16 May 2023
EMA/PRAC/185211/2023

Human Medicines Division

Pharmacovigilance Risk Assessment Committee (PRAC)

Minutes of PRAC meeting on 06-09 February 2023

Chair: Sabine Straus – Vice-Chair: Martin Huber

Health and safety information

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

Disclaimers

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

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

Note on access to documents

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

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1. Introduction

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

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

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

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

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

1.2. Agenda of the meeting on 06-09 February 2023

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 09-12 January 2023

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 09-12 January 2023 were published on the EMA website on 03 May 2023 (EMA/PRAC/141718/2023).

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

2.1. Newly triggered procedures

None

2.2. Ongoing procedures

None

2.3. Procedures for finalisation

None

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

3.1. Newly triggered procedures

3.1.1. Pseudoephedrine (NAP); pseudoephedrine, acetylsalicylic acid (NAP); pseudoephedrine, acetylcysteine, paracetamol (NAP); pseudoephedrine, acrivastine (NAP); pseudoephedrine, ascorbic acid, paracetamol (NAP); pseudoephedrine, cetirizine (NAP); pseudoephedrine, ebastine (NAP); pseudoephedrine, guaifenesin (NAP); pseudoephedrine, ibuprofen (NAP); pseudoephedrine, chlorphenamine (NAP); pseudoephedrine, chlorphenamine, codeine (NAP); pseudoephedrine, chlorphenamine, dextromethorphan (NAP); pseudoephedrine, chlorphenamine, paracetamol (NAP); pseudoephedrine, chlorphenamine, dextromethorphan, paracetamol (NAP); pseudoephedrine, dextromethorphan (NAP); pseudoephedrine, dextromethorphan, paracetamol (NAP); pseudoephedrine, dextromethorphan, ascorbic acid, paracetamol (NAP); pseudoephedrine, dextromethorphan, guaifenesin, paracetamol (NAP); pseudoephedrine, dextromethorphan, guaifenesin, triprolidine (NAP); pseudoephedrine, dextromethorphan, triprolidine (NAP); pseudoephedrine, diphenhydramine, paracetamol (NAP); pseudoephedrine, doxylamine, paracetamol (NAP); pseudoephedrine, loratadine (NAP); pseudoephedrine, paracetamol (NAP); pseudoephedrine, paracetamol, pholcodine (NAP); pseudoephedrine, triprolidine (NAP); pseudoephedrine, triprolidine, guaifenesin (NAP); pseudoephedrine, triprolidine, paracetamol (NAP); pseudoephedrine, desloratadine - AERINAZE (CAP) – EMA/H/A31/1526

Applicant(s): various

PRAC Rapporteur: Eva Jirsová; PRAC Co-rapporteur: Krõõt Aab

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

Background

Pseudoephedrine is a sympathomimetic indicated alone or in combination with other active substances for the symptomatic relief of nasal/sinus congestion with headache, fever and pain associated with the common cold and flu, as well as for the treatment of the symptoms of seasonal allergic rhinitis (hay fever, inflammation of the nasal passages caused by an allergy to pollen) in patients who have nasal congestion (a blocked nose), subject to certain conditions.

The French Medicine Agency (ANSM) sent a letter of notification dated 03 February 2023 triggering a referral under Article 31 of Directive 2001/83/EC for the review of pseudoephedrine-containing products following the assessment of the PSUR single assessment (PSUSA) procedure on ibuprofen/pseudoephedrine (PSUSA/00001711/202207) concluded in February 2023. This relates to data submitted by the MAHs within the PSUSA procedure suggesting a causal relationship between posterior reversible encephalopathy syndrome (PRES), reversible cerebral vasoconstriction syndrome (RCVS) and pseudoephedrine use, based on the compatible and suggestive time to onset, the biological plausibility and the lack of alternative aetiologies for some patients without any risk factors

of PRES/RCVS. For further background, see PRAC minutes January 2023 and see current minutes under 6.3.2.

Considering the seriousness of PRES and RCVS, the overall safety profile of pseudoephedrine and the indications for which the medicines are approved, ANSM referred the matter to PRAC in the interest of the Union for further evaluation and requested that it gives its recommendation as to whether the marketing authorisation(s) for pseudoephedrine-containing product(s) should be maintained, varied, suspended or revoked.

Discussion

PRAC noted the notification letter from ANSM.

PRAC appointed Eva Jirsová as Rapporteur and Krõõt Aab as Co-Rapporteur for the procedure.

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

Summary of recommendation(s)/conclusions

- The Committee adopted a LoQ to the MAHs (EMA/PRAC/55342/2023) and a timetable for the procedure (EMA/PRAC/55340/2023).
- PRAC discussed the option to conduct a public hearing in the context of the current procedure according to the pre-defined criteria set out in the rules of procedure (EMA/11523/2023 Rev 2). It was agreed by the Committee that at this stage in the assessment, in light of the currently available data and the need to determine the appropriate approach to stakeholder engagement, a public hearing would not be appropriate. PRAC can reconsider this at a later stage of the procedure, as needed.

See EMA press release (EMA/56626/2023) entitled 'PRAC starts safety review of pseudoephedrine-containing medicines'.

3.2. Ongoing procedures

3.2.1. Topiramate (NAP); topiramate, phentermine (NAP) - EMEA/H/A-31/1520

Applicant(s): various

PRAC Rapporteur: Ulla Wändel Liminga; PRAC Co-rapporteur: Martin Huber

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

Background

A referral procedure under Article 31 of Directive 2001/83/EC is ongoing for topiramate- and topiramate/phentermine-containing medicines following the publication by *Bjørk et al.*[1] in which the authors concluded on a statistically significant increase of neurodevelopmental disorders, in particular autism spectrum disorders and intellectual disability, in children with prenatal exposure to topiramate. Given the potential increased risk of neurodevelopmental disorders highlighted in this study with in utero exposure to topiramate and the known risk of congenital malformations, the matter was referred to PRAC for further evaluation. For

[1] Bjørk M, Zoega H, Leinonen MK, et al. Association of prenatal exposure to antiseizure medication with risk of autism and intellectual disability. JAMA Neurol. Published online May 31, 2022. doi:10.1001/jamaneurol.2022.1269

further background, see PRAC minutes September 2022[2], PRAC minutes December 2022[3] and PRAC minutes January 2023.

Summary of recommendation(s)/conclusions

- PRAC adopted a revised timetable (EMA/PRAC/702489/2022 rev.2) to reflect the date of the Scientific Advisory Group on Neurology (SAG-N) meeting scheduled on 01 March 2023.
- PRAC discussed the list of participants (LoP) for the SAG-N.

Post-meeting note: on 28 February 2023, PRAC adopted the LoP via written procedure.

3.3. Procedures for finalisation

None

3.4. Re-examination procedures[4]

None

3.5. Others

None

4. Signals assessment and prioritisation[5]

4.1. New signals detected from EU spontaneous reporting systems

4.1.1. Ipilimumab – YERVOY (CAP); nivolumab – OPDIVO (CAP); pembrolizumab – KEYTRUDA (CAP)

Applicant(s): Bristol-Myers Squibb Pharma EEIG (OPDIVO, YERVOY), Merck Sharp & Dohme B.V. (KEYTRUDA)

PRAC Rapporteur: Menno van der Elst

Scope: Signal of capillary leak syndrome (OPDIVO, YERVOY, KEYTRUDA) and cytokine release syndrome (OPDIVO)

EPITT 19880 – New signal

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.

[2] Held on 29 August – 01 September 2022
[3] Held on 28 November - 01 December 2022
[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

During routine signal detection activities, a signal of capillary leak syndrome (CLS) for Opdivo (nivolumab), Yervoy (ipilimumab) and Keytruda (pembrolizumab), and cytokine release syndrome (CRS) for Opdivo (nivolumab) was identified by EMA, based on 23 cases for nivolumab, 13 cases for ipilimumab and 20 cases for pembrolizumab retrieved from EudraVigilance. The Netherlands confirmed that the signal needed initial analysis and prioritisation by PRAC.

Discussion

Having considered the available evidence from EudraVigilance and the literature, PRAC agreed that further evaluation on the signal of CLS for Opdivo (nivolumab), Yervoy (ipilimumab) and Keytruda (pembrolizumab), and CRS for Opdivo (nivolumab) is warranted.

PRAC appointed Menno van der Elst as Rapporteur for the signal.

Summary of recommendation(s)

- The MAHs for Opdivo (nivolumab) and Yervoy (ipilimumab) should submit to EMA, within 60 days, a cumulative review of the signal CLS, while the MAH of Opdivo (nivolumab) should submit to EMA, within 60 days, a cumulative review of both CLS and CRS. All MAHs should submit data on monotherapy and combination therapy for all products and should also submit a proposal for amending the product information and/or the RMP.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.1.2. Tofacitinib – XELJANZ (CAP)

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Signal of acne

Action: For adoption of PRAC recommendation

EPITT 19885 – New signal

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.

During routine signal detection activities, a signal of acne was identified by EMA, based on 40 cases retrieved from EudraVigilance. 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, PRAC considered that there is sufficient evidence to establish a causal association between the treatment with tofacitinib and acne. Therefore, PRAC agreed that an update of the product information is warranted to add acne as an undesirable effect.

Summary of recommendation(s)

- The MAH for Xeljanz (tofacitinib) should submit to EMA, within 30 days, their comments on the proposed update of the product information[6] and provide a proposal for a frequency for acne as undesirable effect, considering incidence rates estimated for tofacitinib based on pooled clinical trial data across various indications.
- A 30-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.2. New signals detected from other sources

None

4.3. Signals follow-up and prioritisation

4.3.1. Adalimumab - AMGEVITA (CAP), AMSPARITY (CAP), HEFIYA (CAP), HUMIRA (CAP) - EMEA/H/C/000481/SDA 126, HULIO (CAP), HUKYNDRA (CAP), HYRIMOZ (CAP), IDACIO (CAP), IMRALDI (CAP), LIBMYRIS (CAP), YUFLYMA (CAP); etanercept – ENBREL (CAP) – EMEA/H/C/000262/SDA 175; infliximab – REMICADE (CAP) – EMEA/H/C/000240/SDA 162

Applicant(s): AbbVie Deutschland GmbH (Humira), Amgen Europe B.V.(Amgevita), Celltrion Healthcare Hungary Kft. (Yuflyma), Fresenius Kabi Deutschland GmbH (Idacio), Janssen Biologics B.V. (Remicade), Pfizer Europe MA EEIG (Amsparity, Enbrel), Sandoz GmbH (Hyrimoz, Hefiya), Samsung Bioepis NL B.V. (Imraldi), Stada Arzneimittel AG (Hukyndra, Libmyris), Viatris Limited (Hulio)

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of menstrual disorder

EPITT 19812 – Follow-up to June 2022

Background

For background information, see PRAC minutes June 2022.

The MAHs for Humira (adalimumab), Remicade (infliximab) and Enbrel (etanercept) replied to the request for information on the signal of menstrual disorder and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence from EudraVigilance and the additional data submitted by the MAHs, PRAC agreed that at this stage, there is insufficient evidence to establish a causal association between the treatment with adalimumab, infliximab or etanercept and 'menstrual cycle and uterine bleeding disorders'.

Summary of recommendation(s)

- The MAHs for Humira (adalimumab) and Remicade (infliximab) should continue to monitor any new cases of menstrual cycle and uterine bleeding disorders as part of routine safety surveillance.

[6] Update of SmPC section 4.8. The package leaflet is to be updated accordingly.

- In the next PSUR[7], the MAH for Enbrel (etanercept) should provide further data on the cases retrieved in the post-marketing setting.

For the full PRAC recommendation, see EMA/PRAC/57497/2023 published on 06 March 2023 on the EMA website.

4.3.2. Bosutinib – BOSULIF (CAP) – EMEA/H/C/002373/SDA 016

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Martin Huber

Scope: Signal of interstitial lung disease (ILD)

EPITT 19843 – Follow-up to October 2022

Background

For background information, see PRAC minutes October 2022[8].

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

Discussion

Having considered the available evidence from EudraVigilance, literature and clinical studies, as well as the already known association between ILD with other active substances within the tyrosine kinase inhibitors (TKIs) class, PRAC considered that there is sufficient evidence to establish a causal relationship between treatment with bosutinib and ILD. Therefore, PRAC agreed that an update of the product information is warranted to add ILD as an undesirable effect with a frequency 'not known'.

Summary of recommendation(s)

- The MAH for Bosulif (bosutinib) should submit to EMA, within 60 days, a variation to amend[9] the product information.

For the full PRAC recommendation, see EMA/PRAC/57497/2023 published on 06 March 2023 on the EMA website.

4.3.3. Colistimethate sodium[10] (NAP)

Applicant(s): various

PRAC Rapporteur: Adam Przybylkowski

Scope: Signal of pseudo-Bartter syndrome

EPITT 19845 – Follow-up to October 2022

Background

For background information, see PRAC minutes October 2022[11].

[7] Data lock point (DLP): 02 February 2023
[8] Held on 26-29 September 2022
[9] Update of SmPC section 4.8. The package leaflet is to be updated accordingly.
[10] For intravenous use only
[11] Held on 26-29 September 2022

The MAHs Sanofi-Aventis and Teva replied to the request for information on the signal of pseudo-Bartter syndrome and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence from EudraVigilance, the literature and the responses from the MAHs, PRAC considered that there is sufficient evidence to establish a causal relationship between colistimethate sodium for intravenous use and pseudo-Bartter syndrome. Therefore, PRAC agreed that an update of the product information for colistimethate sodium-containing products for intravenous use is warranted to add pseudo-Bartter syndrome as a warning and as an undesirable effect with a frequency 'not known'.

Summary of recommendation(s)

- The MAHs for colistimethate sodium-containing products for intravenous use should submit to the relevant National Competent Authorities, within 60 days, a variation to amend[12] the product information.
- In the next PSUR, the MAHs for colistimethate sodium-containing products dry inhalation powder should provide a review of cases of pseudo-Bartter syndrome and relevant metabolic disturbances.

For the full PRAC recommendation, see EMA/PRAC/57497/2023 published on 06 March 2023 on the EMA website.

4.3.4. Nivolumab – OPDIVO (CAP) - EMEA/H/C/003985/SDA 049

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Martin Huber

Scope: Signal of morphoea

EPITT 19839 – Follow-up to October 2022

Background

For background information, see PRAC minutes October 2022[13].

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

Discussion

Having considered the data from EudraVigilance, literature and the responses provided by the MAH, PRAC agreed that at present there is insufficient evidence to establish a causal relationship between the treatment with nivolumab and morphoea.

Summary of recommendation(s)

- The MAH for Opdivo (nivolumab) should continue to closely monitor any new cases of morphoea/scleroderma in future PSURs.

[12] Update of SmPC sections 4.4 and 4.8. The package leaflet is to be updated accordingly.
[13] Held on 26-29 September 2022

4.4. Variation procedure(s) resulting from signal evaluation

None

5. Risk management plans (RMPs)

5.1. Medicines in the pre-authorisation phase

PRAC provided 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 15.1.

5.1.1. Adagrasib - EMEA/H/C/006013

Scope: Treatment of patients with advanced non-small cell lung cancer (NSCLC) with KRAS G12C mutation

5.1.2. Enalapril maleate - EMEA/H/C/005731, PUMA[14]

Scope: Treatment of heart failure

5.1.3. Futibatinib - EMEA/H/C/005627, Orphan

Applicant: Taiho Pharma Netherlands B.V.

Scope: Treatment of cholangiocarcinoma

5.1.4. Glofitamab - EMEA/H/C/005751, Orphan

Scope: Treatment of diffuse large B-cell lymphoma

5.1.5. Ivosidenib - EMEA/H/C/005936, Orphan

Applicant: Les Laboratoires Servier

Scope: Treatment of acute myeloid leukaemia and treatment of metastatic cholangiocarcinoma

5.1.6. Ivosidenib - EMEA/H/C/006174, Orphan

Applicant: Les Laboratoires Servier

Scope: Treatment of acute myeloid leukaemia

[14] Paediatric-use marketing authorisation(s)

5.1.7. Pirtobrutinib - EMEA/H/C/005863, Orphan

Applicant: Eli Lilly Nederland B.V.

