12 June 2023
EMA/PRAC/236189/2023
Human Medicines Division

Pharmacovigilance Risk Assessment Committee (PRAC)

Minutes of PRAC meeting on 13-16 March 2023

Chair: Sabine Straus – Vice-Chair: Martin Huber

Disclaimers

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

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

Note on access to documents

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

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Table of contents

1. Introduction

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

The Chairperson opened the meeting by welcoming all participants. The meeting was held remotely.

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

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

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

1.2. Agenda of the meeting on 13-16 March 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 06-09 February 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 06-09 February 2023 were published on the EMA website on 17 May 2023 (EMA/PRAC/185211/2023).

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

None

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

Summary of recommendation(s)/conclusions

- PRAC received feedback from the Scientific Advisory Group on Neurology (SAG-N) meeting held on 01 March 2023.
- PRAC adopted a second list of outstanding issues (LoOI) to be addressed by the MAHs of topiramate- and topiramate/phentermine-containing medicines in accordance with a revised timetable (EMA/PRAC/702489/2022 rev.3).

3.3. Procedures for finalisation

None

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

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

See Annex I 14.1.

4.2. New signals detected from other sources

None

4.3. Signals follow-up and prioritisation

4.3.1. Ceftriaxone (NAP)

Applicant(s): various

PRAC Rapporteur: Zane Neikena

Scope: Signal of risk of factor V inhibition

EPITT 19853 – Follow-up to November 2022

Background

For background information, see PRAC minutes November 2022.

The MAHs of the innovator ceftriaxone-containing medicinal products replied to the request for information on the signal of risk of factor V inhibition and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence in EudraVigilance, literature, the responses of the MAHs of the innovator ceftriaxone-containing medicinal products, PRAC agreed that there is insufficient evidence at present to establish a causal relationship between ceftriaxone and the risk of factor V inhibition. Therefore, PRAC concluded that no regulatory action is warranted at this stage.

Summary of recommendation(s)

- The MAHs for ceftriaxone-containing medicinal products should submit to EMA, within the next PSUR[6], a cumulative review of cases of factor V inhibition, including data from

[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
[6] DLP 26 May 2023

literature, spontaneous reports and clinical trials studies, as well as a discussion on possible biological plausibility and mechanism of this association.

See EMA/PRAC/103893/2023 published on 11 April 2023 on the EMA website.

4.3.2. Olaparib - LYNPARZA (CAP) - EMEA/H/C/003726/SDA 021

Applicant: AstraZeneca AB

PRAC Rapporteur: Amelia Cupelli

Scope: Signal of hepatocellular damage and hepatitis (HLT)

EPITT 19846 – Follow-up to November 2022

Background

For background information, see PRAC minutes November 2022.

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

Discussion

Having considered the available evidence in EudraVigilance, literature, nonclinical and clinical data and additional data submitted by the MAH, PRAC agreed that the MAH for Lynparza (olaparib) should provide further data in the context of this procedure.

Summary of recommendation(s)

- The MAH for Lynparza (olaparib) should submit to EMA, within 30 days, a review of cases of hepatic enzymes increased from post-marketing and clinical trials data, a review of new cases of hepatotoxicity from any source received after the cut-off date of 01 November 2022, as well as a proposal to amend the product information and/or the RMP, as warranted.
- A 30-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

See EMA/PRAC/103893/2023 published on 11 April 2023 on the EMA website.

4.3.3. Propofol (NAP)

Applicant(s): various

PRAC Rapporteur: Karen Pernille Harg

Scope: Signal of medication errors that could potentially lead to life-threatening/fatal cases

EPITT 19851 – Follow-up to November 2022

Background

For background information, see PRAC minutes November 2022.

The MAHs for propofol-containing products replied to the request for information on the signal of medication errors that could potentially lead to life-threatening/fatal cases and the responses were assessed by the Rapporteur.

Discussion

Having considered the available data in EudraVigilance, scientific literature and the responses from the MAHs for propofol-containing products, PRAC considered that there is sufficient evidence to establish a causal relationship between the risk of contamination of propofol and lack of compliance with recommendations for use in the product information, such as adequate aseptic procedures during preparation and administration of propofol, and the use of vials intended for single use in multiple patients. Therefore, PRAC agreed that an update of the product information is warranted to minimise the risk of contamination.

Summary of recommendation(s)

- The MAHs for propofol-containing products should submit to EMA, within 60 days, a variation to amend[7] the product information.

For the full PRAC recommendation, see EMA/PRAC/103893/2023 published on 11 April 2023 on the EMA website.

4.3.4. Voriconazole - VFEND (CAP) - EMEA/H/C/000387/SDA 092; VORICONAZOLE ACCORD (CAP); VORICONAZOLE HIKMA (CAP); NAP

Applicant: Accord Healthcare S.L.U. (Voriconazole Accord), Hikma Farmaceutica (Portugal), S.A. (Voriconazole Hikma), Pfizer Europe MA EEIG (Vfend), various

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Signal of drug interaction with flucloxacillin leading to subtherapeutic voriconazole levels

EPITT 19849 – Follow-up to November 2022

Background

For background information, see PRAC minutes November 2022.

Discussion

Having considered the evidence from the literature, post-marketing and clinical trials data, taking into account the plausible biological mechanism and the responses from the MAH for Vfend (voriconazole), PRAC agreed that a clinically significant drug interaction where flucloxacillin may decrease the plasma concentration of voriconazole when the medicinal products are administered concomitantly is a reasonable possibility.

Summary of recommendation(s)

- The MAHs for voriconazole- and flucloxacillin-containing medicinal products should submit to EMA, within 60 days, a variation to amend[8] the product information.

For the full PRAC recommendation, see EMA/PRAC/103893/2023 published on 11 April 2023 on the EMA website.

4.4. Variation procedure(s) resulting from signal evaluation

None

[7] Update of labelling of outer and immediate packaging
[8] Update of SmPC section 4.5. The leaflet is updated accordingly

5. Risk management plans (RMPs)

5.1. Medicines in the pre-authorisation phase

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

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

See also Annex I 15.1.

5.1.1. Alpelisib - EMEA/H/C/005468, Orphan

Applicant: Novartis Europharm Limited

Scope: Treatment of patients with severe manifestations of PIK3CA-related overgrowth spectrum

5.1.2. Atogepant monohydrate - EMEA/H/C/005871

Scope: Prophylaxis of migraine in adults who have at least 4 migraine days per month

5.1.3. Coronavirus (COVID-19) vaccine (recombinant protein receptor binding domain fusion heterodimer) – EMEA/H/C/006058

Scope: Booster for active immunisation to prevent COVID-19 in individuals 16 years of age and older who have previously received a messenger RNA (mRNA) COVID-19 vaccine

5.1.4. Piflufolastat (F 18) - EMEA/H/C/005520

Scope: Indicated in imaging in patients undergoing oncologic diagnostic procedures when increased expression of prostate specific membrane antigen is a diagnostic target

5.1.5. Tislelizumab - EMEA/H/C/005919, Orphan

Applicant: Novartis Europharm Limited

Scope: Treatment of adult patients with unresectable, recurrent, locally advanced or metastatic oesophageal squamous cell carcinoma after prior chemotherapy

5.1.6. Tislelizumab - EMEA/H/C/005542

Scope: Treatment of locally advanced or metastatic non-squamous non-small cell lung cancer in adults, treatment of locally advanced or metastatic squamous non-small cell lung cancer in adults, locally advanced or metastatic non-small cell lung cancer after prior chemotherapy in adults

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

See Annex I 15.2.

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

See also Annex I 15.3.

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

Applicant: MediWound Germany GmbH

PRAC Rapporteur: Martin Huber

Scope: Submission of the 24-months' clinical study report (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

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 NexoBrid, a centrally authorised product containing a concentrate of proteolytic enzymes enriched in bromelain. PRAC is responsible for providing advice to CHMP on the necessary updates to the RMP to support this procedure. For further background, see PRAC minutes November 2022.

Summary of advice

- The RMP version 8.2 for NexoBrid (concentrate of proteolytic enzymes enriched in bromelain) in the context of the variation under evaluation by CHMP is considered acceptable.

5.3.2. Remdesivir - VEKLURY (CAP) - EMEA/H/C/005622/II/0046

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Eva Jirsová

Scope: Update of sections 4.6 and 5.1 of the SmPC in order to update information on pregnancy and breast-feeding based on final results from study IMPAACT 2032 listed as a category 3 study in the RMP; this is a phase 4, prospective, open-label, non-randomised study to address PK and safety of remdesivir in pregnant women. The package leaflet is updated accordingly. The RMP version 5.2 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.

CHMP is evaluating a type II variation for Veklury, a centrally authorised product containing remdesivir. PRAC is responsible for providing advice to CHMP on the necessary updates to the RMP to support this procedure.

Summary of advice

- The RMP for Veklury (remdesivir) in the context of the variation procedure under evaluation by CHMP could be considered acceptable provided that an update to RMP version 5.2 is submitted.
- Regarding the list of safety specifications, PRAC agreed to remove 'safety in lactating women' as missing information from the RMP, however it should be kept as safety concern in the PSUR. In addition, PRAC did not support the removal of 'safety in pregnant women' as missing information from the RMP, as cumulative evidence available is considered too low to conclude on the absence of the risk for pregnant women and their infants. As a consequence, the MAH should amend the pharmacovigilance plan accordingly in order to address this safety concern. Finally, the MAH should provide their comments on the wording proposal for the product information regarding breastfeeding.

5.3.3. Sacubitril, valsartan - ENTRESTO (CAP) - EMEA/H/C/004062/X/0044/G

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Anette Kirstine Stark

Scope: Extension application to introduce a new pharmaceutical form associated with two new strengths (6 mg/6 mg granules in capsule for opening and 15 mg/16 mg granules in capsule for opening), grouped with a type II variation (C.I.6.a) in order to extend the indication to include treatment of children and adolescents aged one year or older with chronic heart failure with left ventricular systolic dysfunction, based on the results of Study PANORAMA-HF (CLCZ696B2319): a multicentre, open-label, study to evaluate safety, tolerability, pharmacokinetics and pharmacodynamics of sacubitril/valsartan followed by a 52-week randomised, double-blind, parallel group, active-controlled study to evaluate the efficacy and safety of sacubitril/valsartan compared with enalapril in paediatric patients from 1 month to < 18 years of age with heart failure due to systemic left ventricle systolic dysfunction. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.2 of the SmPC are being updated and the package leaflet is updated accordingly. In addition, an updated RMP version 4.0 was provided as part of the application. Further, the MAH requested a one-year extension of the market protection

Background

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

CHMP is evaluating an extension application for Entresto, a centrally authorised product containing sacubitril/valsartan to add a new pharmaceutical form associated with two new strengths (6 mg/6 mg granules in capsule for opening and 15 mg/16 mg granules in capsule for opening), grouped with a type II variation to add a new therapeutic indication for the treatment of children and adolescents aged one year or older with chronic heart failure with left ventricular systolic dysfunction. PRAC is responsible for providing advice to CHMP on the

necessary updates to the RMP to support this procedure. For further background, see PRAC minutes November 2022.

Summary of advice

- The RMP for Entresto (sacubitril, valsartan) in the context of the extension application under evaluation by CHMP could be considered acceptable provided that an update to RMP version 4.1 is submitted.
- Regarding the safety specifications, PRAC considered that 'long-term effects on growth, bone growth and mineralisation in the paediatric population' should be added as an important potential risk in the RMP. To further characterise this risk, the extension study PANOROMA-HF was considered for inclusion in the RMP as a category 3 PASS provided that further information regarding the PANORAMA-HF PASS, including the synopsis, could support the suitability of this study. Finally, PRAC considered that routine risk minimisation measures are sufficient to minimise the risks of the medicinal product in the proposed indication(s) in light of the current knowledge.

5.3.4. Sacubitril, valsartan - NEPARVIS (CAP) - EMEA/H/C/004343/X/0042/G

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Anette Kirstine Stark

Scope: Extension application to introduce a new pharmaceutical form associated with two new strengths (6 mg/6 mg granules in capsule for opening and 15 mg/16 mg granules in capsule for opening), grouped with a type II variation (C.I.6.a) in order to extend the indication to include treatment of children and adolescents aged one year or older with chronic heart failure with left ventricular systolic dysfunction, based on the results of Study PANORAMA-HF (CLCZ696B2319); a multicentre, open-label, study to evaluate safety, tolerability, pharmacokinetics and pharmacodynamics of sacubitril/valsartan followed by a 52-week randomised, double-blind, parallel group, active-controlled study to evaluate the efficacy and safety of sacubitril/valsartan compared with enalapril in paediatric patients from 1 month to < 18 years of age with heart failure due to systemic left ventricle systolic dysfunction. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.2 of the SmPC are being updated and the package leaflet is updated accordingly. In addition, an updated RMP version 4.0 was provided as part of the application. Further, the MAH requested a one-year extension of the market protection

Background

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

CHMP is evaluating an extension application for Neparvis, a centrally authorised product containing sacubitril/valsartan to add a new pharmaceutical form associated with two new strengths (6 mg/6 mg granules in capsule for opening and 15 mg/16 mg granules in capsule for opening), grouped with a type II variation to add a new therapeutic indication for the treatment of children and adolescents aged one year or older with chronic heart failure with left ventricular systolic dysfunction. PRAC is responsible for providing advice to CHMP on the necessary updates to the RMP to support this procedure. For further background, see PRAC minutes November 2022.

Summary of advice

- The RMP for Neparvis (sacubitril/valsartan) in the context of the variation procedure under evaluation by CHMP could be considered acceptable provided that an update to RMP version 4.1 is submitted.
- Regarding the safety specifications, PRAC considered that 'long-term effects on growth, bone growth and mineralisation in the paediatric population' should be added as an important potential risk in the RMP. To further characterise this risk, the extension study PANOROMA-HF was considered for inclusion in the RMP as a category 3 PASS provided that further information regarding the PANORAMA-HF PASS, including the synopsis, could support the suitability of this study. Finally, PRAC considered that routine risk minimisation measures are sufficient to minimise the risks of the medicinal product in the proposed indication(s) in light of the current knowledge.

5.3.5. Somapacitan - SOGROYA (CAP) - EMEA/H/C/005030/X/0006/G, Orphan

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Martin Huber

Scope: Extension application to add a new strength of 15 mg/1.5 mL solution for injection in pre-filled pen grouped with a type II variation C.I.6 to add a new indication 'Replacement of endogenous growth hormone (GH) in children and adolescents with growth failure due to growth hormone deficiency (GHD)', based on results from the completed main 52-week period of the confirmatory phase 3 trial (4263), supported with long-term data from the phase 2 trial (4172), up to week 208 completed. As a consequence, sections 4.1, 4.2, 4.3, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated and the package leaflet has been updated accordingly. A revised RMP version 3.0 was provided as part of the application

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 line extension for Sogroya, a centrally authorised product containing somapacitan, to include a new indication 'Replacement of endogenous growth hormone (GH) in children and adolescents with growth failure due to growth hormone deficiency (GHD)'. PRAC is responsible for providing advice to CHMP on the necessary updates to the RMP to support this procedure. For further background, see PRAC minutes November 2022.

Summary of advice

- The RMP version 3.1 for Sogroya (somapacitan) in the context of the procedure under evaluation by CHMP is considered acceptable.

6. Periodic safety update reports (PSURs)

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

See also Annex I 16.1.

6.1.1. Belantamab mafodotin - BLENREP (CAP) - PSUSA/00010869/202208

Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

Background

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

Based on the assessment of the PSUR, as well as the data provided by the MAH in the context of an oral explanation, PRAC reviewed the benefit-risk balance of Blenrep, a centrally authorised medicine containing belantamab mafodotin 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 Blenrep (belantamab mafodotin) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add corneal hypoesthesia as an undesirable effect with a frequency 'not known' and a warning/precaution regarding changes of corneal nerves. Therefore, the current terms of the marketing authorisation(s) should be varied[9].
- In the next PSUR, the MAH should provide information on the cases of optic neuropathy identified during the reporting period and discuss any potential causal association with belantamab mafodotin. The MAH should discuss the need for an update of the product information as warranted.

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

6.1.2. Coronavirus (COVID-19) vaccine (Ad26.COV2-S, recombinant) - JCOVDEN (CAP) - PSUSA/00010916/202208

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

Background

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

Discussion and conclusions

[9] 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.

During the PRAC meeting in March 2023, concerns were raised as regards: the well-established safety profile of this vaccine which includes serious adverse drug reactions that have been identified post marketing (i.e. thrombosis with thrombocytopenia syndrome (TTS), venous thromboembolism (VTE), immune thrombocytopenia (ITP), Guillain Barré syndrome (GBS), transverse myelitis, capillary leak syndrome (CLS) and cutaneous small vessel vasculitis), the fact that the vaccine is based on the original Wuhan strain, as well as the epidemiological evolution of the virus, the available possibilities for prevention and treatment of a SARS-CoV-2 infection, and the current risks for serious outcomes of the disease.

To further contextualise the concerns raised above, additional consultations with Emergency Task Force (ETF) and CHMP were requested to take place during the review of the current PSUR.

The PRAC recommendation will therefore be adopted in the next PRAC plenary meeting (11-14 April 2023).

6.1.3. Palbociclib - IBRANCE (CAP) - PSUSA/00010544/202208

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Evaluation of a PSUSA procedure

Background

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

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Ibrance, a centrally authorised medicine containing palbociclib 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 Ibrance (palbociclib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add venous thromboembolism as a warning and as an undesirable effect with a frequency 'common', as well as to add palmar-plantar erythrodysaesthesia syndrome as an undesirable effect with a frequency 'common'. Therefore, the current terms of the marketing authorisation(s) should be varied[10].
- In the next PSUR, the MAH should present a cumulative review of cases of acute kidney injury, including a discussion on possible biological mechanisms, especially in the context of a potential class effect. In addition, the MAH should provide a cumulative review of cases of gastric antral vascular ectasia (GAVE) and gastrointestinal haemorrhages, including a discussion of a potential biological mechanism for the association, with a focus on gastrointestinal disorders causing anaemia. The MAH should also discuss the need for an update of the product information as warranted. In addition,

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

the MAH should update the list of safety concerns within the PSUR and include long-term use as missing information.

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

6.1.4. Patisiran - ONPATTRO (CAP) - PSUSA/00010715/202208

Applicant: Alnylam Netherlands B.V.

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 Onpattro, a centrally authorised medicine containing patisiran 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 Onpattro (patisiran) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add dysphonia as a symptom of infusion-related reactions. Therefore, the current terms of the marketing authorisation(s) should be varied[11].
- In the next PSUR, the MAH should continue to provide a review of fatal cases and of the reports related to the important potential risk of 'consequences of Vitamin A deficiency' in order to determine the adherence to the advice on vitamin A supplementation during treatment with patisiran as a risk minimisation measure to prevent ocular toxicity. In addition, the MAH should provide an updated review of cases of mild transaminases elevated, including data from clinical trials and post-marketing setting. The MAH should also discuss the need for an update of the product information as warranted.

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

6.1.5. Sacubitril, valsartan - ENTRESTO (CAP); NEPARVIS (CAP) - PSUSA/00010438/202207

Applicant(s): Novartis Europharm Limited

PRAC Rapporteur: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

[11] 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.

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 Entresto and Neparvis, centrally authorised medicines containing sacubitril/valsartan 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 Entresto and Neparvis (sacubitril/valsartan) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add hyponatremia as an undesirable effect with a frequency 'uncommon'. Therefore, the current terms of the marketing authorisation(s) should be varied[12].
- In the next PSUR, the MAH should provide a cumulative review of cases of bone growth and density/bone mineralisation as part of the off-label use in the paediatric population. In addition, the MAH should provide a cumulative review of new fatal cases, as well as of cases of eye disorders, including literature evidence supporting a causal relationship based on a possible class effect.

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

6.1.6. Tisagenlecleucel - KYMRIAH (CAP) - PSUSA/00010702/202208

Applicant: Novartis Europharm Limited, ATMP[13]

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 Kymriah, a centrally authorised medicine containing tisagenlecleucel 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 Kymriah (tisagenlecleucel) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.

[12] 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
[13] Advanced therapy medicinal product

- The MAH should submit to EMA, within 90 days, further data on cases of secondary malignancies, as well as of haematological neoplasm.

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

6.1.7. Voxelotor - OXBRYTA (CAP) - PSUSA/00010983/202208

Applicant: Global Blood Therapeutics Netherlands B.V.

PRAC Rapporteur: Jo Robays

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 Oxbryta, a centrally authorised medicine containing voxelotor 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 Oxbryta (voxelotor) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add drug reaction with eosinophilia and systemic symptoms (DRESS) as a warning and as an undesirable effect with frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[14].
- In the next PSUR, the MAH should submit cumulative reviews of cases of DRESS, angioedema and pruritis, and discuss the need to update the product information as warranted. Moreover, the MAH should provide a review of cases of pulmonary embolism/deep vein thrombosis and alanine aminotransferase increase, including data from clinical trials, spontaneous reports and literature. In addition, the MAH should provide a review of cases of safety issues related to abrupt discontinuation of voxelotor and discuss the need to warn patients and HCPs on the risks of abrupt discontinuation of the medicinal product. The MAH should also provide a review of cases of angina pectoris and arthralgia, as well as discuss the associated risks that could be expected due to the concomitant administration of voxelotor and erythropoiesis stimulating agents.

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.

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

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

See also Annex I 16.2.

6.2.1. Oxybutynin - KENTERA (CAP); NAP - PSUSA/00002253/202207

Applicant(s): Teva B.V. (Kentera), various

PRAC Rapporteur: Jo Robays

Scope: Evaluation of a PSUSA procedure

Background

Oxybutynin is a tertiary amine antimuscarinic and has both direct antispasmodic action on the smooth muscle of the bladder detrusor muscle as well as anticholinergic action in blocking the muscarinic effects of acetylcholine on smooth muscle, indicated for urinary incontinence, urgency and frequency in unstable bladder conditions, pollakiuria, cystitis, in the control of vesical hyperactivity seen after surgery of the bladder or prostate or accompanying cystitis, subject to certain conditions.

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(s), PRAC reviewed the benefit-risk balance of Kentera, a centrally authorised medicine containing oxybutynin, and nationally authorised medicines containing oxybutynin 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 oxybutynin-containing product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add palpitation as an undesirable effect with a frequency 'common'. In addition, the product information should be updated to clarify that the patches must not be cut or divided. Therefore, the current terms of the marketing authorisations should be varied[15].
- In the next PSUR, the MAH(s) should provide a cumulative review of cases of falls and fractures, and should discuss the need to update the product information as warranted. The MAH(s) should also update the PSUR list of safety concerns and add dementia as an important potential risk.

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.

[15] Update of SmPC section 4.2, 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion

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

See also Annex I 16.3.

6.3.1. Ketorolac[16] (NAP) - PSUSA/00001811/202207

Applicant(s): various

PRAC Lead: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

Background

Ketorolac is a potent analgesic agent of the non-steroidal anti-inflammatory drug (NSAID) class with analgesic, anti-inflammatory, and antipyretic properties indicated for the short-term management of moderate to severe acute pain that requires analgesia at the opioid level.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing ketorolac 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 ketorolac-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add gastro-intestinal anastomotic leak as a warning. Therefore, the current terms of the marketing authorisation(s) should be varied[17].
- In the next PSUR, the MAH(s) should provide a cumulative review of cases of arterial thrombotic events and discuss the need to update the product information as warranted.

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

6.3.2. Meloxicam (NAP) - PSUSA/00010474/202207

Applicant(s): various

PRAC Lead: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

Background

Meloxicam is a non-steroidal anti-inflammatory drug (NSAID) with anti-inflammatory, analgesic and antipyretic properties, indicated in the symptomatic treatment of painful

[16] Systemic formulation(s) only
[17] Update of SmPC section 4.4. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position.

osteoarthritis (arthrosis, degenerative joint disease), rheumatoid arthritis and ankylosing spondylitis.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing meloxicam 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 meloxicam-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add fixed drug eruption as a warning and as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[18].
- In the next PSUR, the MAH(s) should continue to monitor cases of drug reaction with eosinophilia and systemic symptoms (DRESS) and of intestinal diaphragm-like strictures (intestinal stenosis and intestinal diaphragm disease).

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

6.4. Follow-up to PSUR/PSUSA procedures

See Annex I 16.4.

6.5. Variation procedure(s) resulting from PSUSA evaluation

See also Annex I 16.5.

6.5.1. Erlotinib - TARCEVA (CAP) - EMEA/H/C/000618/II/0071

Applicant: Roche Registration GmbH

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Update of section 4.8 of the SmPC in order to provide a single table listing all ADRs following PSUSA/00001255/202111. 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.

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 current format of SmPC section 4.8 to improve readability and accommodate listing of adverse drug reactions (ADRs) reported in the post-marketing setting without a known frequency. PRAC is

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

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 July 2022.

Summary of recommendation(s)

- Based on the available data and the Rapporteur's assessment, PRAC agreed that the product information should be updated to improve readability of the list of adverse reactions from clinical trials data and post-marketing setting.

6.6. Expedited summary safety reviews[19]

6.6.1. Coronavirus (COVID-19) vaccine (recombinant, adjuvanted) - NUVAXOVID (CAP) - EMEA/H/C/005808/MEA 014.8

Applicant: Novavax CZ, a.s.

PRAC Rapporteur: Gabriele Maurer

Scope: Ninth expedited summary safety report (SSR) for Nuvaxovid (COVID-19 vaccine (recombinant, adjuvanted)) 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 ninth SSR for the safety monitoring of Nuvaxovid (COVID-19 vaccine (recombinant, adjuvanted)). 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, taking into account the low uptake of the vaccine, as well as the characterisation of the safety profile, and since no specific topics that would require prompt review have been identified in the current SSR. The safety profile of Nuvaxovid (COVID-19 vaccine (recombinant, adjuvanted)) will continue to be monitored in future PSURs, with the routine signal detection activities in place, as well as within the additional pharmacovigilance activities as outlined in the RMP of Nuvaxovid (COVID-19 vaccine (recombinant, adjuvanted)).

7. Post-authorisation safety studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)[20]

See Annex I 17.1.

[19] 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

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

7.2. Protocols of PASS non-imposed in the marketing authorisation(s)[21]

See Annex I 17.2.

7.3. Results of PASS imposed in the marketing authorisation(s)[22]

See also Annex I 17.3.

7.3.1. Retinoids[23]: acitretin (NAP), alitretinoin (NAP), isotretinoin (NAP) - EMEA/H/N/PSR/J/0040

Applicant: F.Hoffmann-La Roche Ltd.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Final study report for a Drug Utilisation Study to describe the prescribing practices before and after the update of the pregnancy prevention programme (PPP) for the oral retinoids acitretin, alitretinoin and isotretinoin in order to assess the effectiveness of these updated risk minimisation measures (RMMs) in women of childbearing potential, following an Article 31 referral on retinoid-containing medicinal products (EMEA/H/A-31/1446)

Background

Retinoids are vitamin A derivatives indicated for the treatment of several conditions mainly affecting the skin, including severe acne and psoriasis. Some retinoids are also used to treat certain forms of cancer.

In line with the conclusions reached in February 2018 of the referral procedure under Article 31 of Directive 2001/83/EC (EMEA/H/A-31/1446) conducted by PRAC for retinoid-containing medicinal products, the MAHs of oral retinoids acitretin, alitretinoin and isotretinoin were required as a condition to the marketing authorisations (Annex IV) to conduct a drug utilisation study to assess the effectiveness of the updated risk minimisation measures in women of childbearing potential resulting from this referral procedure. The final study report was submitted to EMA by the MAH Roche. PRAC discussed the final study results.

Summary of recommendation(s) and conclusions

- Based on the review of the final report of the non-interventional PASS entitled 'Evaluation of the effectiveness of pregnancy prevention programme (PPP) for oral retinoids (acitretin, alitretinoin, and isotretinoin): a European before-after drug utilisation study (DUS) using secondary data', PRAC considered that an RSI (request for supplementary information) was necessary before a recommendation could be issued.
- PRAC agreed that a discussion needs to be provided regarding the low effectiveness of risk minimisation measures as assessed by contraceptive use, pregnancy testing and pregnancies exposed to oral retinoids and how can this lack of effectiveness be better understood. As part of the discussion, the MAH should provide a comprehensive literature review of all studies evaluating the effectiveness of the updated risk minimisation measures implemented since the referral, in order to better understand the implementation of the pregnancy prevention programme (PPP) for oral retinoids

[21] 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
[22] In accordance with Article 107p-q of Directive 2001/83/EC
[23] Oral presentations

across the EU. In addition, the consortium should discuss whether a study is necessary to investigate barriers and reasons why certain measures part of the PPP are not always followed in clinical practice and provide a synopsis for this study.

- The MAH should submit responses to the RSI by 18 July 2023.

7.3.2. Valproate[24] (NAP) - EMEA/H/N/PSR/J/0036

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

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: 'Survey among HCP to assess knowledge of healthcare professionals (HCP) and behaviour with regards to pregnancy prevention programme (PPP) as well as receipt/use of a direct healthcare professional communication (DHPC) and educational materials' and 'Survey among patients to assess knowledge of the patients with regards to PPP as well as receipt/use of educational materials'

Background

Sodium valproate is indicated for the treatment of epilepsy and manic episodes when lithium is contraindicated or not tolerated. Valproate is also indicated in the prophylaxis of migraine attacks in some EU Member States.

The MAH Sanofi-Aventis Recherche & Développement, on behalf of a consortium, submitted to EMA the final results version 1.0 of the 'surveys among HCP and patients to assess their knowledge and behaviour with respect to the new risk minimisation measures (RMM) for valproate use in Europe'. For further background, see PRAC minutes November 2021, PRAC minutes June 2022, PRAC minutes November 2022 and PRAC minutes January 2023.

Summary of recommendation(s) and conclusions

- Based on the review of the final report of the non-interventional PASS entitled 'Survey among HCP to assess knowledge of healthcare professionals (HCP) and behaviour with regards to pregnancy prevention programme (PPP) as well as receipt/use of DHPC and educational materials' and 'Survey among patients to assess knowledge of the patients with regards to PPP as well as receipt/use of educational materials' and the MAH's responses to the RSI, PRAC considered that a further request for supplementary information (RSI) was necessary before a recommendation could be issued.
- PRAC discussed the 'core version of the HCP guide' (simplified, restructured by HCP's role/indication and user tested) as well as the 'core version of the patient guide' including a dedicated section for young girls/adolescents, informing about the risks of valproate and actions to be taken when girls experience their first period while on treatment with valproate. PRAC agreed that a further update and user testing of this new section for young girls/adolescents in the patient guide is required. PRAC also noted the input received from the patients and healthcare professional organisations in the context of a stakeholder meeting hosted by EMA to better understand potential barriers and useful enables for the successful implementation of valproate RMMs in clinical practice.
- The MAH should submit responses to the RSI by 20 June 2023.

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

7.4. Results of PASS non-imposed in the marketing authorisation(s)[25]

See also Annex I 17.4.

7.4.1. Golimumab - SIMPONI (CAP) - EMEA/H/C/000992/II/0111

Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of section 4.6 of the SmPC in order to update information on pregnancy based on final results from PASS study CNTO148ART4001 listed as a category 3 study in the RMP; this is an observational prospective cohort study to collect and analyse information pertaining to pregnancy outcomes of women exposed to golimumab during pregnancy. The RMP version 23.2 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 Simponi (golimumab), the MAH conducted a non-imposed non-interventional PASS (CNTO148ART4001, listed as category 3 study in the RMP) to study the exposure to golimumab during pregnancy in patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis: a review and analysis of birth outcomes from the Swedish, Danish, and Finnish medical birth registers. 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).
- The MAH should submit a response to RSI within 30 days to EMA. A 30-day assessment timetable will be followed.

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

See Annex I I 17.5.

7.6. Others

See also Annex I 17.6.

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

7.6.1. Coronavirus (COVID-19) vaccine (inactivated, adjuvanted, adsorbed) - COVID-19 VACCINE (INACTIVATED, ADJUVANTED) VALNEVA (CAP) - EMEA/H/C/006019/MEA 001.1

Applicant: Valneva Austria GmbH

PRAC Rapporteur: Gabriele Maurer

Scope: Position paper on the design and conduct of a pregnancy exposure registry (C-VIPER) to estimate the risk of the most common obstetric outcomes, i.e. pregnancy losses, placentation disorders, gestational diabetes, premature delivery, and COVID-19, neonatal outcomes, i.e. congenital anomalies, low birth weight for gestational age, neonatal intensive care unit admission, and COVID-19, among pregnant women exposed to COVID-19 Vaccine (inactivated, adjuvanted) Valneva from 30 days prior to the first day of the last menstrual period (LMP) to end of pregnancy and their offspring relative to a matched unexposed reference group

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 Valneva (COVID-19 vaccine (inactivated, adjuvanted, adsorbed)), the MAH submitted a position paper regarding the feasibility and conduct of the non-interventional PASS Pregnancy Registry of Women Exposed to COVID-19 Vaccine (inactivated, adjuvanted) Valneva immediately before or during Pregnancy as part of the C-VIPER Registry Consortium (Pregistry-sponsored). PRAC was requested to provide advice to CHMP on the position submitted by the MAH.

Summary of advice

- Based on the available data and the Rapporteur's review, PRAC considered that, although the low uptake of the vaccine is acknowledged and the available population suitable for vaccination with COVID-19 vaccine Valneva is limited, the MAH should explore other options to derive effectiveness and safety, including the possibility to expand the studies to further countries/study centres in order to collect necessary data to fulfil the requirements of the study.
- The MAH should reassess the safety study objectives and feasibility and submit an updated justification by 30 September 2023.

7.6.2. Coronavirus (COVID-19) vaccine (inactivated, adjuvanted, adsorbed) - COVID-19 VACCINE (INACTIVATED, ADJUVANTED) VALNEVA (CAP) - EMEA/H/C/006019/MEA 002.1

Applicant: Valneva Austria GmbH

PRAC Rapporteur: Gabriele Maurer

Scope: Position paper on the design and conduct of a PASS protocol to estimate the incidence of adverse events of special interest (AESIs), including the potential risk of vaccine associated enhanced disease (VAED) and vaccine associated respiratory disease (VAERD), that are medically attended following the administration of COVID-19 Vaccine (inactivated, adjuvanted) Valneva in the real-world immunisation setting. A retrospective

study using health care databases

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 Valneva (COVID-19 vaccine (inactivated, adjuvanted, adsorbed)), the MAH submitted a position paper regarding the feasibility and conduct of the non-interventional to estimate the incidence of AESIs, including the potential risk of VAED and VAERD, that are medically attended following the administration of COVID-19 Vaccine (inactivated, adjuvanted) Valneva in the real-world immunisation setting. PRAC was requested to provide advice to CHMP on the position submitted by the MAH.

Summary of advice

- Based on the available data and the Rapporteur's review, PRAC considered that, although the low uptake of the vaccine is acknowledged and the available population suitable for vaccination with COVID-19 vaccine Valneva is limited, the MAH should explore other options to derive effectiveness and safety, including the possibility to expand the studies to further countries/study centres in order to collect necessary data to fulfil the requirements of the study.
- The MAH should reassess the safety study objectives and feasibility, and submit an updated justification by 30 September 2023.

7.6.3. Coronavirus (COVID-19) vaccine (inactivated, adjuvanted, adsorbed) - COVID-19 VACCINE (INACTIVATED, ADJUVANTED) VALNEVA (CAP) - EMEA/H/C/006019/MEA 006.2

Applicant: Valneva Austria GmbH

PRAC Rapporteur: Gabriele Maurer

Scope: Position paper on the design and conduct of a post-authorisation effectiveness study (PAES) to estimate effectiveness against hospitalisation due to laboratory-confirmed SARS-CoV-2 in severe acute respiratory infection (SARI) patients who have been vaccinated with COVID-19 Vaccine (inactivated, adjuvanted) Valneva

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 Valneva (COVID-19 vaccine (inactivated, adjuvanted, adsorbed)), the MAH submitted a position paper regarding the feasibility and conduct of the PAES to estimate effectiveness against hospitalization due to laboratory-confirmed SARS-CoV-2 in SARI patients who have been vaccinated with COVID-19 Vaccine (inactivated, adjuvanted) Valneva. PRAC was requested to provide advice to CHMP on the position submitted by the MAH.

Summary of advice

- Based on the available data and the Rapporteur's review, PRAC considered that,

although the low uptake of the vaccine is acknowledged and the available population suitable for vaccination with COVID-19 vaccine Valneva is limited, the MAH should explore other options to derive effectiveness and safety, including the possibility to expand the studies to further countries/study centres in order to collect necessary data to fulfil the requirements of the study.

- The MAH should reassess the safety study objectives and feasibility, and submit an updated justification by 30 September 2023.

7.7. New Scientific Advice

None

7.8. Ongoing Scientific Advice

None

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

None

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. Testosterone (NAP) - EE/H/PSUFU/00010631/202112; EE/H/PSUFU/00002908/202112

Applicant(s): various

PRAC Lead: Maia Uusküla

Scope: PRAC consultation on the PSUR single assessment (PSUSA) procedure follow-up measures (PSUFUs) referring to all formulations of testosterone (apart from topical use) (EE/H/PSUFU/00010631/202112) and to testosterone products of topical use (EE/H/PSUFU/00002908/202112) evaluating the labelling updates concerning the risk of central serous chorioretinopathy for all formulations of products containing testosterone, as per the conclusions of the PSUSA procedures PSUSA/00010631/202112 (testosterone all formulations apart from topical use) and PSUSA/00002908/202112 (testosterone topical use) concluded in September 2022, on request of Estonia

Background

Testosterone is a steroid hormone that belongs to the androgens pharmaco-therapeutic group and it is indicated for testosterone replacement therapy in males with conditions associated with primary and secondary hypogonadism (either congenital or acquired) when testosterone deficiency has been confirmed by clinical features and biochemical tests.

In the context of the evaluation of two PSUFU procedures evaluating the labelling updates concerning the risk of central serous chorioretinopathy for all formulations of products containing testosterone, PSUSA procedures PSUSA/00010631/202112 (testosterone all formulations apart from topical use) and PSUSA/00002908/202112 (testosterone topical use) concluded in September 2022, Estonia requested PRAC advice on its assessment.

Summary of advice

- Based on the review of the available information, PRAC concurred with the LMS assessment and considered that there is currently insufficient evidence to update the product information of systemic and topical testosterone-containing products at this stage. Moreover, PRAC agreed that central serous chorioretinopathy (CSCR) associated with testosterone replacement therapy should remain under close monitoring in the upcoming PSURs for testosterone (all formulation apart from topical use) and testosterone (topical use) and should be included as an important potential risk in the summary of safety concerns of the PSURs for testosterone (all formulation apart from topical use) and testosterone (topical use).

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 Tania Schink as the new independent scientific expert nominated by the European Commission (mandate started on 06 March 2023). The PRAC Chair also thanked Ronan Grimes for his contribution as PRAC alternate for Ireland.

12.1.2. Vote by proxy

None

12.2. Coordination with EMA Scientific Committees or CMDh-v

None

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

None

12.4. Cooperation within the EU regulatory network

12.4.1. Coronavirus (COVID-19) pandemic - update

The EMA Secretariat updated PRAC on the activities of the COVID-19 EMA pandemic Task Force (ETF), including an overview of 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 updated PRAC on monkey pox studies and influenza as well as 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

None

12.9. Pharmacovigilance audits and inspections

12.9.1. Pharmacovigilance systems and their quality systems

None

12.9.2. Pharmacovigilance inspections

None

12.9.3. Pharmacovigilance audits

None

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

12.10.1. Periodic safety update reports

None

12.10.2. Granularity and Periodicity Advisory Group (GPAG)

PRAC lead: Menno van der Elst, Maia Uusküla

The EMA Secretariat presented to PRAC on behalf of GPAG the recommendation from the EMA/HMA tactical group on resourcing on the implementation of the Union reference date

(EURD) tool predictions on PSUR frequencies for active substances with data lock points (DLP) in 2025, encompassing a set of approximately 1,000 entries for which PSUR assessments were initially deferred since the PSUR assessment of other active substances was prioritised at the time of the EURD List creation.

The EURD tool is a statistical tool to support the determination of frequencies on a risk-based approach, in line with GVP Module VII. The statistical tool uses readily available data (e.g., age of product, number of ICSRs, number of referrals, number of signals evaluated) to determine a PSUR frequency.

All impacted entries will receive a new DLP and a new frequency for the first PSUR assessment. The implementation of these changes in the EURD List is planned in different phases, starting from April 2023.

The EMA Secretariat also presented an update of activities of the GPAG workplan for 2023.

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 March 2023, 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 March 2023, the updated EURD list was adopted by the CHMP and CMDh at their March 2023 meetings and published on the EMA website, see: Home> Human Regulatory>Post-authorisation>Pharmacovigilance>Periodic safety update reports>> List of Union reference dates and frequency of submission of periodic safety update reports (PSURs)

12.10.5. Coronavirus (COVID-19) pandemic - Consideration on core requirements for PSURs of COVID-19 vaccines - corePSUR19 guidance

At the organisational, regulatory and methodological matters matters (ORGAM) meeting held on 30 March 2023, the EMA Secretariat presented to PRAC a proposal to discontinue the corePSUR19 guidance which was developed in 2021 in order to provide guidance and highlight requirements when drafting the PSURs of COVID-19 vaccines. Due to the changes in the evolution of the pandemic and the vaccination campaigns, the usage pattern of the different vaccines has led to different requirements by vaccine, depending also on the experience gained in the past years following various regulatory procedures and on the available evidence from clinical trials/ real world evidence. Therefore, PRAC acknowledged the discontinuation of the corePSUR19 guidance and agreed that the standard procedures for the preparation of PSURs as defined in good pharmacovigilance practices (GVP) guidelines are now sufficient to continue monitoring the safety profile of the COVID-19 vaccines.

12.10.6. Periodic safety update reports single assessment (PSUSA) – review of 'other considerations' section in the assessment report

PRAC lead: Sabine Straus

The PRAC Chair presented to PRAC a proposal to remove 'other consideration' section from the PSUSA assessment report (AR) for all PSUSA types (CAP only, mix CAP/NAP and NAPs only) in order to streamline the PSUSA AR and the discussions at both PRAC and CMDh levels. Comments were raised during the discussion which triggered the need for follow-up at a subsequent PRAC plenary meeting (10-12 May 2023). It was also agreed to present the topic at CMDh level.

12.10.7. