upadacitinib 15 mg every day (QD) in subjects with nr-axSpA who completed the double-blind period on study drug. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 8.0) are updated accordingly

15.3.37. Upadacitinib - RINVOQ (CAP) - EMEA/H/C/004760/X/0012/G

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Grouped applications consisting of: 1) extension application to add a new strength (45 mg) of the prolonged-release tablets; 2) extension of indication for treatment of adults with moderately to severely active ulcerative colitis who had an inadequate response, lost response or were intolerant to either conventional therapy or a biologic agent. As a consequence, sections 4.1, 4.2, 4.5, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The package leaflet, labelling and the RMP (version 6.0) are updated in accordance

15.3.38. Zanubrutinib - BRUKINSA (CAP) - EMEA/H/C/004978/II/0002

Applicant: BeiGene Ireland Ltd

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication to include treatment of adult patients with marginal zone lymphoma (MZL) who have received at least one-prior anti-cluster of differentiation (CD20)-based therapy based on data from 88 patients with relapsed or refractory (R/R) MZL from two ongoing pivotal studies namely: 1) study BGB-3111-214 (MAGNOLIA): a phase 2, open-label, single-arm study designed to evaluate the safety and efficacy of zanubrutinib in patients with R/R MZL; 2) study BGB-3111-AU-003: a first-in-human, phase 1/2, dose-escalation and selection, pharmacokinetic (PK)/pharmacodynamic (PD), safety, and efficacy study in adult patients with R/R or treatment-naïve B-cell malignancies. As a consequence, sections 4.1, 4.2, 4.5, 4.8 and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 1.1) are updated accordingly. In addition, the MAH requested one additional year of 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 below-mentioned medicines remains favourable in the approved indication(s) and adopted a recommendation to maintain the current terms of the marketing authorisation(s) together with the assessment report. As per the agreed criteria, the procedures listed below were finalised at the PRAC level without further plenary discussion.

The next PSURs should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal, unless changes apply as stated in the outcome of the relevant PSUR/PSUSA procedure(s).

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

16.1.1. Bedaquiline - SIRTURO (CAP) - PSUSA/00010074/202109

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.2. Bupivacaine, meloxicam - ZYNRELEF (CAP) - PSUSA/00010880/202109

Applicant: Heron Therapeutics, B.V.

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

16.1.3. Caplacizumab - CABLIVI (CAP) - PSUSA/00010713/202108

Applicant: Ablynx NV

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.1.4. Cholic acid⁶³ - ORPHACOL (CAP) - PSUSA/00010208/202109

Applicant: Laboratoires CTRS

PRAC Rapporteur: Sofia Trantza

Scope: Evaluation of a PSUSA procedure

16.1.5. Damoctocog alfa pegol - JIVI (CAP) - PSUSA/00010732/202108

Applicant: Bayer AG

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.6. Darunavir, cobicistat, emtricitabine, tenofovir alafenamide - SYMTUZA (CAP) - PSUSA/00010646/202109

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.1.7. Darvadstrocel - ALOFISEL (CAP) - PSUSA/00010676/202109

Applicant: Takeda Pharma A/S, ATMP⁶⁴

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.8. Deferiprone - FERRIPROX (CAP) - PSUSA/00000940/202108

Applicant: Chiesi Farmaceutici S.p.A.

⁶³ Oxosteroid-reductase or hydroxy-steroid dehydrogenase deficiency indication(s) only

⁶⁴ Advanced therapy medicinal product

PRAC Rapporteur: Tiphaine Vaillant
Scope: Evaluation of a PSUSA procedure

16.1.9. Doravirine - PIFELTRO (CAP) - PSUSA/00010729/202108

Applicant: Merck Sharp & Dohme B.V.
PRAC Rapporteur: Ana Sofia Diniz Martins
Scope: Evaluation of a PSUSA procedure

16.1.10. Doravirine, lamivudine, tenofovir disoproxil - DELSTRIGO (CAP) - PSUSA/00010731/202108

Applicant: Merck Sharp & Dohme B.V.
PRAC Rapporteur: Ana Sofia Diniz Martins
Scope: Evaluation of a PSUSA procedure

16.1.11. Dulaglutide - TRULICITY (CAP) - PSUSA/00010311/202109

Applicant: Eli Lilly Nederland B.V.
PRAC Rapporteur: Ilaria Baldelli
Scope: Evaluation of a PSUSA procedure

16.1.12. Duvelisib - COPIKTRA (CAP) - PSUSA/00010939/202109

Applicant: Secura Bio Limited
PRAC Rapporteur: Željana Margan Koletić
Scope: Evaluation of a PSUSA procedure

16.1.13. Esketamine⁶⁵ - SPRAVATO (CAP) - PSUSA/00010825/202109

Applicant: Janssen-Cilag International N.V.
PRAC Rapporteur: Kirsti Villikka
Scope: Evaluation of a PSUSA procedure

16.1.14. Filgotinib - JYSELECA (CAP) - PSUSA/00010879/202109

Applicant: Galapagos N.V.
PRAC Rapporteur: Nikica Mirošević Skvrce
Scope: Evaluation of a PSUSA procedure

⁶⁵ Centrally authorised product(s) only

16.1.15. [Fremanezumab - AJOVY \(CAP\) - PSUSA/00010758/202109](#)

Applicant: TEVA GmbH

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

16.1.16. [Gilteritinib - XOSPATA \(CAP\) - PSUSA/00010832/202109](#)

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.17. [Human coagulation factor VIII, human von Willebrand factor⁶⁶ - VONCENTO \(CAP\) - PSUSA/00010102/202108](#)

Applicant: CSL Behring GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.18. [Ibalizumab - TROGARZO \(CAP\) - PSUSA/00010797/202109](#)

Applicant: Theratechnologies Europe Limited

PRAC Rapporteur: David Olsen

Scope: Evaluation of a PSUSA procedure

16.1.19. [Idebenone⁶⁷ - RAXONE \(CAP\) - PSUSA/00010412/202109](#)

Applicant: Santhera Pharmaceuticals (Deutschland) GmbH

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.1.20. [Isatuximab - SARCLISA \(CAP\) - PSUSA/00010851/202109](#)

Applicant: sanofi-aventis groupe

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

16.1.21. [Lorlatinib - LORVIQUA \(CAP\) - PSUSA/00010760/202109](#)

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Nikica Mirošević Skvrce

⁶⁶ Centrally authorised product(s) only

⁶⁷ Centrally authorised product(s) only

Scope: Evaluation of a PSUSA procedure

16.1.22. Loxapine⁶⁸ - ADASUVE (CAP) - PSUSA/00010113/202108

Applicant: Ferrer Internacional s.a.

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

16.1.23. Mecasermin - INCRELEX (CAP) - PSUSA/00001942/202108

Applicant: Ipsen Pharma

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

16.1.24. Mepolizumab - NUCALA (CAP) - PSUSA/00010456/202109

Applicant: GlaxoSmithKline Trading Services Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.25. Meropenem, vaborbactam - VABOREM (CAP) - PSUSA/00010727/202108

Applicant: Menarini International Operations Luxembourg S.A.

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

16.1.26. Naloxegol - MOVENTIG (CAP) - PSUSA/00010317/202109

Applicant: Kyowa Kirin Holdings B.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

16.1.27. Obiltoxaximab - OBILTOXAXIMAB SFL (CAP) - PSUSA/00010885/202109

Applicant: SFL Pharmaceuticals Deutschland GmbH

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

16.1.28. Pandemic influenza vaccine (H5N1) (whole virion, Vero cell derived, inactivated) - PANDEMIC INFLUENZA VACCINE H5N1 BAXTER (CAP) - PSUSA/00002282/202108

Applicant: Ology Bioservices Ireland Limited

⁶⁸ Pre-dispensed inhalation powder only

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.29. Ponesimod - PONVORY (CAP) - PSUSA/00010940/202109

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

16.1.30. Rilpivirine⁶⁹ - REKAMBYS (CAP) - PSUSA/00010901/202109

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

16.1.31. Sebelipase alfa - KANUMA (CAP) - PSUSA/00010422/202108

Applicant: Alexion Europe SAS

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.32. Solriamfetol - SUNOSI (CAP) - PSUSA/00010831/202109

Applicant: Jazz Pharmaceuticals Ireland Limited

PRAC Rapporteur: Julia Pallos

Scope: Evaluation of a PSUSA procedure

16.1.33. Somapacitan - SOGROYA (CAP) - PSUSA/00010920/202108

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.34. Teduglutide - REVESTIVE (CAP) - PSUSA/00009305/202108

Applicant: Shire Pharmaceuticals Ireland Limited

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Evaluation of a PSUSA procedure

16.1.35. Trabectedin - YONDELIS (CAP) - PSUSA/00003001/202109

Applicant: Pharma Mar, S.A.

⁶⁹ Intramuscular use only

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Evaluation of a PSUSA procedure

16.1.36. Velmanase alfa - LAMZEDE (CAP) - PSUSA/00010677/202109

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

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

16.2.1. Epoetin alfa - ABSEAMED (CAP), BINOCRIT (CAP), EPOETIN ALFA HEXAL (CAP); NAP - PSUSA/00001237/202108

Applicants: Medice Arzneimittel Pütter GmbH & Co. KG (Abseamed), Sandoz GmbH (Binocrit), Hexal AG (Epoetin alfa Hexal), various

PRAC Rapporteur: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

16.2.2. Glycopyrronium⁷⁰ - SIALANAR (CAP); NAP - PSUSA/00010529/202109

Applicants: Proveca Pharma Limited (Sialanar), various

PRAC Rapporteur: Zane Neikena

Scope: Evaluation of a PSUSA procedure

16.2.3. Irbesartan - APROVEL (CAP), IRBESARTAN ZENTIVA (CAP), KARVEA (CAP), irbesartan, hydrochlorothiazide - COAPROVEL (CAP), IRBESARTAN HYDROCHLOROTHIAZIDE ZENTIVA (CAP), KARVEZIDE (CAP); NAP - PSUSA/00010601/202108

Applicants: sanofi-aventis groupe (Aprovel, CoAprovel, Karvea, Karvezide), Zentiva, k.s. (Irbesartan Hydrochlorothiazide Zentiva, Irbesartan Zentiva), various

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

16.2.4. Trientine - CUFENCE (CAP), CUPRIOR (CAP); NAP - PSUSA/00010637/202109

Applicants: Univar Solutions BV (Cufence), Orphalan (Cuprior), various

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

⁷⁰ Treatment of severe sialorrhea (chronic pathological drooling) indication(s) only

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

16.3.1. Aniracetam (NAP) - PSUSA/00010790/202108

Applicant(s): various

PRAC Lead: Jana Lukačšínová

Scope: Evaluation of a PSUSA procedure

16.3.2. Asparaginase, crisantaspase⁷¹ (NAP) - PSUSA/00003161/202108

Applicant(s): various

PRAC Lead: Roxana Dondera

Scope: Evaluation of a PSUSA procedure

16.3.3. Buserelin (NAP) - PSUSA/00000462/202108

Applicant(s): various

PRAC Lead: Annika Folin

Scope: Evaluation of a PSUSA procedure

16.3.4. Cetirizine, pseudoephedrine (NAP) - PSUSA/00000629/202108

Applicant(s): various

PRAC Lead: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

16.3.5. Ciclesonide (NAP) - PSUSA/00000742/202108

Applicant(s): various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.3.6. Dermatophagoides pteronyssinus, dermatophagoides farina^{72 73 74} (NAP) - PSUSA/00010582/202109

Applicant(s): various

PRAC Lead: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

⁷¹ Nationally authorised product(s) only

⁷² Allergen for therapy

⁷³ Oromucosal use only

⁷⁴ Medicinal product(s) authorised via mutually recognition procedure and decentralised procedure only

16.3.7. Esketamine⁷⁵ (NAP) - PSUSA/00001266/202108

Applicant(s): various

PRAC Lead: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

16.3.8. Finasteride (NAP) - PSUSA/00001392/202108

Applicant(s): various

PRAC Lead: Annika Folin

Scope: Evaluation of a PSUSA procedure

16.3.9. Meropenem (NAP) - PSUSA/00001989/202108

Applicant(s): various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.3.10. Penciclovir (NAP) - PSUSA/00002333/202108

Applicant(s): various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.3.11. Pilocarpine⁷⁶ (NAP) - PSUSA/00002410/202108

Applicant(s): various

PRAC Lead: Željana Margan Koletić

Scope: Evaluation of a PSUSA procedure

16.3.12. Rilmenidine (NAP) - PSUSA/00002643/202108

Applicant(s): various

PRAC Lead: Melinda Palfi

Scope: Evaluation of a PSUSA procedure

16.3.13. Tuberculin purified protein derivative (NAP) - PSUSA/00003063/202109

Applicant(s): various

PRAC Lead: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

⁷⁵ Except for centrally authorised product(s)

⁷⁶ Ophthalmic formulation(s) only

16.4. Follow-up to PSUR/PSUSA procedures

16.4.1. Arsenic trioxide - TRISENOX (CAP) - EMEA/H/C/000388/LEG 051.1

Applicant: Teva B.V.

PRAC Rapporteur: Tiphaine Vaillant

Scope: MAH's response to LEG 051 [cumulative review including all available data of cases of paresis, bone marrow necrosis, deafness, melanoma, pancreatic cancer, squamous cell carcinoma and toxic epidermal necrolysis following the addition of these adverse drug reactions (ADRs) in the US product information at the FDA's request, as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00000235/202009) adopted in June 2021] as per the request for supplementary information (RSI) adopted in December 2021⁷⁷

16.5. Variation procedure(s) resulting from PSUSA evaluation

16.5.1. Baricitinib - OLUMIANT (CAP) - EMEA/H/C/004085/II/0031

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Update of section 4.4 of the SmPC in order to add new warnings on major adverse cardiac events (MACE) and amend an existing warning on malignancy and venous thromboembolism (VTE) as requested in the conclusions of the last PSUR single assessment (PSUSA) procedure (PSUSA/00010578/202102) adopted in September 2021 and based on interim results from study I4V-MC-B023: a retrospective observational study to compare baricitinib relative to the standard of care. The package leaflet and the RMP (version 13.1) are updated accordingly. In addition, the MAH submitted a proposal for a direct healthcare professional communication (DHPC) and a communication plan

16.6. Expedited summary safety reviews⁷⁸

16.6.1. Coronavirus (COVID-19) vaccine (recombinant, adjuvanted) (NVX-CoV2373) - NUVAXOVID (CAP MAA) - EMEA/H/C/005808/MEA 014

Applicant: Novavax CZ, a.s.

PRAC Rapporteur: Brigitte Keller-Stanislawski

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

16.6.2. Elasomeran - SPIKEVAX (CAP) - EMEA/H/C/005791/MEA 011.11

Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

⁷⁷ Held 29 November – 02 December 2021

⁷⁸ 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

Scope: Twelfth expedited summary safety report (SSR) for Spikevax (elasomeran) during the coronavirus disease (COVID-19) pandemic

16.6.3. Tozinameran - COMIRNATY (CAP) - EMEA/H/C/005735/MEA 002.12

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Thirteenth expedited summary safety report (SSR) for Comirnaty (tozinameran) 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.

17.1. Protocols of PASS imposed in the marketing authorisation(s)⁷⁹

17.1.1. Evinacumab – EVKEEZA (CAP) - EMEA/H/C/PSP/S/0096.1

Applicant: Regeneron Ireland DAC

PRAC Rapporteur: Annika Folin

Scope: MAH's response to PSP/S/0096 [protocol for a study to evaluate long-term effects of evinacumab treatment in patients with homozygous familial hypercholesterolemia (HoFH), including safety outcomes in patients with HoFH who are ≥ 12 years old, frequency and outcomes of pregnancy in female patients with HoFH, atherosclerosis process over time in patients with HoFH who undergo cardiovascular imaging and frequency of cardiovascular imaging of patients with HoFH] as per the request for supplementary information (RSI) adopted in December 2021⁸⁰

17.1.2. Fenfluramine – FINTEPLA (CAP) - EMEA/H/C/PSP/S/0093.2

Applicant: Zogenix ROI Limited

PRAC Rapporteur: Martin Huber

Scope: MAH's response to PSP/S/0093.1 [protocol for an observational registry to provide data on long-term safety of fenfluramine in routine practice, with a focus on characterising and quantifying the important potential risks of valvular heart disease (VHD) and pulmonary arterial hypertension (PAH) (primary objective), and growth retardation (secondary objective). In addition, data on the frequency of echocardiographic monitoring contribute to assess the effectiveness of risk minimisation measures] as per the request for supplementary information (RSI) adopted in October 2021⁸¹

⁷⁹ In accordance with Article 107n of Directive 2001/83/EC

⁸⁰ Held 29 November – 02 December 2021

⁸¹ Held 27-30 September 2021

17.1.3. Valproate⁸² (NAP) - EMEA/H/N/PSP/J/0094.2

Applicant: Sanofi-Aventis Recherche & Développement

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: MAH's response to PSP/J/0094.1 [protocol for a joint retrospective study of multiple European data sources characterising neurodevelopmental disorders in children exposed in utero to valproate and/or other antiepileptic drugs with long-term follow-up] as per the request for supplementary information (RSI) adopted in November 2021⁸³

17.2. Protocols of PASS non-imposed in the marketing authorisation(s)⁸⁴

17.2.1. Diroximel fumarate - VUMERITY (CAP) - EMEA/H/C/005437/MEA 001

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Martin Huber

Scope: Protocol for study 272MS401: Vumerity (diroximel fumarate) prospective multiple sclerosis (MS) pregnancy exposure registry

17.2.2. Elasmomeran - SPIKEVAX (CAP) - EMEA/H/C/005791/MEA 034.2

Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: MAH's response to MEA 034.1 [protocol for a study monitoring the safety of Spikevax (COVID-19 vaccine) in pregnancy: an observational study using routinely collected health data in five European countries] as per the request for supplementary information (RSI) adopted in September 2021⁸⁵ together with a statistical analysis plan (SAP)

17.2.3. Fenfluramine - FINTEPLA (CAP) - EMEA/H/C/003933/MEA 005.2

Applicant: Zogenix ROI Limited

PRAC Rapporteur: Martin Huber

Scope: MAH's response to MEA 005.1 [protocol for study ZX008-2102: a drug utilisation study (DUS) in Europe to describe fenfluramine use in routine clinical practice [final report expected in August 2025] (from initial opinion/marketing authorisation)] as per the request for supplementary information (RSI) adopted in October 2021⁸⁶

17.2.4. Fenfluramine - FINTEPLA (CAP) - EMEA/H/C/003933/MEA 006.1

Applicant: Zogenix ROI Limited

⁸² Valproic acid, sodium valproate, valproate pivoxil, valproate semisodium, valpriomide, valproate bismuth, calcium valproate, valproate magnesium

⁸³ Held 25-28 October 2021

⁸⁴ 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

⁸⁵ Held 30 August – 02 September 2021

⁸⁶ Held 27-30 September 2021

PRAC Rapporteur: Martin Huber

Scope: MAH's response to MEA 006 [protocol for study ZX008-2104: a European study of the effectiveness of risk minimisation measures for fenfluramine in Dravet syndrome] as per the request for supplementary information (RSI) adopted in October 2021⁸⁷

17.2.5. Netarsudil - RHOKIINSA (CAP) - EMEA/H/C/004583/MEA 001.3

Applicant: Santen Oy

PRAC Rapporteur: Eva Segovia

Scope: MAH's response to MEA 001.2 [protocol for study AR-13324-OBS02: a non-interventional, observational cohort study of 2-year of treatment with Rhokiinsa (netarsudil) compared with non-Rhokiinsa (netarsudil) ocular hypotensive therapy in patients with elevated intraocular pressure due to primary open angle glaucoma or ocular hypertension] as per the request for supplementary information (RSI) adopted in September 2021⁸⁸

17.2.6. Odevixibat - BYLVAY (CAP) - EMEA/H/C/004691/MEA 003

Applicant: Albireo

PRAC Rapporteur: Adam Przybylkowski

Scope: 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 [final study report expected in December 2026]

17.2.7. Odevixibat - BYLVAY (CAP) - EMEA/H/C/004691/MEA 004

Applicant: Albireo

PRAC Rapporteur: Adam Przybylkowski

Scope: Protocol for study A4250-020 (listed as a category 3 study in the RMP): a disease registry to document the natural history of the disease, treatment efficacy, safety, including long-term outcomes, pregnancy, breastfeeding and newborns in patients with progressive familial intrahepatic cholestasis (PFIC)

17.2.8. Risankizumab - SKYRIZI (CAP) - EMEA/H/C/004759/MEA 002.4

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: MAH's response to MEA 002.3 [protocol for study P16-751 on pregnancy exposures and outcomes in psoriasis patients treated with risankizumab: a cohort study utilising large healthcare databases with mother-baby linkage in the United States] as per the request for supplementary information (RSI) adopted in February 2021

⁸⁷ Held 27-30 September 2021

⁸⁸ Held 30 August – 02 September 2021

17.2.9. Somapacitan - SOGROYA (CAP) - EMEA/H/C/005030/MEA 002.2

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Martin Huber

Scope: MAH's response to MEA 002.1 [protocol for study NN8640-4515: a multinational, multicentre, prospective, open label, single-arm, observational, non-interventional PASS to investigate long-term safety of somapacitan in adults with growth hormone deficiency (AGHD) under normal clinical practice conditions (from initial marketing authorisation/opinion)] as per the request for supplementary information (RSI) adopted in January 2022

17.2.10. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/MEA 014.5

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: MAH's response to MEA 014.4 [protocol for study A3921321: a drug utilisation study (DUS) on the utilisation and prescribing patterns of Xeljanz (tofacitinib) in two European countries using administrative claims databases and national registries for assessment, as requested in the conclusions of the referral procedure under Article 20 of Regulation (EC) No 726/2004 (EMEA/H/A-20/1485) finalised in November 2019] as per the request for supplementary information (RSI) adopted in December 2021⁸⁹

17.2.11. Tozinameran - COMIRNATY (CAP) - EMEA/H/C/005735/MEA 011.4

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Amendment to a protocol previously agreed in April 2021 [MEA 011] for study C4591010: a post-approval active surveillance safety study to monitor real-world safety of the Pfizer-BioNTech COVID-19 vaccine (Comirnaty) in the EU

17.2.12. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/MEA 053

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: 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

17.2.13. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/MEA 054

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: Protocol for study PCSIMM004697: an observational longitudinal PASS of Stelara (ustekinumab) in the treatment of psoriasis and psoriatic arthritis - analysis of major

⁸⁹ Held 29 November – 02 December 2021

adverse cardiovascular events (MACE) using Swedish national health registries

17.3. Results of PASS imposed in the marketing authorisation(s)⁹⁰

None

17.4. Results of PASS non-imposed in the marketing authorisation(s)⁹¹

17.4.1. Apremilast - OTEZLA (CAP) - EMEA/H/C/003746/II/0039

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Eva Segovia

Scope: Submission of the final study report (CSR) from the UK Clinical Practice Research Database (CPRD) (listed as a category 3 study in the RMP): an observational study to assess the long-term data of apremilast in patients with psoriasis and psoriatic arthritis. The RMP (version 14.1) is updated accordingly

17.4.2. Defibrotide - DEFITELIO (CAP) - EMEA/H/C/002393/II/0058/G, Orphan

Applicant: Gentium S.r.l.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Grouped variations consisting of: 1) submission of the final study report of the DEFIFrance registry (listed as a category 3 study in the RMP): a national, post-registration observational study of the long-term safety and health outcome of patients treated with Defitelio (defibrotide), including patients with severe hepatic veno-occlusive disease (VOD) after hematopoietic stem-cell transplantation (HSCT) (in fulfilment of LEG 011.3). The RMP (version 9.2) is updated accordingly; 2) submission of an updated RMP (version 9.2) in order to remove reproductive toxicity as a potential risk

17.4.3. Empagliflozin - JARDIANCE (CAP) - EMEA/H/C/002677/WS2223/0066/G; empagliflozin, linagliptin - GLYXAMBI (CAP) - EMEA/H/C/003833/WS2223/0043/G; empagliflozin, metformin - SYNJARDY (CAP) - EMEA/H/C/003770/WS2223/0062/G

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Eva Segovia

Scope: Grouped variations consisting of: 1) submission of the final report from PASS 1245.146 (listed as a category 3 study in the RMP): a 5-year enhanced pharmacovigilance surveillance initiative to survey and characterise spontaneous occurrence and experience of ketoacidotic events in patients treated with empagliflozin-containing products. The RMP is updated accordingly; 2) submission of updated RMPs for Jardiance (version 18.0), for Glyxambi (version 7.0) and for Synjardy (version 12.0) in order to remove bone fracture, classified as an important potential risk and pregnancy/breast-feeding as missing information

⁹⁰ In accordance with Article 107p-q of Directive 2001/83/EC

⁹¹ 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

17.4.4. Human papillomavirus vaccine [types 16, 18] (recombinant, adjuvanted, adsorbed) - CERVARIX (CAP) - EMEA/H/C/000721/II/0114

Applicant: GlaxoSmithkline Biologicals SA

PRAC Rapporteur: Jean-Michel Dogné

Scope: Submission of the final report from study EPI-HPV-048 (listed as a category 3 study in the RMP.): a surveillance study part of a two-phase national human papillomavirus vaccine (HPV) surveillance programme initiated in the UK by the Health Protection Agency in order to evaluate the impact of HPV vaccination on HPV type replacement and to assess the prevalence of type-specific HPV deoxyribonucleic acid (DNA) in young women in England since HPV immunisation using Cervarix (human papillomavirus vaccine) was introduced (in fulfilment of MEA 094). In addition, the submission includes the protocol for study EPI-HPV-099: an observational, retrospective database PASS to assess trends and changes over time in incidence of anal cancer and feasibility for a case-control study in European countries that introduced Cervarix (human papillomavirus vaccine) in their National Immunisation Programmes (NIP) in order to address the safety concern of 'impact and effectiveness against anal lesions and cancer'. The RMP (version 25) is updated accordingly

17.4.5. Sirolimus - RAPAMUNE (CAP) - EMEA/H/C/000273/II/0184

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of the final report from non-interventional study B1741224 (listed as a category 3 study in the RMP): a population-based cohort study to monitor the safety and effectiveness of sirolimus in patients with sporadic lymphangioleiomyomatosis (S-LAM)

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

17.5.1. Etanercept - BENEPALI (CAP) - EMEA/H/C/004007/MEA 002.4

Applicant: Samsung Bioepis NL B.V.

PRAC Rapporteur: Eva Segovia

Scope: Fifth annual interim report from an established nationwide register: British Society for Rheumatology Rheumatoid Arthritis Register (BSRBR-RA) for patients with rheumatological disorders treated with biologic agents, designed as a national prospective study whose primary purpose is to assess long-term toxicity from the use of these agents in routine practice [final report expected in 2027]

17.5.2. Etanercept - BENEPALI (CAP) - EMEA/H/C/004007/MEA 003.4

Applicant: Samsung Bioepis NL B.V.

PRAC Rapporteur: Eva Segovia

Scope: Fifth annual interim report from an established nationwide register: Rheumatoide Arthritis: Beobachtung der Biologika-Therapie (RABBIT) for patients with rheumatological

disorders treated with biologic agents, designed as a national prospective study whose primary purpose is to assess long-term toxicity from the use of these agents in routine practice [final report expected in 2027]

17.5.3. Etanercept - BENEPALI (CAP) - EMEA/H/C/004007/MEA 004.4

Applicant: Samsung Bioepis NL B.V.

PRAC Rapporteur: Eva Segovia

Scope: Fifth annual interim report for study from the Anti-Rheumatic Treatment in Sweden (ARTIS) register: a national prospective, observational, uncontrolled cohort study evaluating the risk of selected adverse events (AEs) in rheumatoid arthritis (RA), juvenile idiopathic arthritis, and other rheumatic disease patients treated with etanercept [final report expected in 2027]

17.5.4. Etanercept - BENEPALI (CAP) - EMEA/H/C/004007/MEA 005.4

Applicant: Samsung Bioepis NL B.V.

PRAC Rapporteur: Eva Segovia

Scope: Fifth annual interim report for study from the British Association of Dermatologists Biologic Interventions Register (BADBIR): a national prospective, observational cohort study of patients with psoriasis, which compares patients treated with biological interventions to a control group not exposed to biologicals [final report expected in 2027]

17.5.5. Infliximab - FLIXABI (CAP) - EMEA/H/C/004020/MEA 009.1

Applicant: Samsung Bioepis NL B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: MAH's response to MEA 009 [interim report for the Chronisch Entzündliche Darmerkrankungen, ein Unabhängiges Register (CEDUR) to describe the long-term effectiveness of treatment with inflammatory bowel disease (IBD) therapies such as drug survival, effectiveness, side effects of treatment combination, and disease activity achieved] as per the request for supplementary information (RSI) adopted in November 2021⁹²

17.5.6. Infliximab - FLIXABI (CAP) - EMEA/H/C/004020/MEA 010.1

Applicant: Samsung Bioepis NL B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: MAH's response to MEA 010 [interim report for the Czech Register of inflammatory bowel disease (IBD) Patients on Biological Therapy (CREDIT) to monitor effectiveness of total population of IBD patients on biological medication in the Czech Republic and regular analytical evaluation of the effectiveness] as per the request for supplementary information (RSI) adopted in November 2021⁹³

⁹² Held 25-28 October 2021

⁹³ Held 25-28 October 2021

17.5.7. Octocog alfa - KOGENATE BAYER (CAP) - EMEA/H/C/000275/MEA 086.10

Applicant: Bayer AG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Twelfth annual European Haemophilia Safety Surveillance (EUHASS) report for study 14149 (listed as a category 3 study in the RMP): evaluation of cases with adverse events (AEs) of special interest in the EUHASS registry [final clinical study report (CSR) expected in December 2021]

17.5.8. Octocog alfa - KOVALTRY (CAP) - EMEA/H/C/003825/MEA 004.4

Applicant: Bayer AG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Twelfth annual European Haemophilia Safety Surveillance (EUHASS) report for study 14149 (listed as a category 3 study in the RMP): evaluation of cases with adverse events (AEs) of special interest in the EUHASS registry [final clinical study report (CSR) expected in December 2021]

17.5.9. Inotersen - TEGSEDI (CAP) - EMEA/H/C/004782/MEA 001.7

Applicant: Akcea Therapeutics Ireland Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Annual progress report for study TEG4001: a prospective, non-interventional, long-term, multinational cohort safety study of patients with hereditary transthyretin amyloidosis with polyneuropathy (hATTR-PN)

17.5.10. Ruriocog alfa pegol - ADYNOVI (CAP) - EMEA/H/C/004195/ANX 002.1

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Interim report for study SHP660-403: a PASS to investigate the potential effects of PEG accumulation in the choroid plexus of the brain and other tissues/organs, [final study report expected in Q1 2029] (from initial opinion/marketing authorisation(s) (MA))

17.5.11. Tisagenlecleucel - KYMRIA[®] (CAP) - EMEA/H/C/004090/ANX 003.7

Applicant: Novartis Europharm Limited, ATMP⁹⁴

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Fourth semi-annual report for study CCTL019B2401: a non-interventional PASS to further characterise the safety, including long-term safety, of Kymriah (tisagenlecleucel) based on data from a disease registry in acute lymphoblastic leukaemia (ALL) and diffuse large B-cell lymphoma (DLBCL) patients (European Society for Blood and Marrow Transplant Society Registry (EBMT) data only)

⁹⁴ Advanced therapy medicinal product

17.5.12. [Tozinameran - COMIRNATY \(CAP\) - EMEA/H/C/005735/MEA 010.3](#)

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 [final clinical study report (CSR) expected in December 2023]

17.6. Others

17.6.1. [Coronavirus \(COVID-19\) vaccine \(ChAdOx1-S \[recombinant\]\) - VAXZEVRIA \(CAP\) - EMEA/H/C/005675/MEA 006.3](#)

Applicant: AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

Scope: Statistical analysis plan (SAP) for study COVID-19 vaccines International Pregnancy Exposure Registry (C-VIPER) (listed as a category 3 study in the RMP): a pregnancy registry of women exposed to Vaxzevria (AZD1222 – COVID-19 vaccine) immediately before or during pregnancy (from initial opinion/marketing authorisation(s) (MA))

17.6.2. [Elasomeran - SPIKEVAX \(CAP\) - EMEA/H/C/005791/MEA 004.5](#)

Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Submission of a statistical analysis plan (SAP) for study mRNA-1273-P904 (study 1) (listed as a category 3 study in the RMP): a post-authorisation active surveillance safety study using secondary data to monitor real-world safety of Spikevax (COVID-19 mRNA-1273 vaccine) in Europe - an enhanced pharmacovigilance study to provide additional evaluation of adverse events of special interest (AESI) and emerging validated safety signals in European populations and electronic database assessment of use in pregnant women [final clinical study report (CSR) expected in December 2023]

17.6.3. [Icatibant - FIRAZYR \(CAP\) - EMEA/H/C/000899/MEA 034](#)

Applicant: Takeda Pharmaceuticals International AG

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Proposal for discontinuation of icatibant outcome survey (IOS): a prospective, international, observational open-ended disease registry designed to document over time the routine clinical outcomes of adult and paediatric patients with hereditary angioedema (HAE; HAE types I and II and HAE with normal C1-esterase inhibitor), angiotensin converting enzyme inhibitor (ACE-I)-induced angioedema, non-histaminergic idiopathic angioedema, and acquired angioedema; and notification of change to the legal entity sponsoring the study

17.7. New Scientific Advice

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

17.8. Ongoing Scientific Advice

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

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

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

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

Based on the review of the available pharmacovigilance data for the below-listed medicines 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. Afamelanotide - SCENESSE (CAP) - EMEA/H/C/002548/S/0041 (without RMP)

Applicant: Clinuvel Europe Limited

PRAC Rapporteur: Martin Huber

Scope: Annual reassessment of the marketing authorisation

18.1.2. Defibrotide - DEFITELIO (CAP) - EMEA/H/C/002393/S/0057 (with RMP)

Applicant: Gentium S.r.l.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Annual reassessment of the marketing authorisation

18.1.3. Susoctocog alfa - OBIZUR (CAP) - EMEA/H/C/002792/S/0044 (without RMP)

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Annual reassessment of the marketing authorisation

18.1.4. Tagraxofusp - ELZONRIS (CAP) - EMEA/H/C/005031/S/0012 (without RMP)

Applicant: Stemline Therapeutics B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Annual reassessment of the marketing authorisation

18.2. Conditional renewals of the marketing authorisation

18.2.1. Ataluren - TRANSLARNA (CAP) - EMEA/H/C/002720/R/0067 (without RMP)

Applicant: PTC Therapeutics International Limited

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Conditional renewal of the marketing authorisation

18.2.2. Belantamab mafodotin - BLENREP (CAP) - EMEA/H/C/004935/R/0010 (without RMP)

Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Annika Folin

Scope: Conditional renewal of the marketing authorisation

18.2.3. Bulevirtide - HEPCLUDEX (CAP) - EMEA/H/C/004854/R/0013 (without RMP)

Applicant: Gilead Sciences Ireland Unlimited Company

PRAC Rapporteur: Adam Przybylkowski

Scope: Conditional renewal of the marketing authorisation

18.2.4. Cemiplimab - LIBTAYO (CAP) - EMEA/H/C/004844/R/0029 (without RMP)

Applicant: Regeneron Ireland Designated Activity Company (DAC)

PRAC Rapporteur: Menno van der Elst

Scope: Conditional renewal of the marketing authorisation

18.2.5. Idecabtagene vicleucel - ABECMA (CAP) - EMEA/H/C/004662/R/0014 (with RMP)

Applicant: Bristol-Myers Squibb Pharma EEIG, ATMP⁹⁵

PRAC Rapporteur: Annika Folin

Scope: Conditional renewal of the marketing authorisation

18.2.6. Imlifidase - IDEFIRIX (CAP) - EMEA/H/C/004849/R/0007 (without RMP)

Applicant: Hansa Biopharma AB

⁹⁵ Advanced therapy medicinal product

PRAC Rapporteur: Menno van der Elst

Scope: Conditional renewal of the marketing authorisation

18.2.7. Pretomanid - DOVPRELA (CAP) - EMEA/H/C/005167/R/0010 (without RMP)

Applicant: Mylan IRE Healthcare Limited

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Conditional renewal of the marketing authorisation

18.3. Renewals of the marketing authorisation

18.3.1. Copper (⁶⁴Cu) chloride - CUPRYMINA (CAP) - EMEA/H/C/002136/R/0023 (without RMP)

Applicant: A.C.O.M. - Advanced Center Oncology Macerata - S.R.L.

PRAC Rapporteur: Ilaria Baldelli

Scope: 5-year renewal of the marketing authorisation

18.3.2. Dupilumab - DUPIXENT (CAP) - EMEA/H/C/004390/R/0053 (without RMP)

Applicant: sanofi-aventis groupe

PRAC Rapporteur: Kimmo Jaakkola

Scope: 5-year renewal of the marketing authorisation

18.3.3. Entecavir - ENTECAVIR ACCORD (CAP) - EMEA/H/C/004458/R/0011 (without RMP)

Applicant: Accord Healthcare S.L.U.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: 5-year renewal of the marketing authorisation

18.3.4. Entecavir - ENTECAVIR MYLAN (CAP) - EMEA/H/C/004377/R/0008 (with RMP)

Applicant: Mylan Pharmaceuticals Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: 5-year renewal of the marketing authorisation

18.3.5. Lacosamide - LACOSAMIDE ACCORD (CAP) - EMEA/H/C/004443/R/0015 (without RMP)

Applicant: Accord Healthcare S.L.U.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: 5-year renewal of the marketing authorisation

18.3.6. Nitisinone - NITISINONE MDK (CAP) - EMEA/H/C/004281/R/0013 (without RMP)

Applicant: MendeliKABS Europe Limited

PRAC Rapporteur: Iliara Baldelli

Scope: 5-year renewal of the marketing authorisation

18.3.7. Telotristat ethyl - XERMELO (CAP) - EMEA/H/C/003937/R/0032 (without RMP)

Applicant: Ipsen Pharma

PRAC Rapporteur: Adam Przybylkowski

Scope: 5-year renewal of the marketing authorisation

19. Annex II – List of participants

Including any restrictions with respect to involvement of members / alternates / experts following evaluation of declared interests for the 04-07 April 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	Netherlands	No interests declared	Full involvement
Jan Neuhauser	Member	Austria	No interests declared	Full involvement
Sonja Hrabcik	Alternate	Austria	No interests declared	Full involvement
Jean-Michel Dogné	Member	Belgium	No interests declared	Full involvement
Maria Popova-Kiradjieva	Member	Bulgaria	No interests declared	Full involvement
Nikica Mirošević Skvrce	Member	Croatia	No interests declared	Full involvement
Željana Margan Koletić	Alternate	Croatia	No interests declared	Full involvement
Panagiotis Psaras	Alternate	Cyprus	No interests declared	Full involvement
Eva Jirsová	Member	Czechia	No interests declared	Full involvement
Anette Kirstine Stark	Member	Denmark	No interests declared	Full involvement
Marie Louise Schougaard Christiansen	Alternate	Denmark	No interests declared	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Maia Uusküla	Member	Estonia	No interests declared	Full involvement
Krõõt Aab	Alternate	Estonia	No interests declared	Full involvement
Kirsti Villikka	Member	Finland	No interests declared	Full involvement
Kimmo Jaakkola	Alternate	Finland	No interests declared	Full involvement
Tiphaine Vaillant	Member	France	No interests declared	Full involvement
Nathalie Gault	Alternate	France	No interests declared	Full involvement
Martin Huber	Member (Vice-Chair)	Germany	No interests declared	Full involvement
Brigitte Keller-Stanislowski	Alternate	Germany	No interests declared	Full involvement
Sofia Trantza	Member	Greece	No interest declared	Full involvement
Georgia Gkegka	Alternate	Greece	No interest declared	Full involvement
Julia Pallos	Member	Hungary	No participation in final deliberations and voting on:	4.3.1. Abatacept – ORENCIA (CAP) - EMEA/H/C/000701/SDA/068 5.3.1. Belatacept - NULOJIX (CAP) - EMEA/H/C/002098/II/0079/G 18.2.5. Idecabtagene vicleucel - ABECMA (CAP) - EMEA/H/C/004662/R/0014 (with RMP)
Melinda Palfi	Alternate	Hungary	No interests declared	Full involvement
Guðrún Stefánsdóttir	Member	Iceland	No participation in final deliberations and voting on:	17.4.1. Apremilast - OTEZLA (CAP) - EMEA/H/C/003746/II/0039
Rhea Fitzgerald	Member	Ireland	No interests declared	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Ronan Grimes	Alternate	Ireland	No interests declared	Full involvement
Amelia Cupelli	Member	Italy	No interests declared	Full involvement
Ilaria Baldelli	Alternate	Italy	No interests declared	Full involvement
Zane Neikena	Member	Latvia	No interests declared	Full involvement
Zane Stade	Alternate	Latvia	No interests declared	Full involvement
Rugile Pilviniene	Member	Lithuania	No interests declared	Full involvement
Lina Seibokiene	Alternate (Mandate as alternate for Lithuania started on 25/03/2022)	Lithuania	No participation in discussion, final deliberations and voting on:	14.1.1. Rivaroxaban - RIVAROXABAN ACCORD (CAP); RIVAROXABAN MYLAN (CAP); XARELTO (CAP); NAP
Nadine Petitpain	Member	Luxembourg	No restrictions applicable to this meeting	Full involvement
John Joseph Borg	Member	Malta	No interests declared	Full involvement
Menno van der Elst	Member	Netherlands	No interests declared	Full involvement
Liana Gross-Martirosyan	Alternate	Netherlands	No interests declared	Full involvement
Karen Pernille Harg	Alternate	Norway	No interests declared	Full involvement
Adam Przybylkowski	Member	Poland	No interests declared	Full involvement
Ana Diniz Martins	Member	Portugal	No interests declared	Full involvement
Marcia Sofia Sanches de Castro Lopes Silva	Alternate	Portugal	No interests declared	Full involvement
Roxana Dondera	Member	Romania	No interests declared	Full involvement
Alexandra - Maria Spurni	Alternate	Romania	No interests declared	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Marek Juracka	Member	Slovakia	No interests declared	Full involvement
Anna Mareková	Alternate	Slovakia	No interests declared	Full involvement
Milena Radoha-Bergoc	Alternate	Slovenia	No participation in final deliberations and voting on:	11.1.1. Ibuprofen (NAP) - DE/H/0392/II/032 /G 14.1.1. Rivaroxaban - RIVAROXABAN ACCORD (CAP); RIVAROXABAN MYLAN (CAP); XARELTO (CAP); NAP 16.3.4. Cetirizine, pseudoephedrine (NAP) - PSUSA/00000629/202108 16.3.8. Finasteride (NAP) - PSUSA/00001392/202108
Eva Segovia	Member	Spain	No interests declared	Full involvement
Maria del Pilar Rayon	Alternate	Spain	No interests declared	Full involvement
Ulla Wändel Liminga	Member	Sweden	No interests declared	Full involvement
Annika Folin	Alternate	Sweden	No interests declared	Full involvement
Annalisa Capuano	Member	Independent scientific expert	No interests declared	Full involvement
Milou Daniel Drici	Member	Independent scientific expert	No interests declared	Full involvement
Maria Teresa Herdeiro	Member	Independent scientific expert	No interests declared	Full involvement
Patricia McGettigan	Member	Independent scientific expert	No interests declared	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Hedvig Nordeng	Member	Independent scientific expert	No interests declared	Full involvement
Laurence de Fays	Expert	Belgium	No interests declared	Full involvement
Martine Sabbe	Expert	Belgium	No interests declared	Full involvement
Françoise Guillaume	Expert	Belgium	No interests declared	Full involvement
Petra Kaftanová	Expert	Czechia	No interests declared	Full involvement
Mária Kováčová	Expert	Czechia	No interests declared	Full involvement
Petra Vacková	Expert	Czechia	No interests declared	Full involvement
Alexander Braathen	Expert	Denmark	No interests declared	Full involvement
Karin Susanne Erneholm	Expert	Denmark	No restrictions applicable to this meeting	Full involvement
Helle Gerda Olsen	Expert	Denmark	No interests declared	Full involvement
Marianne Hald Clemmensen	Expert	Denmark	No restrictions applicable to this meeting	Full involvement
Helene Stenbæk Hansen	Expert	Denmark	No restrictions applicable to this meeting	Full involvement
Marian Hjortlund Allon	Expert	Denmark	No interests declared	Full involvement
Kristina Laursen	Expert	Denmark	No interests declared	Full involvement
Pernille Lynge Gammelgaard	Expert	Denmark	No interests declared	Full involvement
Per Sindahl	Expert	Denmark	No restrictions applicable to this meeting	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Ditte Søgaard	Expert	Denmark	No restrictions applicable to this meeting	Full involvement
Emma Louise Nautrup Ravn Stadsbjerg	Expert	Denmark	No interests declared	Full involvement
Josiane Uwera	Expert	Denmark	No restrictions applicable to this meeting	Full involvement
Helve Vestman	Expert	Estonia	No interests declared	Full involvement
Samuel Crommelynck	Expert	France	No restrictions applicable to this meeting	Full involvement
Vincent Gazin	Expert	France	No interests declared	Full involvement
Marie-Caroline Pesquidous	Expert	France	No restrictions applicable to this meeting	Full involvement
Wafa Rajhi	Expert	France	No restrictions applicable to this meeting	Full involvement
Youssef Shaim	Expert	France	No restrictions applicable to this meeting	Full involvement
Roberto Frontini	Expert	Germany	No restrictions applicable to the meeting	Full involvement
Doris Höschele	Expert	Germany	No interests declared	Full involvement
Jelena Katic	Expert	Germany	No interests declared	Full involvement
Sabine Kudicke	Expert	Germany	No interests declared	Full involvement
Tobias Lamkemeyer	Expert	Germany	No interests declared	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Dennis Lex	Expert	Germany	No restrictions applicable to this meeting	Full involvement
Tania Meier	Expert	Germany	No interests declared	Full involvement
Aine McKenna	Expert	Ireland	No interests declared	Full involvement
Ruchika Sharma	Expert	Ireland	No restrictions applicable to this meeting	Full involvement
Paula Boudewina van Hennik	Expert	Netherlands	No interests declared	Full involvement
Carla Herberts	Expert	Netherlands	No restrictions applicable to this meeting	Full involvement
Anne Taams	Expert	The Netherlands	No restrictions applicable to this meeting	Full involvement
Carla Torre	Expert	Portugal	No restrictions applicable to this meeting	Full involvement
Fernanda Inês Carvalho Pereira Ribeiro Vaz	Expert	Portugal	No interests declared	Full involvement
Helena Calero Garnacho	Expert	Spain	No restrictions applicable to this meeting	Full involvement
Natividad Galiana Llorca	Expert	Spain	No restrictions applicable to this meeting	Full involvement
Blanca García-Ochoa Martín	Expert	Spain	No interests declared	Full involvement
Elena Martínez Alonso	Expert	Spain	No interests declared	Full involvement
Charlotte Backman	Expert	Sweden	No interests declared	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Henrik Dahllöf	Expert	Sweden	No restrictions applicable to this meeting	Full involvement
Karin Hellgren	Expert	Sweden	No restrictions applicable to this meeting	Full involvement
Filip Josephson	Expert	Sweden	No interests declared	Full involvement
Anna Schölin	Expert	Sweden	No interests declared	Full involvement
A representative from the European Commission attended the meeting				
Meeting run with support from relevant EMA staff				
Experts were 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>