Scope: Treatment of mantle cell lymphoma (MCL)

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

See also Annex 15.2.

5.2.1. Coronavirus (COVID-19) vaccine (Ad26.COV2-S, recombinant) - JCOVDEN (CAP) - EMEA/H/C/005737/II/0065

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of an updated RMP version 5.1 in order to update the clinical exposure and risk sections

Background

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

PRAC is evaluating a type II variation procedure for Jcovden, a centrally authorised medicine containing coronavirus (COVID-19) vaccine (Ad26.COV2-S, recombinant), to update the RMP to reflect the introduction of updated clinical exposure and risk sections. PRAC is responsible for adopting an outcome based on the assessment report from the PRAC Rapporteur, to be further considered at the level of CHMP, responsible for adopting an opinion on this variation. For further background, see PRAC minutes December 2022[15].

S**ummary of advice**

- The RMP version 5.3 for Jcovden (coronavirus (COVID-19) vaccine (Ad26.COV2-S, recombinant)) in the context of the variation procedure under evaluation by PRAC is considered acceptable.

5.2.2. Micafungin - MYCAMINE (CAP) - EMEA/H/C/000734/II/0047

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Martin Huber

Scope: Update of Annex II and the RMP to version 23.0 to include the results of the non-interventional PASS 9463-PV-0002: effectiveness check of the prescriber checklist for Mycamine (micafungin)

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.

[15] Held on 28 November – 01 December 2022

PRAC is evaluating a type II variation procedure for Mycamine, a centrally authorised medicine containing micafungin, to update the RMP to reflect the introduction of the results of the non-interventional PASS 9463-PV-0002. PRAC is responsible for adopting an outcome based on the assessment report from the PRAC Rapporteur, to be further considered at the level of CHMP, responsible for adopting an opinion on this variation. For further background, see PRAC minutes September 2022[16] and PRAC minutes December 2022[17].

S**ummary of advice**

- The RMP version 23.2 for Mycamine (micafungin) in the context of the variation procedure under evaluation by PRAC is considered acceptable.

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

See also Annex 15.3.

5.3.1. Coronavirus (COVID-19) vaccine (ChAdOx1-S [recombinant]) - VAXZEVRIA (CAP) - EMEA/H/C/005675/II/0084/G

Applicant: AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

Scope: Submission of an updated RMP version 6.1 in order to request the discontinuation of the category 1 study D8111C00010 and remove it from the Annex II; this is an interventional safety study of AZD1222 vaccine in immunocompromised adults. In addition, the MAH proposes the reassessment of safety concerns and changes to due dates of additional pharmacovigilance activities

Background

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

CHMP is evaluating a type II variation for Vaxzevria, a centrally authorised product containing coronavirus (COVID-19) vaccine (ChAdOx1-S [recombinant]), to update RMP version 6.1 in order to discontinue the category 1 study D8111C00010 and remove it from the Annex II. PRAC is responsible for providing advice to CHMP on the necessary updates to the RMP to support this procedure.

Summary of advice

- The RMP version 6.3 for Vaxzevria (COVID-19 vaccine (ChAdOx1-S [recombinant])) in the context of the variation procedure under evaluation by PRAC and CHMP is considered acceptable.

[16] Held on 29 August – 01 September 2022
[17] Held on 28 November – 01 December 2022

6. Periodic safety update reports (PSURs)

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

See also Annex 16.1.

6.1.1. Inotersen - TEGSEDI (CAP) - PSUSA/00010697/202207

Applicant: Akcea Therapeutics Ireland Limited

PRAC Rapporteur: Rhea Fitzgerald

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 Tegsedi, a centrally authorised medicine containing inotersen and issued a recommendation on its marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Tegsedi (inotersen) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the existing warning on thrombocytopenia regarding prolonged latency and to include the frequency 'common' for glomerulonephritis as an undesirable effect in the package leaflet. Therefore, the current terms of the marketing authorisation(s) should be varied[18].
- In the next PSUR, the MAH should provide a cumulative review of cases of coagulopathy and international normalised ratio (INR) increased, of chronic kidney disease and chronic renal impairment, of tubulointerstitial nephritis, of haemolytic anaemia and of use in pregnancy, as well as a review of cases of angioedema. The MAH should also discuss the need to advise healthcare professionals regarding the presence of antibodies to Tegsedi (inotersen) in case of hypersensitivity reactions. In addition, the MAH should update the list of PSUR safety concerns and include hepatotoxicity as an important identified risk.
- The MAH should submit to EMA, within 60 days, a review of cases of drug induced liver injury (DILI), including 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.

[18] Update of SmPC section 4.4. The package leaflet and Annex II-D 'Conditions or restrictions with regard to the safe and effective use of the medicinal product' are updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion.

6.1.2. Perampanel - FYCOMPA (CAP) - PSUSA/00009255/202207

Applicant: Eisai GmbH

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 Fycompa, a centrally authorised medicine containing perampanel 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 Fycompa (perampanel) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add psychotic disorder as a warning and as an undesirable effect with a frequency 'uncommon'. Therefore, the current terms of the marketing authorisation(s) should be varied[19].

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

6.1.3. Voretigene neparvovec - LUXTURNA (CAP) - PSUSA/00010742/202207

Applicant: Novartis Europharm Limited, ATMP[20]

PRAC Rapporteur: Gabriele Maurer

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 Luxturna, a centrally authorised medicine containing voretigene neparvovec 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 Luxturna (voretigene neparvovec) in the approved indication(s) remains unchanged.

[19] 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.
[20] Advanced therapy medicinal product

- Nevertheless, the product information should be updated to amend the existing information on chorioretinal atrophy as an undesirable effect to include further information on chorioretinal atrophy occurring also outside of the bleb area, with cases of retinal atrophy extending to the fovea with visual impairment. Therefore, the current terms of the marketing authorisation(s) should be varied[21].
- In the next PSUR, the MAH should provide a review of cases of vitritis and/or outer retinal infiltrates with a special focus on the impact on vision and the development of chorioretinal atrophies. In addition, the MAH should propose an update of the product information in case the trend for an increasing reporting rate for intraocular inflammation and and/or infection is continued in the next reporting interval.

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)

None

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

See also Annex 16.3.

6.3.1. Carbetocin (NAP) - PSUSA/00000546/202206

Applicant(s): various

PRAC Lead: Jana Lukačišinová

Scope: Evaluation of a PSUSA procedure

Background

Carbetocin is a synthetic long-lasting oxytocin agonistic analogue, indicated for the prevention of uterine atony and excessive bleeding following delivery of the infant by caesarean section under epidural or spinal anaesthesia and following a vaginal delivery.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing carbetocin 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 carbetocin-containing product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add bradycardia which can lead to cardiac arrest (only for intravenous administration) and hypersensitivity

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

(including anaphylactic reaction) as undesirable effects, with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[22].

- In the next PSUR, the MAH(s) should provide cumulative reviews on the risk of placental retention. In addition, the MAH(s) should assess whether any pattern of the risk of adverse effects is observed with incorrect rapid or prolonged administration of carbetocin (off-label use), as well as provide a detailed review of cases of cardiac arrhythmias (with a special focus on QT prolongation/torsade de point). The MAH(s) should also discuss if any update of the product information is warranted.

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

6.3.2. Ibuprofen, pseudoephedrine (NAP) - PSUSA/00001711/202207

Applicant(s): various

PRAC Lead: Nathalie Gault

Scope: Evaluation of a PSUSA procedure

Background

Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID) with anti-pyretic, analgesic, and anti-inflammatory properties, while pseudoephedrine is an alpha agonist acting as a nasal decongestant. In combination, ibuprofen/pseudoephedrine is indicated for the symptomatic relief of nasal/sinus congestion with headache, fever and pain associated with the common cold and flu in adults and adolescents over 12 or 15 years old, subject to certain conditions.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing ibuprofen/pseudoephedrine 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 ibuprofen/pseudoephedrine-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) for ibuprofen/pseudoephedrine-containing products should provide a review of cases related to ischaemic events. The MAH(s) should also provide a review of cases of cross-allergy between pseudoephedrine and other sympathomimetics, including data from literature and post-marketing setting.

This is without prejudice to a thorough review of pseudoephedrine-containing product(s) within an appropriate procedure to assess all available data and determine the impact of the risks of posterior reversible encephalopathy syndrome and reversible cerebral vasoconstriction syndrome (PRES/RCVS) on the benefit-risk balance of pseudoephedrine-containing products (see section 3.1.1).

[22] 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

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. Ropinirole (NAP) - PSUSA/00002661/202207

Applicant(s): various

PRAC Lead: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

Background

Ropinirole is a potent non-ergoline D2/D3 dopamine agonist indicated for the treatment of Parkinson's disease (PD) as monotherapy, or in combination with levodopa. Ropinirole is also indicated for symptomatic treatment of moderate to severe idiopathic restless legs syndrome (RLS).

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing ropinirole 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 ropinirole-containing product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add spontaneous penile erection and hiccups as undesirable effects with a frequency 'not known' and 'uncommon' respectively. Therefore, the current terms of the marketing authorisation(s) should be varied[23].
- In the next PSUR, the MAH(s) should provide cumulative reviews of cases of dropped head syndrome, including data from literature, clinical trials and post-marketing setting. The MAH(s) should also comment the publication by *Matsumoto H. et al., 2018*[24]. In addition, the MAH(s) should provide cumulative reviews of cases of sexual dysfunction and erectile dysfunction (MedDRA PTs[25]), including data from post-marketing setting and clinical trials, along with a literature review and a discussion on the mechanism of action. The MAH(s) should discuss whether an updated of the product information is warranted.

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

[23] Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion.
[24] Matsumoto H, Akahori T, Hatano K, Hashida H. Botulinum toxin treatment of paraspinal muscles for improving abnormal posture in Parkinson's disease. Basal Ganglia. 2018;12:(1-3)
[25] Medical dictionary for regulatory activities – Preferred terms

6.4. Follow-up to PSUR/PSUSA procedures

6.4.1. Dolutegravir - TIVICAY (CAP) - EMEA/H/C/002753/LEG 015.2

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Martin Huber

Scope: MAH's response to LEG 0015.1 [Submission of all available data/results for study RESPOND (International Cohort Consortium of Infectious Disease): a prospective, multi-cohort collaboration study of people living with human immunodeficiency virus (HIV) across Europe and Australia as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00010075/202101) adopted in September 2021] as per the request for supplementary information (RSI) adopted in September 2022

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 to submit all available data/results from the RESPOND study. The responses were assessed by the Rapporteur for further PRAC advice. For further background, see PRAC minutes September 2021[26], PRAC minutes February 2022 and PRAC minutes September 2022[27].

Summary of advice/conclusion(s)

- Based on the available data and the Rapporteur's assessment, PRAC agreed that the data from the RESPOND study may show a trend towards a higher risk for hypertension in patients treated with integrase strand transfer inhibitors (INSTIs). However, considering the study limitations, PRAC concluded that there is insufficient evidence, at present, to establish a causal relationship between dolutegravir and the risk of hypertension and agreed that no further regulatory action is deemed necessary.

6.4.2. Dolutegravir, abacavir, lamivudine - TRIUMEQ (CAP) - EMEA/H/C/002754/LEG 010.2

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Martin Huber

Scope: MAH's response to LEG 010.1 [Submission of all available data/results for study RESPOND (International Cohort Consortium of Infectious Disease): a prospective, multi-cohort collaboration study of people living with human immunodeficiency virus (HIV) across Europe and Australia as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00010075/202101) adopted in September 2021] as per as per the request for supplementary information (RSI) adopted in September 2022

Background

[26] Held on 30 August – 02 September 2021
[27] Held on 29 August – 01 September 2022

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 to submit all available data/results from the RESPOND study. The responses were assessed by the Rapporteur for further PRAC advice. For further background, see PRAC minutes September 2021[28], PRAC minutes February 2022 and PRAC minutes September 2022[29].

Summary of advice/conclusion(s)

- Based on the available data and the Rapporteur's assessment, PRAC agreed that the data from the RESPOND study may show a trend towards a higher risk for hypertension in patients treated with integrase strand transfer inhibitors (INSTIs). However, considering the study limitations, PRAC concluded that there is insufficient evidence, at present, to establish a causal relationship between dolutegravir and the risk of hypertension and agreed that no further regulatory action is deemed necessary.

6.4.3. Dolutegravir, lamivudine - DOVATO (CAP) - EMEA/H/C/004909/LEG 005.2

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: David Olsen

Scope: MAH's response to LEG 005.1 [Submission of all available data/results for study RESPOND (International Cohort Consortium of Infectious Disease): a prospective, multi-cohort collaboration study of people living with human immunodeficiency virus (HIV) across Europe and Australia as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00010075/202101) adopted in September 2021] as per the request for supplementary information (RSI) adopted in September 2022

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 to submit all available data/results from the RESPOND study. The responses were assessed by the Rapporteur for further PRAC advice. For further background, see PRAC minutes September 2021, PRAC minutes February 2022 and PRAC minutes September 2022.

Summary of advice/conclusion(s)

- Based on the available data and the Rapporteur's assessment, PRAC agreed that the data from the RESPOND study may show a trend towards a higher risk for hypertension in patients treated with integrase strand transfer inhibitors (INSTIs). However, considering the study limitations, PRAC concluded that there is insufficient evidence, at present, to establish a causal relationship between dolutegravir and the risk of hypertension and agreed that no further regulatory action is deemed necessary.

[28] Held on 30 August – 02 September 2021
[29] Held on 29 August – 01 September 2022

6.4.4. Nirmatrelvir, ritonavir - PAXLOVID (CAP) - EMEA/H/C/005973/REC 017.1

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Martin Huber

Scope: MAH's response to REC 017 [A safety review for myalgia covering safety data from ongoing early access worldwide and notably from US (Emergency Use Authorisation) and literature data with cut-off date 31st March should be provided by April 2022, awaiting for a global safety review planned to be submitted covering the 3 applicant's sponsored clinical studies (EPIC-HR, EPIC-SR and study in PEP) in June 2022 (requested by CHMP and assessed by PRAC)] as per the request for supplementary information (RSI) adopted in October 2022[30]

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 to submit further data on myalgia and hypertension cases. The responses were assessed by the Rapporteur for further PRAC advice. For further background, see PRAC minutes June 2022 and PRAC minutes October 2022[31].

Summary of advice/conclusion(s)

- Based on the available data and the Rapporteur's assessment, PRAC agreed that the MAH should submit a variation, within 60 days, to update the product information to include myalgia as an undesirable effect and propose a frequency accordingly.

6.5. Variation procedure(s) resulting from PSUSA evaluation

See also 16.5.

6.5.1. Daratumumab - DARZALEX (CAP) - EMEA/H/C/004077/II/0063, Orphan

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Inês Ribeiro-Vaz

Scope: Update of section 4.4 of the SmPC in order to update the warnings and precautions for myocardial infarction and ocular events following PSUR single assessment (PSUSA) procedure (PSUSA/00010498/202111) concluded in June 2022, based on the cumulative review of the relevant cases retrieved from the MAH's global safety database, clinical database, epidemiological evaluation and literature review. The package leaflet 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.

[30] Held on 26 - 29 September 2022
[31] Held on 26 - 29 September 2022

Following the evaluation of the most recently submitted PSUR(s) for the above-mentioned medicine(s), PRAC requested the MAH to submit a variation to update the product information on the warnings and precautions for myocardial infarction and ocular events. PRAC is responsible for adopting an outcome based on the assessment report from the PRAC Rapporteur, to be further considered at the level of CHMP, responsible for adopting an opinion on this variation. For further background, see PRAC minutes June 2022.

Summary of recommendation(s)

- Based on the available data and the Rapporteur's assessment, PRAC agreed to amend the product information[32] to add ocular events as a warning. Regarding the myocardial infarction in the context of infusion-related reactions, PRAC concluded that there is insufficient evidence at this stage to warrant an update of the product information.
- In the next PSUR, the MAH should closely monitor cases of myocardial infarction.

6.6. Expedited summary safety reviews[33]

6.6.1. Coronavirus (COVID-19) vaccine (inactivated, adjuvanted, adsorbed) - COVID-19 VACCINE (INACTIVATED, ADJUVANTED) VALNEVA (CAP) - EMEA/H/C/006019/MEA 009.5

Applicant: Valneva Austria GmbH

PRAC Rapporteur: Gabriele Maurer

Scope: Sixth expedited summary safety report (SSR) for covid-19 vaccine (inactivated, adjuvanted) Valneva during the coronavirus disease (COVID-19) pandemic

Background

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

PRAC assessed the sixth summary safety review (SSR) for the safety monitoring of COVID-19 vaccine (inactivated, adjuvanted) Valneva (COVID-19 vaccine (inactivated, adjuvanted, adsorbed)). PRAC is responsible for adopting the conclusions of its assessment of the SSR.

Summary of advice/conclusion(s)

- PRAC agreed that no further SSRs are required, in view of the low-exposure and since no new safety-related topics that would require prompt review have been identified in the current SSR. The safety profile of COVID-19 vaccine (inactivated, adjuvanted) Valneva will continue to be monitored via routine pharmacovigilance activities.

[32] Update of sections 4.4 and 4.8 of the SmPC. The package is updated accordingly.
[33] 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

7. Post-authorisation safety studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)[34]

See Annex I 17.1.

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

See also Annex I 17.2.

7.2.1. Valoctocogene roxaparvovec - ROCTAVIAN (CAP) - EMEA/H/C/005830/MEA 003

Applicant: BioMarin International Limited, ATMP[36]

PRAC Rapporteur: Menno van der Elst

Scope: To inform the impact of BMN 270 on fertility, general toxicity, teratology, and germline transmission in females of childbearing potential and establish an adequate waiting period after BMN 270 infusion following which female patients can become pregnant

Background

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

As part of the RMP for Roctavian (valoctocogene roxaparvovec), the MAH was required to conduct a category 3 PASS in order to address the risk of embryo-foetal developmental toxicity. The MAH submitted a draft protocol for PRAC to assess first whether the proposed study is appropriate to address the post-authorisation commitment. PRAC was requested to provide advice to CHMP on the draft protocol submitted by the MAH.

Summary of advice

- PRAC was of the view that the proposed study to investigate the embryo-foetal developmental toxicity is not considered appropriate to conclude on the possibility of vertical transmission of the AAV5 via the mother. PRAC also considered, that, in order to investigate the vertical transmission of the AAV5 vector, the MAH should follow a step wise approach, by performing a thorough literature review and provide a discussion on the biodistribution of AAVs and vertical transmission of AAVs, followed by a discussion on the need for a biodistribution study in female animals, with a justification for the species used, investigating the biodistribution of the product valoctocogene roxaparvovec into the ovary.

[34] In accordance with Article 107n of Directive 2001/83/EC
[35] 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
[36] Advanced Therapy Medicinal Product

7.3. Results of PASS imposed in the marketing authorisation(s)[37]

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

Applicant: Nordic Group BV

PRAC Rapporteur: Jean-Michel Dogné

Scope: Nordic Aprotinin Patient Registry to record utilisation information on patients at cardiac surgery centers

Background

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

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

The MAH for Trasylol (aprotinin) submitted to EMA the final results of the study entitled: 'Nordic Aprotinin Patient Registry (NAPaR): a multicentre, non-interventional PASS with active surveillance via patient exposure registry' enrolling patients undergoing cardiac surgery on cardiopulmonary bypass and exposed to aprotinin at all centres in EU. PRAC is responsible for issuing a recommendation on the final study results including the assessment of the MAH's responses to requests for supplementary information (RSI). For further background, see PRAC minutes April 2021 and PRAC minutes September 2021[38], PRAC minutes February 2022 and PRAC minutes October 2022[39].

Summary of recommendation(s) and conclusions

- Based on the review of the final report of the registry study, the MAH's responses to the RSI and the Rapporteur's assessment, PRAC considered that a further RSI is necessary before a final recommendation can be issued.
- Regarding the risk minimisation measures (RMMs), PRAC considered that the educational material for healthcare professionals (HCPs) should be updated to include information about the uncertainty on the role of aprotinin in risks of mortality and severe haemorrhage in off-label use. In addition, PRAC was of the view that, taking into account the key messages intended to be communicated to healthcare professionals (HCPs), the letter proposed by the MAH should be rather considered as a 'cover letter' accompanying the educational material instead of a direct healthcare professional communication (DHPC). The MAH should also submit a proposal on the methods used to measure the effectiveness of the RMMs at national level.
- The MAH should submit responses to the request for supplementary information within 30 days to EMA. A 30 days-assessment timetable will be followed.

[37] In accordance with Article 107p-q of Directive 2001/83/EC
[38] Held on 30 August – 02 September 2021
[39] Held on 26 – 29 September 2022

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

Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Rhea Fitzgerald

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

Background

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

As a condition to the marketing authorisation(s) (Annex II-D), the MAH was required to conduct a PASS to evaluate the long-term effects of lumacaftor and ivacaftor combination therapy in patients with cystic fibrosis.

The final study report was submitted to EMA by the MAH Vertex Pharmaceuticals (Ireland) Limited. PRAC discussed the final study results in addition to the MAH's responses to two requests for supplementary information (RSI). PRAC is responsible for evaluating the PASS final results. For further background, see PRAC minutes May 2022 and PRAC minutes October 2022[40].

Summary of recommendation(s) and conclusions

- Based on the review of the final report of the non-interventional PASS entitled 'an observational study to evaluate the utilisation patterns and long-term effects of lumacaftor and ivacaftor combination therapy in patients with cystic fibrosis, PRAC considered that the benefit-risk balance of Orkambi (lumacaftor/ivacaftor) remains unchanged. As a consequence, PRAC recommended that the terms of the marketing authorisation(s) for Orkambi (lumacaftor/ivacaftor) should be varied to remove the PASS as an obligation from Annex II-D on 'Conditions or restrictions with regard to the safe and effective use of the medicinal product', as well as to remove Orkambi (lumacaftor/ivacaftor) from the list of products under additional monitoring.

7.4. Results of PASS non-imposed in the marketing authorisation(s)[41]

See also Annex 17.4.

7.4.1. Human papillomavirus 9-valent vaccine (recombinant, adsorbed) - GARDASIL 9 (CAP) - EMEA/H/C/003852/II/0063

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Jean-Michel Dogné

Scope: Update of section 4.6 of the SmPC in order to include additional information on exposure during pregnancy, based on the final report of the US Pregnancy Registry, listed as a category 3 study in the RMP; the package leaflet is updated accordingly. The RMP

[40] Held on 26 – 29 September 2022
[41] 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

version 5.1 has also been submitted

Background

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

As stated in the RMP of Gardasil 9 (human papillomavirus 9-valent vaccine (recombinant, adsorbed)), the MAH conducted a category 3 study entitled: 'Pregnancy Registry for Gardasil 9 (Human Papillomavirus 9-Valent Vaccine, Recombinant)' to acquire and analyse information on exposures and pregnancy outcomes to better describe the safety profile of pregnancy exposures to Human Papillomavirus 9-Valent Vaccine, Recombinant (9vHPV) vaccine. The Rapporteur assessed the MAH's final study report.

Summary of advice

- Based on the available data and the Rapporteur's review, PRAC considered that the ongoing variation assessing the final study report could be considered acceptable provided that the MAH submits satisfactory responses to a request for supplementary information (RSI).
- PRAC considered that an update of the product information to include the results of the pregnancy registry is warranted. In addition, PRAC agreed that the pregnancy registry can be discontinued and that the MAH should remove 'exposure during pregnancy' as missing information from the list of safety concerns in the RMP. Also, PRAC agreed to remove 'long-term effectiveness and immunogenicity' as missing information from the list of safety concerns, considering this topic is related to efficacy and not to the safety profile, and to update the pharmacovigilance plan accordingly.

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

See also 17.5.

7.5.1. Teriflunomide - AUBAGIO (CAP) - EMEA/H/C/002514/MEA 005.6

Applicant: Sanofi Winthrop Industrie

PRAC Rapporteur: Martin Huber

Scope: MAH's response to MEA 005.5 [1) eighth annual progress report for pregnancy registry OBS13499 (US/CA): teriflunomide pregnancy outcome exposure registry: a 'teratology information specialists (OTIS)' autoimmune diseases in pregnancy project, 2) fifth annual progress report for OBS12751 (international): an international pregnancy exposure registry of women with multiple sclerosis (MS) exposed to Aubagio (teriflunomide)] as per request for supplementary information (RSI) adopted in October 2022

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.

The MAH had committed to perform two pregnancy registry studies (OBS13499 and OBS12751) (listed as category 3 studies in the RMP) to monitor reports of use and/or adverse events in pregnancy, and pregnancy outcomes to better assess and characterise teratogenicity. The interim results of these studies were assessed by the Rapporteur for PRAC review.

Summary of advice

- PRAC agreed with the MAH's proposal to replace both existing pregnancy registries (OBS12751 and OBS13499) with an 'enhanced' pharmacovigilance measure to better evaluate the impact of teriflunomide exposure during pregnancy on pregnancy and infant outcomes, in view of the very low recruitment rates of both studies. Additionally, PRAC considered that the healthcare professionals (HCPs) guide should be amended to include information on reminding/requesting to report pregnancy cases and that no call for reporting of pregnancy cases should be included in the patient card.

7.6. Others

See Annex I 17.6.

7.7. New Scientific Advice

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

7.8. Ongoing Scientific Advice

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

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

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

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

8.1. Annual reassessments of the marketing authorisation

See Annex I 18.1.

8.2. Conditional renewals of the marketing authorisation

See Annex I 18.2.

8.3. Renewals of the marketing authorisation

See Annex I 18.3.

9. Product related pharmacovigilance inspections

9.1. List of planned pharmacovigilance inspections

None

9.2. Ongoing or concluded pharmacovigilance inspections

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

9.3. Others

None

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

10.1. Safety related variations of the marketing authorisation

None

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

None

10.3. Other requests

None

10.4. Scientific Advice

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

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

11.1. Safety related variations of the marketing authorisation

11.1.1. Hydroxychloroquine (NAP) - DK/H/PSUFU/00001693/202104

Applicant(s): various

PRAC Lead: Marie Louise Schougaard Christiansen

Scope: PRAC consultation on the need for further evaluation of the risk of hepatotoxicity and teratogenicity, and/or any labelling updates for hydroxychloroquine, as per the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00001693/202104)

concluded in December 2021, on request of Denmark

Background

Hydroxychloroquine is an aminoquinoline indicated for the treatment of lupus erythematosus, systemic lupus erythematosus (SLE), cutaneous lupus erythematosus (CLE), discoid lupus erythematosus (DLE) and lupus erythematosus disseminated. It is also indicated for the treatment of rheumatoid arthritis (RA), juvenile chronic polyarthritis, systemic juvenile chronic arthritis and juvenile arthritis. In addition, it is indicated for the suppressive treatment and treatment of acute attacks of malaria due to Plasmodium vivax, Plasmodium malariae, Plasmodium ovale and susceptible strains of Plasmodium falciparum. Finally, it is indicated for the treatment of polymorphic light eruption (PLE), scleroderma and photosensitive dermatitis.

Based on the assessment of the recent PSUSA procedure for hydroxychloroquine (PSUSA/00001693/202104) concluded in December 2021, PRAC considered that reviews of available evidence in relation to risks of hepatotoxicity and congenital malformations should be further assessed. For further background, see PRAC minutes December 2021[42]. On request of CMDh, MAHs for nationally approved hydroxychloroquine-containing product(s) (Sanofi, Alfasigma S.p.A. and Zentiva) submitted the requested safety reviews for evaluation within a periodic safety update follow-up (PSU FU) procedure. In the context of the ongoing evaluation of the PSU FU procedure (DK/H/PSUFU/00001693/202104), Denmark, as lead Member State (LMS), requested PRAC advice on its assessment.

Summary of advice

- Based on the review of the available information and evidence, PRAC supported the Lead Member State (LMS) assessment that the product information should be updated to add drug-induced liver injury (DILI) including hepatocellular injury, cholestatic liver injury, acute hepatitis, mixed hepatocellular/cholestatic liver injury as a warning and as an undesirable effect with a frequency 'not known'. In addition, PRAC considered that the product information should be updated to add warnings on hepatitis B reactivation and on the risk of congenital malformations. Regarding hepatitis C reactivation, PRAC considered that further assessment is needed and advised the LMS that the MAH(s) for nationally approved hydroxychloroquine-containing product(s) (Sanofi, Alfasigma S.p.A. and Zentiva) should present, in the next PSUR a cumulative review of the potential risk of herpes zoster reactivation, tuberculosis reactivation and hepatitis C reactivation in relation to hydroxychloroquine exposure, including a thorough review and discussion of a plausible immunosuppressive mechanism of action.

11.1.2. Lisdexamfetamine (NAP) - SE/H/1839/01-06/II/40; SE/H/1825/0103/II/29

Applicant(s): Shire Pharmaceuticals Ireland Limited

PRAC Lead: Ulla Wandel Liminga

Scope: PRAC consultation on type II variations evaluating the risk of intestinal ischaemia, increased bleeding tendency and vasoconstriction/vasospasm as per conclusions of the PSUSA procedure (PSUSA/00010289/202202) concluded in October 2022, on request of Sweden

[42] Held on 28 November – 01 December 2022

Background

Lisdexamfetamine dimesylate is a therapeutically inactive amphetamine prodrug indicated for the treatment of attention-deficit/hyperactivity disorder (ADHD) in adult patients.

In the context of the evaluation of a type II variation procedure on assessing the risk of intestinal ischaemia, increased bleeding tendency and vasoconstriction/vasospasm as per conclusions of the PSUSA procedure (PSUSA/00010289/202202) concluded in October 2022[43], Sweden requested PRAC advice on its assessment.

Summary of advice

- Based on the review of the available information and evidence, PRAC supported the Lead Member State (LMS) assessment that the product information should be updated to add epistaxis as an undesirable effect with a frequency 'uncommon'. PRAC also supported the LMS proposal not to update the product information with respect to vasoconstriction/vasospasm, or regarding terms of increased tendency to bleed in general. Regarding intestinal ischaemia, PRAC concluded that at present there is insufficient evidence to warrant an update of the product information. PRAC also agreed to update the package leaflet in order to add vomiting as an overdose symptom.

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 Gabriele Maurer, replacing Brigitte Keller-Stanislawski, as the new alternate for Germany.

12.1.2. PRAC working group - Best practice guide on using PRAC plenary time efficiently and effectively – update on the implementation of quantitative goals – Q4 2022

In line with the adopted PRAC best practice guidance (BPG) on Committee efficiency (see PRAC minutes May 2016 and PRAC minutes June 2018) and the adopted implementation plan for the BPG including goals to measure compliance with the recommendations (see PRAC minutes June 2016 and PRAC minutes June 2018), the EMA secretariat updated PRAC at the organisational, regulatory and methodological matters (ORGAM) meeting on 23 February 2023, on the quantitative measures collected for Q4 2022 of PRAC meetings. For previous update, see PRAC minutes November 2022[44].

12.1.3. Vote by proxy

None

[43] Held on 26-29 September 2022
[44] Held on 24-27 October 2022

12.2. Coordination with EMA Scientific Committees or CMDh-v

None

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

12.3.1. Oncology European Specialised Expert Community (ESEC) - update and request for nominations

The EMA Secretariat presented to PRAC the mandate, the objectives and the rules of procedures of the Oncology ESEC, as well as its membership composition. PRAC members were invited to nominate experts to be part of the group by sending their nominations in writing.

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 the ongoing clinical trials to evaluate the safety and efficacy of medicines in development as potential treatments for COVID-19, as well as study results on effectiveness of COVID-19 mRNA vaccines' (booster dose and adapted mRNA bivalent vaccines) against the new Omicron subvariants. The EMA Secretariat also provided to PRAC an update on the Ebola Sudan outbreak and the candidate vaccines to be included in the upcoming clinical trials.

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. PRAC workload statistics – Q4 2022

At the organisational, regulatory and methodological matters (ORGAM) meeting on 23 February 2023, the EMA secretariat presented to PRAC the quarterly and cumulative figures to estimate the evolution of the PRAC workload for Q4 2022, by reflecting on the number of procedures and agenda items covered at each PRAC plenary meeting. For previous update, see PRAC minutes November 2022[45].

[45] Held on 24-27 October 2022

12.8.2. EU Pharmacovigilance system - quarterly workload measures and performance indicators – Q4 2022 and predictions

At the organisational, regulatory and methodological matters (ORGAM) meeting on 23 February 2023, the EMA Secretariat presented to PRAC an overview of the quarterly figures on the EMA pharmacovigilance system-related workload and performance indicators. For previous update, see PRAC minutes November 2022[46].

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

In line with the criteria for plenary presentation of updates to the EURD List adopted by PRAC in December 2021, PRAC endorsed the draft revised EURD list, version November 2022, reflecting the PRAC's comments impacting on the data lock point (DLP) and PSUR submission frequencies of the substances/combinations PRAC endorsed the newly allocated Rapporteurs for upcoming PSUSAs in accordance with the principles previously endorsed by PRAC (see PRAC minutes April 2013).

Post-meeting note: following the PRAC meeting of February 2023, the updated EURD list was adopted by the CHMP and CMDh and published on the EMA website, see: Home> Human Regulatory>Pharmacovigilance>Periodic safety update reports>EURD list> List of

[46] Held on 24-27 October 2022

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

None

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

12.13.2. EudraVigilance Expert Working Group (EV-EWG) - work programme 2023-2024

At the organisational, regulatory and methodological matters (ORGAM) meeting on 23 February 2023, the EMA Secretariat presented to PRAC the composition of the EudraVigilance Expert Working Group (EV-EWG) as well as the draft work programme reflecting the key activities to be performed for 2023-2024. PRAC agreed with the EV-EWG work programme for 2023-2024.

12.14. Risk management plans and effectiveness of risk minimisations

12.14.1. Risk management systems

None

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

None

12.15. Post-authorisation safety studies (PASS)

12.15.1. Post-authorisation Safety Studies – imposed PASS

None

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

None

12.16. Community procedures

12.16.1. Referral procedures for safety reasons

None

12.17. Renewals, conditional renewals, annual reassessments

None

12.18. Risk communication and transparency

12.18.1. Public participation in pharmacovigilance

None

12.18.2. Safety communication

None

12.19. Continuous pharmacovigilance

12.19.1. Incident management

None

12.20. Impact of pharmacovigilance activities

12.20.1. Study report on the impact of EU label changes for fluoroquinolone-containing medicinal products for systemic and inhalation use: post-referral prescribing trends – follow up

PRAC lead: Martin Huber, Eva Jirsová

PRAC continued the discussion of the study "Impact of European Union Label Changes for Fluoroquinolone Containing Medicinal Products for Systemic and Inhalation Use" (EUPAS37856). The findings of the study indicated that fluoroquinolone prescribing within

the primary care setting decreased over time in the six countries included in the study. Overall, the extent of the decrease observed in these six countries was limited, indicating that risk minimisation measures for fluoroquinolones had a modest impact in terms of reducing fluoroquinolone prescribing in the primary care setting. PRAC carefully reflected on the information submitted and concerns raised by patient representatives regarding a potential lack of adherence to risk minimisation measures implemented following the 2018 referral procedure for fluoroquinolones, and testimonies from patients who experienced disabling, long-lasting and potentially irreversible adverse events following use of fluoroquinolones. PRAC agreed to proceed with a further review of the study results which will take into account other relevant data. PRAC noted the challenges associated with the implementation of risk minimisation measures, particularly with regards to changes in prescribing behaviour and discussed how to further develop a communication and engagement strategy, targeting a broad range of stakeholders at both national and EU level, in order to further enhance implementation and adherence to risk minimisation measures for fluoroquinolones. This strategy will be developed in collaboration with EMA and adopted by PRAC following the conclusion of the review.

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

As a follow-up to the discussion held at the January 2023 PRAC meeting, and after taking into account the comments received, PRAC adopted the revised process for prioritisation and regulatory follow-up of impact research commissioned under the remit of PRAC Strategy on measuring the impact of pharmacovigilance activities with further clarification on the roles and responsibilities of PRAC (Co-)Rapporteurs and PRAC Sponsors of impact research and focus on regulatory oversight and follow-up on impact study results. For background, see PRAC minutes January 2023.

12.21. Others

12.21.1. Data analysis and real world interrogation network (DARWIN EU) – update

At the organisational, regulatory and methodological matters (ORGAM) meeting on 23 February 2023, the EMA Secretariat presented to PRAC the regular progress update on the establishment of the DARWIN EU® Coordination Centre, including the status of the initiated studies, information about the data partners, as well as a list of studies that were performed in the first year of establishment and the ones planned for the second year. The EMA Secretariat also provided the timelines for the preparation of the real-world evidence (RWE) experience report.

12.21.2. DARWIN EU – Drug utilisation study of antibiotics in the 'Watch' category of the WHO AwaRe classification of antibiotics for evaluation and monitoring of use

At the organisational, regulatory and methodological matters (ORGAM) meeting on 23 February 2023, the EMA Secretariat presented to PRAC the summary of the findings of the "DARWIN EU® - Drug Utilisation Study of Antibiotics in the 'Watch' category of the WHO AWaRe classification of antibiotics for evaluation and monitoring of use" study (EUPAS103381). This drug utilisation study using data from databases from 5 European countries including The Netherlands, United Kingdom, Spain, Germany and France aims to

characterise the incidence of prescription of 141 antibiotics, including their indication and treatment duration, for the period 2012-2021, stratified by year and country. PRAC acknowledged the utility of the results of the study as additional data from European countries in the monitoring of antibiotics use as part of the work on antimicrobial resistance. PRAC also noted that the study findings, which included data showing the use of fluoroquinolones declining or remaining stable over time, are complementary to the assessment of the impact study results for fluoroquinolones (see 12.20.1). PRAC concurred with the PRAC sponsors' recommendation that no immediate regulatory action was warranted as a result of this study. The report will be published in the EU PAS Register (EUPAS103381). The MAHs of medicinal products containing antibiotics should continue to review all emerging evidence on antibiotics use as part of their safety monitoring, including results from this study, in upcoming PSURs.

12.21.3. DARWIN EU - Study on drug utilisation of valproate-containing medicinal products in women of childbearing potential (EUPAS50789)

The EMA Secretariat presented the summary of the findings of the 'DARWIN EU® - Drug utilisation of valproate-containing medicinal products in women of childbearing potential' study (EUPAS50789). The study's objectives were to (1) characterise the prevalence and incidence of use of valproate-containing medicines, and alternative therapies among women aged 12 to 55 years of age, stratified by calendar year and age, and to (2) characterise the use of valproate-containing medicines among women aged 12 to 55 years of age, stratified by indication, calendar year and age, in six European databases from Belgium, Finland, Germany, The Netherlands, Spain and United Kingdom. PRAC noted that the prevalence of use of valproate in women aged 12-55 decreased between 2010 and 2021 for most analysed datasets. Younger age groups (<45) had a lower prevalence compared to ≥45, and which decreased over time, halving the initial prevalence at the end of the study for most databases. Incidence of use of valproate showed a decreasing pattern for all age groups in all databases. PRAC acknowledged the results of the study as additional data from several European countries in the monitoring of valproate use and noted that the findings are in line with the results of a previously commissioned drug utilisation study investigating the impact of EU label changes and revised pregnancy prevention programme (PPP) for medicinal products containing valproate (EUPAS31001). PRAC concurred with the Rapporteur's recommendation that no immediate regulatory action was warranted as a result of this study. The report will be published in the EUPAS® Register (EUPAS50789). The MAHs of valproate-containing medicinal products should continue to review all evidence as part of their safety monitoring of this topic.

12.21.4. EMA-funded study on spinal muscular atrophy disease (SMA)

At the organisational, regulatory and methodological matters (ORGAM) meeting on 23 February 2023, the EMA Secretariat presented to PRAC the status and the timelines for the study based on data from TREAT-NMD registry to assess the progression of spinal muscular atrophy (SMA) in view of available treatment and which was contracted by EMA at the request of the Committee for Advanced Therapies (CAT).

13. Any other business

None

14. Annex I – Signals assessment and prioritisation[47]

As per the agreed criteria for new signal(s), PRAC adopted without further plenary discussion the recommendation of the Rapporteur to request MAH(s) to submit a cumulative review following standard timetables[48].

14.1. New signals detected from EU spontaneous reporting systems

None

14.2. New signals detected from other sources

None

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 medicine(s) mentioned below under evaluation for initial marketing authorisation application. Information on the medicines containing the active substance(s) listed below will be made available following the CHMP opinion on their marketing authorisation(s).

15.1.1. Dabigatran etexilate - EMEA/H/C/005922

Scope: Prevention of venous thromboembolic events

15.1.2. Eculizumab - SB12 (CAP MAA) - EMEA/H/C/006036

Scope: Treatment of paroxysmal nocturnal haemoglobinuria

15.1.3. Lacosamide - LACOSAMIDE ADROIQ (CAP MAA) - EMEA/H/C/006047

Scope: Treatment of epilepsy

15.1.4. Sugammadex - SUGAMMADEX ADROIQ (CAP MAA) - EMEA/H/C/006046

Scope: Reversal of neuromuscular blockade induced by rocuronium or vecuronium

[47] 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

[48] 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

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 medicine(s) mentioned below.

15.2.1. Velaglucerase alfa - VPRIV (CAP) - EMEA/H/C/001249/II/0061

Applicant: Takeda Pharmaceuticals International AG Ireland Branch

PRAC Rapporteur: Martin Huber

Scope: Submission of an updated RMP version 12 in order to remove certain risks from the list of safety concerns

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 medicine(s) mentioned below.

15.3.1. Atezolizumab - TECENTRIQ (CAP) - EMEA/H/C/004143/II/0074

Applicant: Roche Registration GmbH

PRAC Rapporteur: Inês Ribeiro-Vaz

Scope: Submission of the final report from study MO39171 listed as a category 3 study in the RMP in order to fulfil MEA/008. This is a Phase III/IV, Single Arm, multicentre, interventional study of Atezolizumab to Investigate Long-term Safety and Efficacy in previously treated Patients with Locally Advanced or Metastatic Non-small Cell Lung Cancer (NSCLC). The RMP version 23 has also been submitted

15.3.2. Atidarsagene autotemcel - LIBMELDY (CAP) - EMEA/H/C/005321/II/0011/G, Orphan

Applicant: Orchard Therapeutics (Netherlands) B.V., ATMP[49]

PRAC Rapporteur: Gabriele Maurer

Scope: Grouped variations consisting of: 1) update of sections 4.2, 4.4, 4.5, 4.8, and 5.1 of the SmPC in order to remove the option of using bone marrow (BM) as a cellular source for the manufacture of Libmeldy, as a result of an evolution of clinical practices and also to rationalise the manufacture of this highly complex medicinal product; the package leaflet and labelling are updated accordingly. In addition, the MAH took the opportunity to remove ANX/002 from the Annex II and to introduce minor editorial changes to the product information. The RMP version 1.3 has also been submitted; 2) other quality related variations

15.3.3. Avapritinib - AYVAKYT (CAP) - EMEA/H/C/005208/II/0022, Orphan

Applicant: Blueprint Medicines (Netherlands) B.V.

[49] Advanced therapy medicinal product

PRAC Rapporteur: Menno van der Elst

Scope: Update of sections 4.2 and 5.2 of the SmPC in order to change posology recommendations and to update pharmacokinetic information for use in patients with severe hepatic impairment based on the final results from study BLU-285-0107 listed as a category 3 study in the RMP; this is a phase 1, open-label, single-dose study to investigate the influence of severe hepatic impairment on the pharmacokinetics of avapritinib. The package leaflet is updated accordingly. The RMP version 3.0 has also been submitted. In addition, the MAH took the opportunity to bring the product information in line with the latest QRD template version 10.3

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

Applicant: Roche Registration GmbH

PRAC Rapporteur: Ulla Wändel Liminga

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

15.3.5. Concentrate of proteolytic enzymes enriched in bromelain - NEXOBRID (CAP) - EMEA/H/C/002246/II/0057, Orphan

Applicant: MediWound Germany GmbH

PRAC Rapporteur: Martin Huber

Scope: Submission of the 24-months' CSR addendum of the MW2010-03-02 (DETECT) category 1 study; a multicentre, multinational, randomised, controlled, assessor blinded study, performed in subjects with thermal burns, to evaluate the efficacy and safety of NexoBrid compared to gel vehicle and compared to standard of care. The provision of the CSR addresses the post-authorisation measure ANX 001.7. An updated RMP version 8.0 was provided as part of the application

15.3.6. Eculizumab - SOLIRIS (CAP) - EMEA/H/C/000791/II/0126, Orphan

Applicant: Alexion Europe SAS

PRAC Rapporteur: Monica Martinez Redondo

Scope: Extension of indication to include treatment of paediatric patients with refractory generalised myasthenia gravis (gMG) for Soliris, based on interim results from study ECU-MG-303; this is an open-label, multicentre, phase 3 study to evaluate the efficacy, safety, pharmacokinetics and pharmacodynamics of intravenous (IV) eculizumab in paediatric patients aged 6 to less than 18 years with acetylcholine receptor-antibody (AChR-Ab) positive (+) refractory gMG. 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. Version 20.0 of the RMP has also been submitted. In addition, the MAH took the opportunity to update section 4.8 of the SmPC in order to update the frequency of the list of adverse drug reactions (ADRs) based on cumulative safety data and to introduce minor editorial changes to the product information

15.3.7. Faricimab - VABYSMO (CAP) - EMEA/H/C/005642/II/0002

Applicant: Roche Registration GmbH

PRAC Rapporteur: Inês Ribeiro-Vaz

Scope: Update of sections 4.2, 4.4, 4.8 and 5.1 of the SmPC in order to update efficacy and safety information and to update the warnings and the list of adverse drug reactions (ADRs), based on longer-term results from studies GR40306 (TENAYA) and GR40844 (LUCERNE); these are phase 3, multicentre, randomised, double-masked, active comparator-controlled, 112-week studies to evaluate the efficacy and safety of faricimab in patients with neovascular age-related macular degeneration (nAMD); the package leaflet is updated accordingly. The RMP version 2.0 has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the product information

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

Applicant: Alnylam Netherlands B.V.

PRAC Rapporteur: Martin Huber

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

15.3.9. Granisetron - SANCUSO (CAP) - EMEA/H/C/002296/II/0061

Applicant: Kyowa Kirin Holdings B.V.

PRAC Rapporteur: Rugile Pilviniene

Scope: Update of sections 4.4, 4.6, 4.7, 4.8, 4.10 and 5.3 of the SmPC in order to add 'Serotonin syndrome' and 'Application site Reactions' to the list of adverse drug reactions (ADRs) with frequency 'unknown'; as well as 'Application site Irritation' with frequency 'uncommon' based on post-marketing data and literature. The MAH also proposes to update sections 4.4 and 4.5 of the SmPC to add drug-drug interaction information with buprenorphine/opioids and serotonergic medicinal products based on post-marketing data and literature. The package leaflet has been updated accordingly. The RMP version 5 has also been submitted. In addition, the MAH took the opportunity to introduce editorial changes in the SmPC.

15.3.10. Lenalidomide - REVLIMID (CAP) - EMEA/H/C/000717/II/0123

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Tiphaine Vaillant

Scope: Update of section 4.4 of the SmPC, Annex IID and Article 127a and the tools/documents included in the Educational Healthcare Professional Kit, in order to

harmonise the terminology utilised in the RMP and product information documents relating to the safety concern of teratogenicity and its risk minimisation measure of the Pregnancy Prevention Plan (PPP) across the 3 immunomodulatory imide drugs (IMiDs). These proposed changes will only have a limited impact on the National Competent Authority (NCA)-approved content/text of the educational materials, and the key messages to the HCP and patients. Furthermore, the regulatory obligations regarding the PPP will not be impacted. The MAH is also taking the opportunity to update the RMP with PASS Protocol milestones. The updated RMP version 38 was provided

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

Applicant: Eisai GmbH

PRAC Rapporteur: David Olsen

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

15.3.12. Lisocabtagene maraleucel - BREYANZI (CAP) - EMEA/H/C/004731/II/0005

Applicant: Bristol-Myers Squibb Pharma EEIG, ATMP[50]

PRAC Rapporteur: Gabriele Maurer

Scope: Extension of indication to include treatment of adult patients with Second-line (2L) Transplant Intended (TI) Large B-Cell Lymphoma (LBCL) for BREYANZI, based on interim analyses from pivotal study JCAR017-BCM-003: a global randomised multicentre phase III trial to compare the efficacy and safety of JCAR017 to standard of care in adult subjects with high-risk, transplant-eligible relapsed or refractory aggressive B-cell Non-Hodgkin Lymphomas (TRANSFORM). As a consequence, sections 4.1, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet is updated in accordance. Version 2.0 of the RMP has also been submitted

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

Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Rhea Fitzgerald

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

[50] Advanced therapy medicinal product

RMP has also been submitted

15.3.14. Methotrexate - NORDIMET (CAP) - EMEA/H/C/003983/II/0027

Applicant: Nordic Group B.V.

PRAC Rapporteur: Martin Huber

Scope: Extension of indication to include treatment of moderate to severe recalcitrant disabling psoriasis for Nordimet, based on literature. As a consequence, sections 4.1 and 4.2 of the SmPC are updated. The package leaflet is updated in accordance. The RMP (version 6.0) of the RMP has also been submitted

15.3.15. Oritavancin - TENKASI (CAP) - EMEA/H/C/003785/X/0036

Applicant: Menarini International Operations Luxembourg S.A.

PRAC Rapporteur: Adam Przybylkowski

Scope: Extension application to add a new strength of 1200 mg for powder for concentrate for solution for infusion. The RMP (version 4) is updated accordingly

15.3.16. Pomalidomide - IMNOVID (CAP) - EMEA/H/C/002682/II/0047, Orphan

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Monica Martinez Redondo

Scope: Update of section 4.4 of the SmPC, Annex IID and Article 127a and the tools/documents included in the Educational Healthcare Professional Kit, in order to harmonise the terminology utilised in the RMP and product information documents relating to the safety concern of teratogenicity and its risk minimisation measure of the Pregnancy Prevention Plan across the 3 immunomodulatory imide drugs (IMiDs). These proposed changes will only have a limited impact on the National Competent Authority (NCA)-approved content/text of the educational materials, and the key messages to the HCP and patients. Furthermore, the regulatory obligations regarding the pregnancy prevention plan (PPP) will not be impacted. The updated RMP version 16 was provided

15.3.17. Pralsetinib - GAVRETO (CAP) - EMEA/H/C/005413/II/0010

Applicant: Roche Registration GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of sections 4.8, 5.1 and 5.2 of the SmPC in order to update efficacy and safety information in the treatment of adult patients with RET fusion-positive advanced non-small cell lung cancer (NSCLC) based on final results (NSCLC indication) from study ARROW/BO42863, a Phase 1/2 Study of the Highly-selective RET Inhibitor, BLU 667, in Patients With Thyroid Cancer, Non-Small Cell Lung Cancer (NSCLC), and Other Advanced Solid Tumours listed as a specific obligation in the Annex II. The RMP version 1.5 has also been submitted

15.3.18. Ranibizumab - LUCENTIS (CAP) - EMEA/H/C/000715/II/0101

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of sections 4.2, 4.4, 4.8 and 5.1 of the SmPC in order to update information on preterm infants based on final results from study CRFB002H2301E (RAINBOW extension), listed as a PAES in the Annex II; this is an extension study to evaluate the long-term efficacy and safety of ranibizumab compared with laser therapy for the treatment of infants born prematurely with retinopathy of prematurity. The Annex II and package leaflet are updated accordingly. The RMP version 22.0 has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the product information

15.3.19. Relugolix, estradiol, norethisterone acetate - RYEQO (CAP) - EMEA/H/C/005267/II/0013/G

Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Martin Huber

Scope: Extension of indication to include treatment of moderate to severe pain associated with endometriosis for RYEQO in adult women of reproductive age with a history of previous medical or surgical treatment for their endometriosis, based on final results from studies MVT-601-3101 and MVT-601-3102 and final results up to 104 weeks from study MVT-601-3103. Studies 3101 and 3102 are pivotal, phase III, randomised, double-blind, placebo-controlled, safety and efficacy studies to evaluate relugolix with E2 and NETA as a combination therapy for pain associated with endometriosis. Study 3103 is an open-label extension study including patients who completed one of the two pivotal studies and met the eligibility criteria, regardless of their treatment assignment in the pivotal studies. In the extension part all patients received relugolix combination therapy. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC were updated. The package leaflet is updated in accordance. Update of section 4.5 of the SmPC to update information regarding Drug-Drug Interaction based on final results of DDI studies MVT-601-54, MVT-601-55 and MVT-601-57. Study MVT-601-54 is a 2-part interventional open-label study to assess the potential effects of erythromycin on the PK of the 3 components of Ryeqo. Study MVT-601-55 is an interventional open label fixed single sequence cross-over study to assess whether a 6-hour dose separation is sufficient to mitigate absorption mediated increased exposure to relugolix and study MVT-601-057 is a 2-part study to assess the potential effect of relugolix on the PK of total dabigatran. The updated RMP version (2.0) has also been submitted. As part of the application, the MAH also requests an extension of the market protection by one additional year

15.3.20. Remdesivir - VEKLURY (CAP) - EMEA/H/C/005622/II/0044/G

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Eva Jirsová

Scope: Update of sections 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC in order to change posology recommendations for patients with renal impairment, remove an existing warning on renal impairment and update the safety and efficacy information based on final results from studies GS US 540 5912 and GS-US-540-9015, listed as category 3 studies in the

RMP. Study GS US 540 5912 is a phase 3 randomised, double-blind, placebo-controlled, parallel group, multicentre study evaluating the efficacy and safety of remdesivir in participants with severely reduced kidney function who were hospitalized for COVID-19, while study GS-US-540-9015 is a phase 1, multicentre, open-label, single-dose study to evaluate the single-dose pharmacokinetic (PK) of remdesivir in participants with normal and impaired renal function. The package leaflet is updated accordingly. The RMP version 5.1 has also been submitted. In addition, the MAH took the opportunity to introduce minor edits to the product information

15.3.21. Thalidomide - THALIDOMIDE BMS (CAP) - EMEA/H/C/000823/II/0076

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Tiphaine Vaillant

Scope: Update of section 4.4 of the SmPC, Annex IID and Article 127a and the tools/documents included in the Educational Healthcare Professional Kit, in order to harmonise the terminology utilised in the RMP and product information documents relating to the safety concern of teratogenicity and its risk minimisation measure of the Pregnancy Prevention Plan (PPP) across the 3 immunomodulatory imide drugs (IMiDs). These proposed changes will only have a limited impact on the National Competent Authority (NCA)-approved content/text of the educational materials, and the key messages to the HCP and patients. Furthermore, the regulatory obligations regarding the PPP will not be impacted. The MAH is also taking the opportunity to update the RMP with PASS Protocol milestones, and to make some editorial changes in the labelling. The updated RMP version 20 was provided

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 medicine(s) mentioned below remains favourable in the approved indication(s) and adopted a recommendation to maintain the current terms of the marketing authorisation(s) together with the assessment report. As per the agreed criteria, the procedures listed below were finalised at 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. Aclidinium bromide - BRETARIS GENUAIR (CAP); EKLIRA GENUAIR (CAP) - PSUSA/00009005/202207

Applicant(s): Covis Pharma Europe B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.2. Alectinib - ALECENSA (CAP) - PSUSA/00010581/202207

Applicant: Roche Registration GmbH

PRAC Rapporteur: Jana Lukacisinova

Scope: Evaluation of a PSUSA procedure

16.1.3. Asfotase alfa - STRENSIQ (CAP) - PSUSA/00010421/202207

Applicant: Alexion Europe SAS

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

16.1.4. Avapritinib - AYVAKYT (CAP) - PSUSA/00010878/202207

Applicant: Blueprint Medicines (Netherlands) B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.5. Beclometasone, formoterol, glycopyrronium bromide - RIARIFY (CAP); TRIMBOW (CAP); TRYDONIS (CAP) - PSUSA/00010617/202207

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

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.1.6. Belatacept - NULOJIX (CAP) - PSUSA/00000311/202206

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Mari Thorn

Scope: Evaluation of a PSUSA procedure

16.1.7. Birch bark extract[51] - FILSUVEZ (CAP) - PSUSA/00010446/202207

Applicant: Amryt Pharmaceuticals DAC

PRAC Rapporteur: Zane Neikena

Scope: Evaluation of a PSUSA procedure

16.1.8. Brexucabtagene autoleucel - TECARTUS (CAP) - PSUSA/00010903/202207

Applicant: Kite Pharma EU B.V. ATMP[52]

PRAC Rapporteur: Menno van der Elst

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

Scope: Evaluation of a PSUSA procedure

16.1.9. Brinzolamide, brimonidine tartrate - SIMBRINZA (CAP) - PSUSA/00010273/202206

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

16.1.10. Budesonide[53] - JORVEZA (CAP) - PSUSA/00010664/202207

Applicant: Dr. Falk Pharma GmbH

PRAC Rapporteur: Zane Neikena

Scope: Evaluation of a PSUSA procedure

16.1.11. Carfilzomib - KYPROLIS (CAP) - PSUSA/00010448/202207

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Evaluation of a PSUSA procedure

16.1.12. Casirivimab, imdevimab - RONAPREVE (CAP) - PSUSA/00010963/202207

Applicant: Roche Registration GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.13. Cenegermin - OXERVATE (CAP) - PSUSA/00010624/202207

Applicant: Dompe farmaceutici S.p.A.

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.1.14. Cladribine[54] - MAVENCLAD (CAP) - PSUSA/00010634/202207

Applicant: Merck Europe B.V.

PRAC Rapporteur: Inês Ribeiro-Vaz

Scope: Evaluation of a PSUSA procedure

16.1.15. Daridorexant - QUVIVIQ (CAP) - PSUSA/00010993/202207

Applicant: Idorsia Pharmaceuticals Deutschland GmbH

PRAC Rapporteur: Ana Sofia Diniz Martins

[53] Centrally authorised products indicated for eosinophilic esophagitis only
[54] For treatment of multiple sclerosis only

Scope: Evaluation of a PSUSA procedure

16.1.16. Finerenone - KERENDIA (CAP) - PSUSA/00010978/202207

Applicant: Bayer AG

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.17. Glecaprevir, pibrentasvir - MAVIRET (CAP) - PSUSA/00010620/202207

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.1.18. Glucagon[55] - BAQSIMI (CAP); OGLUO (CAP) - PSUSA/00010826/202207

Applicant(s): Eli Lilly Nederland B.V. (Baqsimi), Tetris Pharma B.V. (Ogluo)

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

16.1.19. Glucarpidase - VORAXAZE (CAP) - PSUSA/00010968/202207

Applicant: SERB S.A.S.

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.20. Guselkumab - TREMFYA (CAP) - PSUSA/00010652/202207

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Gabriele Maurer

Scope: Evaluation of a PSUSA procedure

16.1.21. Icosapent ethyl - VAZKEPA (CAP) - PSUSA/00010922/202207

Applicant: Amarin Pharmaceuticals Ireland Limited

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.22. Imipenem, cilastatin, relebactam - RECARBRIO (CAP) - PSUSA/00010830/202207

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Adam Przybylkowski

[55] Centrally authorised product(s) only

Scope: Evaluation of a PSUSA procedure

16.1.23. Indacaterol, glycopyrronium, mometasone - ENERZAIR BREEZHALER (CAP); ZIMBUS BREEZHALER (CAP) - PSUSA/00010861/202207

Applicant(s): Novartis Europharm Limited

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.1.24. L-lysine hydrochloride, l-arginine hydrochloride - LYSAKARE (CAP) - PSUSA/00010786/202207

Applicant: Advanced Accelerator Applications

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.25. Neratinib - NERLYNX (CAP) - PSUSA/00010712/202207

Applicant: Pierre Fabre Medicament

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.26. Odevixibat - BYLVAY (CAP) - PSUSA/00010949/202207

Applicant: Albireo

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.27. Pneumococcal polysaccharide conjugate vaccine (15 valent, adsorbed) - VAXNEUVANCE (CAP) - PSUSA/00010975/202207

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Gabriele Maurer

Scope: Evaluation of a PSUSA procedure

16.1.28. Relugolix - ORGOVYX (CAP) - PSUSA/00010994/202207

Applicant: Accord Healthcare S.L.U.

PRAC Rapporteur: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

16.1.29. Remimazolam - BYFAVO (CAP) - PSUSA/00010924/202207

Applicant: Paion Deutschland GmbH

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

16.1.30. Romosozumab - EVENITY (CAP) - PSUSA/00010824/202207

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

16.1.31. Salmeterol, fluticasone propionate[56] - BROPAIR SPIROMAX (CAP); SEFFALAIR SPIROMAX (CAP) - PSUSA/00010928/202207

Applicant(s): Teva B.V.

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.1.32. Sofosbuvir, velpatasvir, voxilaprevir - VOSEVI (CAP) - PSUSA/00010619/202207

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.1.33. Spheroids of human autologous matrix-associated chondrocytes - SPHEROX (CAP) - PSUSA/00010630/202207

Applicant: Rejuvenate GmbH, ATMP[57]

PRAC Rapporteur: Gabriele Maurer

Scope: Evaluation of a PSUSA procedure

16.1.34. Tagraxofusp - ELZONRIS (CAP) - PSUSA/00010896/202207

Applicant: Stemline Therapeutics B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.35. Tasimelteon - HETLIOZ (CAP) - PSUSA/00010394/202207

Applicant: Vanda Pharmaceuticals Netherlands B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

[56] Centrally authorised product(s) only
[57] Advanced therapy medicinal product

16.1.36. Tecovirimat - TECOVIRIMAT SIGA (CAP) - PSUSA/00010971/202207

Applicant: SIGA Technologies Netherlands B.V.

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.37. Vericiguat - VERQUVO (CAP) - PSUSA/00010950/202207

Applicant: Bayer AG

PRAC Rapporteur: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

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

None

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

16.3.1. Acamporsate (NAP) - PSUSA/00000016/202207

Applicant(s): various

PRAC Lead: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

16.3.2. Amorolfine (NAP) - PSUSA/00000185/202206

Applicant(s): various

PRAC Lead: Melinda Palfi

Scope: Evaluation of a PSUSA procedure

16.3.3. Apis mellifera (801), apis mellifera venom[58,59] (NAP) - PSUSA/00010722/202207

Applicant(s): various

PRAC Lead: Mari Thorn

Scope: Evaluation of a PSUSA procedure

16.3.4. Benserazide, levodopa (NAP) - PSUSA/00000330/202206

Applicant(s): various

PRAC Lead: Melinda Palfi

[58] With or without adjuvant
[59] Allergen for diagnostic and/or therapy

Scope: Evaluation of a PSUSA procedure

16.3.5. Betula verrucosa[60,61] (NAP) - PSUSA/00010815/202207

Applicant(s): various

PRAC Lead: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

16.3.6. Cilastatin, imipenem (NAP) - PSUSA/00000748/202206

Applicant(s): various

PRAC Lead: Karen Pernille Harg

Scope: Evaluation of a PSUSA procedure

16.3.7. Delapril, manidipine (NAP); delapril, indapamide (NAP) - PSUSA/00010496/202206

Applicant(s): various

PRAC Lead: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.3.8. Flecainide (NAP) - PSUSA/00001396/202206

Applicant(s): various

PRAC Lead: Karen Pernille Harg

Scope: Evaluation of a PSUSA procedure

16.3.9. Ganciclovir (NAP) - PSUSA/00001516/202206

Applicant(s): various

PRAC Lead: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

16.3.10. Glimepiride (NAP) - PSUSA/00001534/202206

Applicant(s): various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.3.11. Hydroquinidine (NAP) - PSUSA/00001688/202207

Applicant(s): various

[60] Allergen for therapy
[61] Sublingual tablet(s) only

PRAC Lead: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

16.3.12. Human coagulation factor XIII (NAP) - PSUSA/00001622/202206

Applicant(s): various

PRAC Lead: Gabriele Maurer

Scope: Evaluation of a PSUSA procedure

16.3.13. Itopride (NAP) - PSUSA/00010606/202206

Applicant(s): various

PRAC Lead: Rugilė Pilvinienė

Scope: Evaluation of a PSUSA procedure

16.3.14. Ketotifen[62] (NAP) - PSUSA/00001812/202206

Applicant(s): various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.3.15. Methylaminolevulinate (NAP) - PSUSA/00002019/202206

Applicant(s): various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.3.16. Mitoxantrone (NAP) - PSUSA/00002076/202206

Applicant(s): various

PRAC Lead: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

16.3.17. Nitrous oxide (NAP); nitrous oxide, oxygen (NAP) - PSUSA/00010572/202206

Applicant(s): various

PRAC Lead: John Joseph Borg

Scope: Evaluation of a PSUSA procedure

16.3.18. Pentamidine (NAP) - PSUSA/00002338/202206

Applicant(s): various

[62] Ophthalmic formulations only

PRAC Lead: Jo Robays

Scope: Evaluation of a PSUSA procedure

16.3.19. Phentermine, topiramate (NAP) - PSUSA/00010956/202207

Applicant(s): various

PRAC Lead: Mari Thorn

Scope: Evaluation of a PSUSA procedure

16.3.20. Sulfamethizole (NAP) - PSUSA/00010561/202206

Applicant(s): various

PRAC Lead: Marie Louise Schougaard Christiansen

Scope: Evaluation of a PSUSA procedure

16.3.21. Theophylline (NAP) - PSUSA/00002921/202206

Applicant(s): various

PRAC Lead: Maria Popova-Kiradjieva

Scope: Evaluation of a PSUSA procedure

16.3.22. Vespula SPP (802), wasp venom[63,64] (NAP) - PSUSA/00010721/202207

Applicant(s): various

PRAC Lead: Mari Thorn

Scope: Evaluation of a PSUSA procedure

16.4. Follow-up to PSUR/PSUSA procedures

None

16.5. Variation procedure(s) resulting from PSUSA evaluation

16.5.1. Laronidase - ALDURAZYME (CAP) - EMEA/H/C/000477/II/0085

Applicant: Genzyme Europe BV

PRAC Rapporteur: Nathalie Gault

Scope: To update section 4.2 of the SmPC in order to modify the administration instructions following the periodic safety update single assessment (PSUSA) procedure (PSUSA/00001830/202104) adopted in December[65] 2021 based on literature review. The package leaflet is updated accordingly. The RMP version 1.0 has also been submitted

[63] With or without adjuvant
[64] Allergen for diagnostic and/or therapy
[65] Held on 29 November – 02 December 2021

16.6. Expedited summary safety reviews[66]

None

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

Based on the assessment of the following PASS protocol(s), result(s), interim result(s) or feasibility study(ies), and following endorsement of the comments received, 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)[67]

17.1.1. Avapritinib - AYVAKYT (CAP) - EMEA/H/C/PSA/S/0092.1

Applicant: Blueprint Medicines

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to PSA/S/0092 [Substantial amendment to a protocol for BLU-285-1406: observational study evaluating safety and efficacy of avapritinib in the first line treatment of patients with Platelet derived Growth Factor Alpha D842V mutated gastrointestinal stromal tumour] as per the request for supplementary information (RSI) adopted in November[68] 2022

17.1.2. Axicabtagene ciloleucel - YESCARTA (CAP) - EMEA/H/C/PSA/S/0102

Applicant: Kite Pharma EU B.V., ATMP[69]

PRAC Rapporteur: Anette Kirstine Stark

Scope: Substantial amendment to a protocol for a long-term, non-interventional study of recipients of Yescarta for treatment of relapsed or refractory Diffuse Large B-cell Lymphoma and Primary Mediastinal B-cell Lymphoma

17.1.3. Teduglutide - REVESTIVE (CAP) - EMEA/H/C/PSA/S/0086.1

Applicant: Shire Pharmaceuticals Ireland Limited

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: MAH's response to PSA/S/0086 [Substantial amendment (version 8.0) to a protocol previously agreed in June 2022 (PSA/S/0082.1) for study TED-R13-002: a prospective, multicentre registry for patients with short bowel syndrome] as per the request for supplementary information (RSI) adopted in

[66] 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
[67] In accordance with Article 107n of Directive 2001/83/EC
[68] Held on 24-27 October 2022
[69] Advanced therapy medicinal product

17.1.4. Valproate[70] (NAP) - EMEA/H/N/PSA/J/0091.1

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

PRAC Rapporteur: Jean-Michel Dogné

Scope: MAH's response to PSA/J/0091 [Substantial amendment to an agreed protocol for a non-interventional retrospective longitudinal study, conducted in the United Kingdom and France to evaluate and identify the best practices for switching of valproate and related substances in clinical practice [VALSE study (VALNAC09344)], as required in the outcome of the referral procedure under Article 31 of Directive 2001/83/EC on valproate and related substances, completed in February 2018 (EMEA/H/A-31/1454)] as per the request for supplementary information (RSI) adopted in October[71] 2022

17.2. Protocols of PASS non-imposed in the marketing authorisation(s)[72]

17.2.1. Acalabrutinib - CALQUENCE (CAP) - EMEA/H/C/005299/MEA 002.6

Applicant: AstraZeneca AB

PRAC Rapporteur: Željana Margan Koletić

Scope: MAH's response to MEA 002.4 [protocol amendment to include a cohort to Study D8220C00008: phase 3b, multicentre, open-label, single-arm in subjects with chronic lymphocytic leukaemia (ASSURE) to address missing information around moderate to severe cardiac impaired patients in subjects treated with Calquence(acalabrutinib)] as per the request for supplementary information (RSI) adopted in July 2022

17.2.2. Cinacalcet - MIMPARA (CAP) - EMEA/H/C/000570/MEA 035.5

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Mari Thorn

Scope: MAH's response to MEA 35.4 [Amendment to a previously agreed protocol for study 20180204 (listed as category 3 study in the RMP): an observational registry study to evaluate the use and safety of cinacalcet among paediatric patients with secondary hyperparathyroidism] as per the request for supplementary information (RSI) adopted in October[73] 2022

17.2.3. Cladribine - MAVENCLAD (CAP) - EMEA/H/C/004230/MEA 002.4

Applicant: Merck Europe B.V.

PRAC Rapporteur: Inês Ribeiro-Vaz

Scope: Amendment to a previously agreed protocol for study MS 700568-0002 (CLARION) (listed as category 3 study in the RMP): prospective, observational cohort study evaluating the safety profile, in terms of incidence of adverse events of special interest, in patients

[70] Valproic acid, sodium valproate, valproate pivoxil, valproate semisodium, valpriomide, valproate bismuth, calcium valproate, valproate magnesium
[71] Held on 26-29 September 2022
[72] 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
[73] Held on 26-29 September 2022

with highly active relapsing multiple sclerosis (RMS) newly started on oral cladribine

17.2.4. Cladribine - MAVENCLAD (CAP) - EMEA/H/C/004230/MEA 003.2

Applicant: Merck Europe B.V.

PRAC Rapporteur: Inês Ribeiro-Vaz

Scope: Amendment to a previously agreed protocol for study MS700568-0004: Pregnancy outcomes in women exposed to oral cladribine: a multi-country cohort database study - CLEAR

17.2.5. Coronavirus (COVID-19) vaccine (Ad26.COV2-S, recombinant) - JCOVDEN (CAP) - EMEA/H/C/005737/MEA 010.3

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of a revised protocol for VAC31518COV4001 (listed as category 3 study in the RMP): a post-authorisation, observational study to assess the safety of Ad26.COV2.S using health insurance claims and/or electronic health record (EHR) database(s) in the United States, including FDA feedback

17.2.6. Coronavirus (COVID-19) vaccine (B.1.351 variant, prefusion Spike delta TM protein, recombinant) - VIDPREVTYN BETA (CAP) - EMEA/H/C/005754/MEA 002

Applicant: Sanofi Pasteur

PRAC Rapporteur: Jana Lukacisinova

Scope: Submission of a protocol for study VAT 00007: Post-authorisation, observational study to assess the safety of VidPrevtyn Beta using routinely collected secondary data in Europe through VAC4EU. A non-interventional PASS to assess the occurrence of pre-specified AESIs and safety concerns following administration of VidPrevtyn Beta as a booster dose in a real-world setting

17.2.7. Diroximel fumarate - VUMERITY (CAP) - EMEA/H/C/005437/MEA 002.2

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Martin Huber

Scope: MAH's response to MEA 002.1 [protocol for 272MS403 (study number changed from Study SE-VUM-12146 to) (listed as category 3 study in the RMP): an observational study utilising data from 'big data' multiple sclerosis registries to evaluate the long-term safety of Vumerity (diroximel fumarate) and Tecfidera (dimethyl fumarate)] as per request for supplementary information (RSI) adopted in October 2022

17.2.8. Efgartigimod alfa - VYVGART (CAP) - EMEA/H/C/005849/MEA 002

Applicant: Argenx

PRAC Rapporteur: Rhea Fitzgerald

Scope: Submission of a protocol for a PASS to characterise the risks and missing information outlined in the risk management plan including serious infections, use of live/attenuated vaccines, use with monoclonal antibodies, long-term safety and use in immunocompromised patients and evaluate whether there are specific and/or unexpected patterns of adverse events

17.2.9. Efgartigimod alfa - VYVGART (CAP) - EMEA/H/C/005849/MEA 004

Applicant: Argenx

PRAC Rapporteur: Rhea Fitzgerald

Scope: Submission of a protocol for a PASS to characterise the missing information use in pregnant woman outlined in the risk management plan

17.2.10. Efgartigimod alfa - VYVGART (CAP) - EMEA/H/C/005849/MEA 005

Applicant: Argenx

PRAC Rapporteur: Rhea Fitzgerald

Scope: Submission of a protocol for a PASS to characterise the missing information use in patients with moderate and severe renal impairment outlined in the risk management plan

17.2.11. Efgartigimod alfa - VYVGART (CAP) - EMEA/H/C/005849/MEA 006

Applicant: Argenx

PRAC Rapporteur: Rhea Fitzgerald

Scope: Submission of a protocol for a PASS to characterise the missing information effect on vaccination efficacy outlined in the risk management plan

17.2.12. Fexinidazole - FEXINIDAZOLE WINTHROP (Art 58[74]) - EMEA/H/W/002320/MEA 002.2

Applicant: Sanofi Winthrop Industrie

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Protocol for study FEXINC09395: a prospective observational study of the safety of fexinidazole for human African trypanosomiasis

17.2.13. Inclisiran - LEQVIO (CAP) - EMEA/H/C/005333/MEA 004.2

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Kimmo Jaakkola

Scope: Amendments of protocol for study CKJX839A12011: a non-interventional PASS to estimate the proportion of major congenital malformations among pregnancies exposed to inclisiran during pregnancy reported to Novartis amongst (i) live births and (ii) live births plus still births plus termination of pregnancy for foetal anomaly (TOPFA) - Inclisiran

[74] 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)

pregnancy outcomes intensive monitoring (PRIM)

17.2.14. Lenalidomide - REVLIMID (CAP) - EMEA/H/C/000717/MEA 046.6

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Tiphaine Vaillant

Scope: MAH's response to MEA 046.5 [Substantial amendment to a protocol previously endorsed in November 2017 for study CC-5013-MCL-005 to further investigate and characterise the association of lenalidomide and tumour flare reaction (TFR)/high tumour burden following the extension of indication for the treatment of adult patients with relapsed and/or refractory mantle cell lymphoma (RRMCL)] as per the request for supplementary information (RSI) adopted in September[75] 2022

17.2.15. Natalizumab - TYSABRI (CAP) - EMEA/H/C/000603/MEA 067.2

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Gabriele Maurer

Scope: Amendment of protocol (v.9.0) for TOP study (Tysabri Observational Programme, Study Protocol IMA-06-02): a PASS, open-label, multinational, multicentre, prospective, observational study, to address the long-term safety profile and long-term impact on disease activity and progression of natalizumab with marketed use, and the impact of treatment on disability in particular by comparing the results with prospectively determined controls from established databases; the amendment aims to extend patient follow up from 10 to 15 years

17.2.16. Nirmatrelvir, ritonavir - PAXLOVID (CAP) - EMEA/H/C/005973/MEA 008

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Martin Huber

Scope: Initial protocol for study C4671037: use and safety of Paxlovid during pregnancy and among patients with moderate or severe hepatic or renal impairment

17.2.17. Nirmatrelvir, ritonavir - PAXLOVID (CAP) - EMEA/H/C/005973/MEA 009.1

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Martin Huber

Scope: Revised initial protocol for study C4671047: use and safety of Paxlovid among patients with moderate or severe hepatic or renal impairment

17.2.18. Coronavirus (COVID-19) vaccine (recombinant, adjuvanted) - NUVAXOVID (CAP) - EMEA/H/C/005808/MEA 006.1

Applicant: Novavax CZ, a.s.

PRAC Rapporteur: Gabriele Maurer

[75] Held on 29 August – 01 September 2022

Scope: MAH's response to MEA 006 [Updated protocol for study 2019nCoV-404: US PASS to evaluate the pooled of risk of selected adverse events of special interest (AESI) within specified time periods after vaccination with Nuvaxovid using a claim and/or electronic healthcare record (her) database] as per the request for supplementary information (RSI) adopted in October[76] 2022

17.2.19. Odevixibat - BYLVAY (CAP) - EMEA/H/C/004691/MEA 003.2

Applicant: Albireo

PRAC Rapporteur: Adam Przybylkowski

Scope: Submission of an updated study protocol (version 1.0) for study A4250-019 (listed as a category 3 study in the RMP): prospective registry-based study of the long-term safety of odevixibat in patients with progressive familial intrahepatic cholestasis (PFIC) to collect safety data on hepatotoxicity, diarrhoea, fat-soluble vitamins and fat-soluble nutrients in patients treated with odevixibat

17.2.20. Ofatumumab - KESIMPTA (CAP) - EMEA/H/C/005410/MEA 004.1

Applicant: Novartis Ireland Limited

PRAC Rapporteur: Amelia Cupelli

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

17.2.21. Pegcetacoplan - ASPAVELI (CAP) - EMEA/H/C/005553/MEA 002.1

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Kimmo Jaakkola

Scope: Submission of revised protocol for study Sobi.PEGCET-301: non-imposed, non-interventional PASS using registry data for pegcetacoplan to evaluate the occurrence of serious infections in patients with paroxysmal nocturnal haemoglobinuria (PNH) treated with pegcetacoplan

17.2.22. Pegcetacoplan - ASPAVELI (CAP) - EMEA/H/C/005553/MEA 003.1

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Kimmo Jaakkola

Scope: submission of revised protocol for study Sobi.PEGCET-302: non-imposed, non-interventional PASS for assessment of pregnancy outcomes in patients with paroxysmal nocturnal haemoglobinuria (PNH) exposed to pegcetacoplan during pregnancy

[76] Held on 26-29 September 2022

17.2.23. Pegvaliase - PALYNZIQ (CAP) - EMEA/H/C/004744/MEA 005.5

Applicant: BioMarin International Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Submission of a revised protocol for study 165-504: a global, multicentre study to assess maternal, foetal and infant outcomes of exposure to Palynziq (pegvaliase) during pregnancy and breastfeeding

17.2.24. Rimegepant - VYDURA (CAP) - EMEA/H/C/005725/MEA 001.1

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Anette Kirstine Stark

Scope: MAH's response to MEA 001 [Protocol for study BHV3000-402: a prospective, registry-based, observational study to assess maternal, fetal and infant outcomes following exposure to rimegepant together with a statistical analysis plan (SAP)] as per the request for supplementary information (RSI) adopted in September[77] 2022

17.2.25. Rimegepant - VYDURA (CAP) - EMEA/H/C/005725/MEA 002.1

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Anette Kirstine Stark

Scope: MAH's response to MEA 002 [Protocol for study BHV3000-403: retrospective cohort study of pregnancy outcomes in women exposed to rimegepant during pregnancy together with a statistical analysis plan (SAP)] as per the request for supplementary information (RSI) adopted in September[78] 2022

17.2.26. Rimegepant - VYDURA (CAP) - EMEA/H/C/005725/MEA 003.1

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Anette Kirstine Stark

Scope: MAH's response to MEA 003 [Submission of protocol for study BHV3000-408: a PASS of rimegepant in patients with migraine and a history of cardiovascular diseases together with a statistical analysis plan (SAP)] as per the request for supplementary information (RSI) adopted in October[79] 2022

17.2.27. Somatrogon - NGENLA (CAP) - EMEA/H/C/005633/MEA 001

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Submission of a protocol for study C0311023: an active surveillance study to monitor the real-world long-term safety of somatrogon among paediatric patients in Europe

[77] Held on 29 August – 01 September 2022
[78] Held on 29 August – 01 September 2022
[79] Held on 26-29 September 2022

17.2.28. Venetoclax - VENCLYXTO (CAP) - EMEA/H/C/004106/MEA 015.1

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Eva Jirsová

Scope: Submission of revised protocol for study P22-907 (listed as category 3 study in the RMP): a one-time, cross-sectional survey study evaluating the effectiveness of the DHPC and of the revised venetoclax SmPC among hematologists in select European countries

17.2.29. Venetoclax - VENCLYXTO (CAP) - EMEA/H/C/004106/MEA 016.1

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Eva Jirsová

Scope:Submission of a revised protocol for study P22-905 (listed as category 3 study in the RMP): a one-time, cross-sectional survey study to evaluate effectiveness of the patient card among adult patients recently treated with venetoclax for chronic lymphocytic leukemia (CLL)per usual care in select European countries

17.3. Results of PASS imposed in the marketing authorisation(s)[80]

None

17.4. Results of PASS non-imposed in the marketing authorisation(s)[81]

17.4.1. Alirocumab - PRALUENT (CAP) - EMEA/H/C/003882/II/0077

Applicant: Sanofi Winthrop Industrie

PRAC Rapporteur: Gabriele Maurer

Scope: Submission of the final report from the PASS study ALIROC08577: a non-interventional drug utilisation study of alirocumab in special populations using two U.S. healthcare databases

17.4.2. Empagliflozin, linagliptin - GLYXAMBI (CAP) - EMEA/H/C/003833/WS2406/0049; empagliflozin - JARDIANCE (CAP) - EMEA/H/C/002677/WS2406/0075; empagliflozin, metformin - SYNJARDY (CAP) - EMEA/H/C/003770/WS2406/0068

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Update of section 4.4 of the SmPC in order to remove an existing warning on hepatic injury based on final results from the PASS 1245-96 listed as a category 3 study in the RMP for Jardiance and Synjardy; this is a PASS in patients with type 2 diabetes mellitus (T2DM) to assess the risk of acute liver injury, acute kidney injury and chronic kidney disease, severe complications of urinary tract infection, genital infections, and diabetic ketoacidosis among patients treated with empagliflozin compared to patients treated with DPP-4inhibitors. The RMP versions for Jardiance (RMP version 20.0), Synjardy (RMP version

[80] In accordance with Article 107p-q of Directive 2001/83/EC
[81] 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

13.0) and Glyxambi (RMP version 8.0) have also been submitted. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet for Glyxambi (in fulfilment of MEA 003.9)

17.4.3. Glycerol phenylbutyrate - RAVICTI (CAP) - EMEA/H/C/003822/II/0044, Orphan

Applicant: Immedica Pharma AB

PRAC Rapporteur: Amelia Cupelli

Scope: Submission of the final report from study HZNP-RAV-401 (listed as category 3 study in the RMP): European Post-Authorisation Registry for Ravicti (glycerol phenylbutyrate) Oral Liquid in Partnership with the European Registry and Network for Intoxication Type Metabolic Diseases (E-IMD) The RMP version 7.4 has also been submitted

17.4.4. Idelalisib - ZYDELIG (CAP) - EMEA/H/C/003843/II/0056

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Martin Huber

Scope: Submission of the final report from study GS-EU-313-4172 listed as a category 3 study in the RMP. This is a non-interventional study to assess the safety profile of idelalisib in patients with refractory follicular lymphoma (FL) with primary objective to assess the overall safety profile of idelalisib monotherapy in patients with refractory FL

17.4.5. Insulin human - INSUMAN (CAP) - EMEA/H/C/000201/II/0142

Applicant: Sanofi-Aventis Deutschland GmbH

PRAC Rapporteur: Jean-Michel Dogné

Scope: Submission of the final report from study HUBIN-C-06380 listed as a category 3 study in the RMP. This is an observational prospective PASS designed to gain additional longitudinal and long-term safety data related to the use of Insuman Implantable 400 IU/mL via an IP implantable pump in a European observational cohort of patients with type 1 diabetes. The RMP version 5.0 has also been submitted

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

Applicant: Orexigen Therapeutics Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: Submission of the final report from study NB-542 listed as a category 3 PASS in the RMP. This is a cross-sectional survey aimed to evaluate the effectiveness of the Mysimba Physician Prescribing Checklist (PPC) among physicians in the EU. The RMP version 12.6 has also been submitted

17.4.7. Rituximab - RIXATHON (CAP) - EMEA/H/C/003903/WS2387/0063; RIXIMYO (CAP) - EMEA/H/C/004729/WS2387/0064

Applicant: Sandoz GmbH

PRAC Rapporteur: Anette Kirstine Stark

Scope: Submission of the final report from study GP13-501 following procedure EMEA/H/C/PSUSA/00002652/201811. This is a prospective, open-label, single-arm, non-interventional, multicenter study describing the effectiveness and safety of biosimilar rituximab administered in combination with CHOP chemotherapy for the treatment of patients with previously untreated CD20-positive diffuse large B-cell lymphoma in current clinical practice

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

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Gabriele Maurer

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

17.4.9. Vortioxetine - BRINTELLIX (CAP) - EMEA/H/C/002717/II/0037

Applicant: H. Lundbeck A/S

PRAC Rapporteur: Jo Robays

Scope: Submission of the final report from study 16034N listed as a category 3 study in the RMP. This is a non-interventional PASS of vortioxetine in Europe: an analysis of European automated healthcare databases. The RMP version 4.0 has also been submitted

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

17.5.1. Aflibercept - EYLEA (CAP) - EMEA/H/C/002392/MEA 021

Applicant: Bayer AG

PRAC Rapporteur: Nathalie Gault

Scope: First annual safety report evaluating the intraocular pressure increase with the Eylea

17.5.2. Alemtuzumab - LEMTRADA (CAP) - EMEA/H/C/003718/ANX 010.7

Applicant: Sanofi Belgium

PRAC Rapporteur: Anette Kirstine Stark

Scope: Interim report 2 for study DUT0008: non-interventional PASS to investigate drug utilisation and safety monitoring patterns for Lemtrada (alemtuzumab)

17.5.3. Denosumab - PROLIA (CAP) - EMEA/H/C/001120/LEG 041.2

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Mari Thorn

Scope: MAH's response to LEG 041.1 [Annual interim report year 11 for study 20090522: a PASS on denosumab global safety assessment among women with postmenopausal osteoporosis (PMO) and men with osteoporosis in multiple observational databases] as per the request for supplementary information (RSI) adopted in March

17.5.4. Elasomeran - SPIKEVAX (CAP) - EMEA/H/C/005791/MEA 003.9

Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Seventh interim report for study P903 (listed as a category 3 study in the RMP): a post authorisation safety study of Spikevax (elasomeran) in the US - an enhanced pharmacovigilance study to provide additional evaluation of adverse events of special interest (AESI) and emerging validated safety signals

17.5.5. Elasomeran - SPIKEVAX (CAP) - EMEA/H/C/005791/MEA 066.2

Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: First interim report for study mRNA-1273-P911: long-term outcomes of myocarditis following administration of Spikevax (COVID-19 vaccine mRNA)

17.5.6. Fenfluramine - FINTEPLA (CAP) - EMEA/H/C/003933/MEA 002.1

Applicant: Zogenix ROI Limited

PRAC Rapporteur: Martin Huber

Scope: MAH's response to MEA 002 [Progress report for study ZX008-1503: an open-label extension trial to assess the long-term safety of ZX008 (fenfluramine hydrochloride) oral solution as an adjunctive therapy in children and young adults with Dravet syndrome] as per the request for supplementary information (RSI) adopted in October[82] 2022

17.5.7. Filgrastim - NIVESTIM (CAP) - EMEA/H/C/001142/MEA 015.7

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Kirsti Villikka

Scope: Sixth annual report for study ZOB-NIV-1513 (C1121008): a multinational, multicentre, prospective, non-interventional PASS in healthy donors (HDs) exposed to Nivestim (biosimilar filgrastim) for haematopoietic stem cell (HSC) mobilisation (NEST)

17.5.8. Inotersen - TEGSEDI (CAP) - EMEA/H/C/004782/MEA 007.3

Applicant: Akcea Therapeutics Ireland Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Second interim report for study TEG4005: a pregnancy surveillance programme of

[82] Held on 26-29 September 2022

infants and women exposed to Tegsedi (inotersen) during pregnancy

17.5.9. Ipilimumab - YERVOY (CAP) - EMEA/H/C/002213/MEA 036.5

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to MEA 036.4 [Submission of the progress report for study CA184557: Long-term follow-up of ipilimumab treated paediatric patients enrolled in the Dutch melanoma treatment registry (DMTR)] as per the request for supplementary information (RSI) adopted in September[83] 2022

17.5.10. Mogamulizumab - POTELIGEO (CAP) - EMEA/H/C/004232/MEA 001.2

Applicant: Kyowa Kirin Holdings B.V.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Interim report for a PASS to characterise the safety of allogeneic haematopoietic stem cell transplantation (HSCT) in patients with cutaneous T-cell lymphoma (CTCL) treated with mogamulizumab

17.5.11. Ocrelizumab - OCREVUS (CAP) - EMEA/H/C/004043/MEA 004.2

Applicant: Roche Registration GmbH

PRAC Rapporteur: Gabriele Maurer

Scope: Interim report for study BA39730 (listed as a category 3 study in the RMP): a long term surveillance study to assess and characterize the long-term safety data from the use of ocrelizumab in treated patients with multiple sclerosis (MS)

17.5.12. Pitolisant - WAKIX (CAP) - EMEA/H/C/002616/ANX 001.5

Applicant: Bioprojet Pharma

PRAC Rapporteur: Kirsti Villikka

Scope: Fifth annual interim study report for study P15-11: a 5-year multicentre, observational PASS to document the utilisation of Wakix (pitolisant) in the treatment of narcolepsy with or without cataplexy and to collect information on its long-term safety when used in routine medical practice [final results expected in 2023]

17.5.13. Risdiplam - EVRYSDI (CAP) - EMEA/H/C/005145/MEA 007.3

Applicant: Roche Registration GmbH

PRAC Rapporteur: Jan Neuhauser

Scope: Interim results for study BN42833: a phase 4, non-interventional surveillance study for risdiplam [final study report expected in Q4/2031]

[83] Held on 29 August – 01 September 2022

17.5.14. Teriflunomide - AUBAGIO (CAP) - EMEA/H/C/002514/MEA 005.7

Applicant: Sanofi Winthrop Industrie

PRAC Rapporteur: Martin Huber

Scope: 1) Ninth annual progress report for pregnancy registry OBS13499 (US/CA): teriflunomide pregnancy outcome exposure registry: a 'teratology information specialists (OTIS)' autoimmune diseases in pregnancy project, 2) Sixth annual progress report for OBS12751 (international): an international pregnancy exposure registry of women with multiple sclerosis (MS) exposed to Aubagio (teriflunomide)

17.5.15. Tolvaptan - JINARC (CAP) - EMEA/H/C/002788/ANX 002.3

Applicant: Otsuka Pharmaceutical Netherlands B.V.

PRAC Rapporteur: Amelia Cupelli

Scope: MAH's response to ANX 002.2 [interim report for study 156-12-299: a non-interventional PASS to investigate the risks of hepatotoxicity, basal cell carcinoma and glaucoma associated with the use of Jinarc (tolvaptan). In addition, the study investigates pregnancy outcomes in patients treated with Jinarc (tolvaptan), patterns of medicinal product utilisation especially with regards to off-label use and use in patients over 50 years old as well as adverse drug reactions (ADRs) associated with long term use of Jinarc (tolvaptan) [final clinical study report (CSR) expected by: Q1/2026]] as per the request for supplementary information (RSI) adopted in September[84] 2020

17.5.16. Tozinameran - COMIRNATY (CAP) - EMEA/H/C/005735/MEA 037.3

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Monitoring report for study C4591009: a non-interventional PASS in US to assess the occurrence of safety events of interest, including myocarditis and pericarditis, among individuals in the general US population and in subcohorts of interest within selected data sources participating in the US Sentinel System

17.5.17. Turoctocog alfa pegol - ESPEROCT (CAP) - EMEA/H/C/004883/ANX 001.2

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Gabriele Maurer

Scope: Second study progress report for study NN7088-4029: A multinational, prospective, open labelled, non-controlled, non-interventional post-authorisation study of turoctocog alfa pegol (N8-GP) during long-term routine prophylaxis and treatment of bleeding episodes in patients with haemophilia A

[84] Held on 31 August – 03 September 2022

17.6. Others

17.6.1. Radium (Ra^{223}) - XOFIGO (CAP) - EMEA/H/C/002653/ANX 013.3

Applicant: Bayer AG

PRAC Rapporteur: Rugile Pilviniene

Scope: MAH's response to ANX 013.2 [Request for deletion of ANX 013.1 post-approval commitment (study 20511): an open-label, multicentre, non-randomised Phase 1 study that has been requested by the European Commission as a result of the referral procedure (EMEA/H/A-20/1459/C/002653/0028) to further characterize the correlation between the extent of the disease, the dose and the distribution of radium-223 in bone metastases versus sites of impaired bone health versus normal bone structure] as per the request for supplementary information adopted in October[85] 2022

17.6.2. Tozinameran - COMIRNATY (CAP) - EMEA/H/C/005735/MEA 037.4

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Administrative letter update for clinical study to capture safety events (based on AESI) including myocarditis and pericarditis, in individuals of any age who received tozinameran since its availability under an EUA using electronic health records and claims data from data partners participating in the Sentinel System (study C4591009)

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 medicine(s) listed below and the CHMP Rapporteur's assessment report, PRAC considered that either the renewal of the marketing authorisation procedure could be concluded - and supported the renewal of their marketing authorisations for an unlimited or additional period, as applicable - or no amendments to the specific obligations of the marketing authorisation under exceptional

[85] Held on 26-29 September 2022

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. Cerliponase alfa - BRINEURA (CAP) - EMEA/H/C/004065/S/0038 (without RMP)

Applicant: BioMarin International Limited

PRAC Rapporteur: Mari Thorn

Scope: Annual reassessment of the marketing authorisation

18.1.2. Cholic acid - ORPHACOL (CAP) - EMEA/H/C/001250/S/0048 (without RMP)

Applicant: Laboratoires CTRS

PRAC Rapporteur: Sofia Trantza

Scope: Annual reassessment of the marketing authorisation

18.1.3. Idebenone - RAXONE (CAP) - EMEA/H/C/003834/S/0032 (without RMP)

Applicant: Santhera Pharmaceuticals (Deutschland) GmbH

PRAC Rapporteur: Amelia Cupelli

Scope: Annual reassessment of the marketing authorisation

18.1.4. Obiltoxaximab - NYXTHRACIS (CAP) - EMEA/H/C/005169/S/0008 (without RMP)

Applicant: SFL Pharmaceuticals Deutschland GmbH

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Annual reassessment of the marketing authorisation

18.1.5. Tocofersolan - VEDROP (CAP) - EMEA/H/C/000920/S/0044 (without RMP)

Applicant: Recordati Rare Diseases

PRAC Rapporteur: Melinda Palfi

Scope: Annual reassessment of the marketing authorisation

18.2. Conditional renewals of the marketing authorisation

18.2.1. Andexanet alfa - ONDEXXYA (CAP) - EMEA/H/C/004108/R/0034 (without RMP)

Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: Conditional renewal of the marketing authorisation

18.2.2. Mosunetuzumab - LUNSUMIO (CAP) - EMEA/H/C/005680/R/0001 (without RMP)

Applicant: Roche Registration GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Conditional renewal of the marketing authorisation

18.2.3. Selumetinib - KOSELUGO (CAP) - EMEA/H/C/005244/R/0010 (with RMP)

Applicant: AstraZeneca AB

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Conditional renewal of the marketing authorisation

18.3. Renewals of the marketing authorisation

18.3.1. Axicabtagene ciloleucel - YESCARTA (CAP) - EMEA/H/C/004480/R/0056 (with RMP)

Applicant: Kite Pharma EU B.V., ATMP[86]

PRAC Rapporteur: Anette Kirstine Stark

Scope: 5-year renewal of the marketing authorisation

18.3.2. Binimetinib - MEKTOVI (CAP) - EMEA/H/C/004579/R/0024 (without RMP)

Applicant: Pierre Fabre Medicament

PRAC Rapporteur: Inês Ribeiro-Vaz

Scope: 5-year renewal of the marketing authorisation

18.3.3. Caplacizumab - CABLIVI (CAP) - EMEA/H/C/004426/R/0042 (without RMP)

Applicant: Ablynx NV

PRAC Rapporteur: Jan Neuhauser

Scope: 5-year renewal of the marketing authorisation

18.3.4. Daunorubicin, cytarabine - VYXEOS LIPOSOMAL (CAP) - EMEA/H/C/004282/R/0037 (without RMP)

Applicant: Jazz Pharmaceuticals Ireland Limited

PRAC Rapporteur: Inês Ribeiro-Vaz

Scope: 5-year renewal of the marketing authorisation

18.3.5. Deferiprone - DEFERIPRONE LIPOMED (CAP) - EMEA/H/C/004710/R/0011 (with RMP)

Applicant: Lipomed GmbH

[86] Advanced Therapy Medicinal Product

PRAC Rapporteur: Tiphaine Vaillant

Scope: 5-year renewal of the marketing authorisation

18.3.6. Durvalumab - IMFINZI (CAP) - EMEA/H/C/004771/R/0055 (without RMP)

Applicant: AstraZeneca AB

PRAC Rapporteur: David Olsen

Scope: 5-year renewal of the marketing authorisation

18.3.7. Encorafenib - BRAFTOVI (CAP) - EMEA/H/C/004580/R/0029 (without RMP)

Applicant: Pierre Fabre Medicament

PRAC Rapporteur: Rugile Pilviniene

Scope: 5-year renewal of the marketing authorisation

18.3.8. Eravacycline - XERAVA (CAP) - EMEA/H/C/004237/R/0023 (with RMP)

Applicant: Paion Deutschland GmbH

PRAC Rapporteur: Adam Przybylkowski

Scope: 5-year renewal of the marketing authorisation

18.3.9. Lipegfilgrastim - LONQUEX (CAP) - EMEA/H/C/002556/R/0077 (without RMP)

Applicant: Teva B.V.

PRAC Rapporteur: Kirsti Villikka

Scope: 5-year renewal of the marketing authorisation

18.3.10. Nitisinone - NITYR (CAP) - EMEA/H/C/004582/R/0015 (with RMP)

Applicant: Cycle Pharmaceuticals (Europe) Limited

PRAC Rapporteur: Amelia Cupelli

Scope: 5-year renewal of the marketing authorisation

18.3.11. Patisiran - ONPATTRO (CAP) - EMEA/H/C/004699/R/0031 (without RMP)

Applicant: Alnylam Netherlands B.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: 5-year renewal of the marketing authorisation

18.3.12. Pomalidomide - IMNOVID (CAP) - EMEA/H/C/002682/R/0049 (without RMP)

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Monica Martinez Redondo

Scope: 5-year renewal of the marketing authorisation

18.3.13. Tisagenlecleucel - KYMRIAH (CAP) - EMEA/H/C/004090/R/0068 (without RMP)

Applicant: Novartis Europharm Limited, ATMP[87]

PRAC Rapporteur: Gabriele Maurer

Scope: 5-year renewal of the marketing authorisation

18.3.14. Vonicog alfa - VEYVONDI (CAP) - EMEA/H/C/004454/R/0027 (with RMP)

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Mari Thorn

Scope: 5-year renewal of the marketing authorisation

19. Annex II – List of participants

including any restrictions with respect to involvement of members / alternates / experts following evaluation of declared interests for the 06-09 FEB 2023 meeting. Participants marked with "a" attended the plenary session while those marked with "b" attended ORGAM.

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Sabine Straus [a,b]	Chair	The Netherlands	No interests declared	
Jan Neuhauser [b]	Member	Austria	No interests declared	
Sonja Hrabcik [a]	Alternate	Austria	No interests declared	
Jean-Michel Dogné [a,b]	Member	Belgium	No interests declared	
Jo Robays [a,b]	Alternate	Belgium	No interests declared	
Maria Popova-Kiradjieva [a,b]	Member	Bulgaria	No interests declared	
Nikica Mirošević Skvrce [a,b]	Member	Croatia	No interests declared	
Željana Margan Koletić [a,b]	Alternate	Croatia	No interests declared	
Elena Kaisis [a,b]	Member	Cyprus	No interests declared	

[87] Advanced therapy medicinal product

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Panagiotis Psaras [a,b]	Alternate	Cyprus	No interests declared	
Eva Jirsová [a,b]	Member	Czechia	No interests declared	
Jana Lukacisinova [a,b]	Alternate	Czechia	No interests declared	
Anette Kristine Stark [a,b]	Member	Denmark	No interests declared	
Marie Louise Schougaard Christiansen [a,b]	Alternate	Denmark	No interests declared	
Krõõt Aab [a]	Alternate	Estonia	No interests declared	
Kirsti Villikka [a]	Member	Finland	No interests declared	
Kimmo Jaakkola [a,b]	Alternate	Finland	No interests declared	
Tiphaine Vaillant [a,b]	Member	France	No interests declared	
Nathalie Gault [a,b]	Alternate	France	No interests declared	
Martin Huber [a]	Member (Vice-Chair)	Germany	No interests declared	
Gabriele Maurer [a,b]	Alternate	Germany	No participation in final deliberations and voting on:	4.1.1. Ipilimumab – YERVOY (CAP); nivolumab – OPDIVO (CAP); pembrolizumab – KEYTRUDA (CAP) 4.3.4. Nivolumab – OPDIVO (CAP) - EMEA/H/C/003985/SDA 049
Sophia Trantza [a,b]	Member	Greece	No interests declared	
Georgia Gkegka [a]	Alternate	Greece	No interests declared	
Julia Pallos [a,b]	Member	Hungary	No participation in final deliberations	4.1.1. Ipilimumab – YERVOY (CAP); nivolumab – OPDIVO (CAP);

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			and voting on:	pembrolizumab – KEYTRUDA (CAP) 4.3.4. Nivolumab – OPDIVO (CAP) - EMEA/H/C/003985/SDA 049 15.3.10. Lenalidomide - REVLIMID (CAP) - EMEA/H/C/000717/II/0123 15.3.12. Lisocabtagene maraleucel - BREYANZI (CAP) - EMEA/H/C/004731/II/0005 15.3.16. Pomalidomide - IMNOVID (CAP) - EMEA/H/C/002682/II/0047, Orphan 15.3.21. Thalidomide - THALIDOMIDE BMS (CAP) - EMEA/H/C/000823/II/0076 16.1.6. Belatacept - NULOJIX (CAP) - PSUSA/00000311/202206 17.2.14. Lenalidomide - REVLIMID (CAP) - EMEA/H/C/000717/MEA 046.6

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				17.5.9. Ipilimumab - YERVOY (CAP) - EMEA/H/C/002213/MEA 036.5 18.3.12. Pomalidomide - IMNOVID (CAP) - EMEA/H/C/002682/R/0049 (without RMP)
Guðrún Stefánsdóttir [a,b]	Member	Iceland	No participation in final deliberations and voting on:	4.3.1. Adalimumab - AMGEVITA (CAP), AMSPARITY (CAP), HEFIYA (CAP), HUMIRA (CAP) - EMEA/H/C/000481/SDA 126, HULIO (CAP), HUKYNDRA (CAP), HYRIMOZ (CAP), IDACIO (CAP), IMRALDI (CAP), LIBMYRIS (CAP), YUFLYMA (CAP); etanercept – ENBREL (CAP) – EMEA/H/C/000262/SDA 175; infliximab – REMICADE (CAP) – EMEA/H/C/000240/SDA 162 16.1.11. Carfilzomib - KYPROLIS (CAP) - PSUSA/00010448/202207 17.2.2. Cinacalcet -

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				MIMPARA (CAP) - EMEA/H/C/000570/MEA 035.5 17.5.3. Denosumab - PROLIA (CAP) - EMEA/H/C/001120/LEG 041.2
Ronan Grimes [a,b]	Alternate	Ireland	No interests declared	
Amelia Cupelli [a,b]	Member	Italy	No interests declared	
Valentina Di Giovanni [a,b]	Alternate	Italy	No interests declared	
Zane Neikena [a,b]	Member	Latvia	No interests declared	
Rugile Pilviniene [a]	Member	Lithuania	No interests declared	
Lina Seibokiene [a]	Alternate	Lithuania	No restrictions applicable to this meeting	
Anne-Cécile Vuillemin [a,b]	Alternate	Luxembourg	No interests declared	
John Joseph Borg [a]	Member (CHMP member)	Malta	No interests declared	
Menno van der Elst [a,b]	Member	Netherlands	No interests declared	
Liana Gross-Martirosyan [a,b]	Alternate	Netherlands	No interests declared	
David Olsen [a]	Member	Norway	No participation in final deliberations and voting on:	3.1.1. Ibuprofen, pseudoephedrine (NAP) - EMEA/H/XXXX 16.1.16. Finerenone - KERENDIA (CAP) - PSUSA/00010978/202207 16.1.37. Vericiguat -

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				VERQUVO (CAP) - PSUSA/00010950/202207 17.5.1. Aflibercept - EYLEA (CAP) - EMEA/H/C/002392/MEA 021 17.6.1. Radium (Ra223) - XOFIGO (CAP) - EMEA/H/C/002653/ANX 013.3
Karen Pernille Harg [a,b]	Alternate	Norway	No interests declared	
Adam Przybylkowski [a]	Member	Poland	No interests declared	
Katarzyna Ziolkowska [b]	Alternate	Poland	No interests declared	
Ana Diniz Martins [a,b]	Member	Portugal	No interests declared	
Ines Ribeiro-Vaz [a]	Alternate	Portugal	No interests declared	
Roxana Dondera [a]	Member	Romania	No interests declared	
Alexandra - Maria Spurni [a]	Alternate (mandate ended on 16/02/2023)	Romania	No interests declared	
Irina Sandu [b]	Alternate (mandate started on 17/02/2023)	Romania	No interests declared	
Anna Mareková [a,b]	Member	Slovakia	No interests declared	
Lucia Kuráková [a,b]	Alternate	Slovakia	No interests declared	
Milena Radoha-Bergoc [a,b]	Alternate	Slovenia	No participation in final deliberations	3.1.1. Ibuprofen, pseudoephedrine (NAP) - EMEA/H/XXXX

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			and voting on:	11.1.1. Hydroxychloroquine (NAP) - DK/H/PSUFU/00001693/202104 PSUFU
Maria del Pilar Rayon [a,b]	Member	Spain	No interests declared	
Monica Martinez Redondo [a,b]	Alternate	Spain	No interests declared	
Ulla Wändel Liminga [a,b]	Member	Sweden	No interests declared	
Mari Thorn [a]	Alternate	Sweden	No interests declared	
Annalisa Capuano [a]	Member	Independent scientific expert	No interests declared	
Milou Daniel Drici [a,b]	Member	Independent scientific expert	No interests declared	
Maria Teresa Herdeiro [a,b]	Member	Independent scientific expert	No interests declared	
Patricia McGettigan [a,b]	Member	Independent scientific expert	No interests declared	
Hedvig Nordeng [a]	Member	Independent scientific expert	No interests declared	
Roberto Frontini [a,b]	Member	Healthcare Professionals' Representative	No restrictions applicable to this meeting	
Salvatore Messana [a]	Alternate	Healthcare Professionals' Representative	No interests declared	
Marko Korenjak [a]	Alternate	Patients' Organisation Representative	No restrictions applicable to this meeting	
Christelle Bizimungu [a]	Expert	Belgium	No restrictions applicable to this meeting	
Laurence de Fays [a]	Expert	Belgium	No interests declared	
Martine Sabbe [a]	Expert	Belgium	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Françoise Wuillaume [a]	Expert	Belgium	No interests declared	
Michaela Dlouhá [a]	Expert	Czechia	No interests declared	
Anna Kroupová [a]	Expert	Czechia	No interests declared	
Lucie Skálová [a]	Expert	Czechia	No interests declared	
Alexander Braathen [a]	Expert	Denmark	No interests declared	
Marianne Hald Clemmensen [a]	Expert	Denmark	No restrictions applicable to this meeting	
Kirsten Egebjerg Juul [a]	Expert	Denmark	No interests declared	
Annette Cleveland Nielsen [a]	Expert	Denmark	No restrictions applicable to this meeting	
Helle Gerda Olsen [a]	Expert	Denmark	No interests declared	
Aynur Sert [a]	Expert	Denmark	No interests declared	
Caroline Marie Voss [a,b]	Expert	Denmark	No interests declared	
Helve Vestman [a]	Expert	Estonia	No interests declared	
Violaine Closson Carella [a]	Expert	France	No interests declared	
Pauline Dayani [a]	Expert	France	No interests declared	
Camille De-Kervasdoue [a]	Expert	France	No interests declared	
Vincent Gazin [a]	Expert	France	No interests declared	
Marie-Caroline Pesquidous [a]	Expert	France	No restrictions applicable to this meeting	
Cecile Taddei [a]	Expert	France	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Dominique Gaston-Tischberger [a]	Expert	Germany	No interests declared	
Thomas Grueger [a]	Expert	Germany	No interests declared	
Dennis Lex [a,b]	Expert	Germany	No interests declared	
Dario Ortiz [a]	Expert	Germany	No interests declared	
Eamon O'Murchu [a]	Expert	Ireland	No interests declared	
Michal Pirozynski [a]	Expert	Malta	No interests declared	
Carla Herberts [a]	Expert	Netherlands	No interests declared	
Paul Ten Berg [a]	Expert	Netherlands	No interests declared	
Anja Van Haren [b]	Expert	Netherlands	No interests declared	
Carla Torre [a]	Expert	Portugal	No interests declared	
Natividad Galiana [a]	Expert	Spain	No restrictions applicable to this meeting	
Carmen Gallego [a]	Expert	Spain	No interests declared	
Consuelo Mejías [a]	Expert	Spain	No interests declared	
Charlotte Backman [a,b]	Expert	Sweden	No interests declared	
Annica Nordin [a]	Expert	Sweden	No interests declared	
Charlotte Welsh [a]	Expert	Sweden	No restrictions applicable to this meeting	
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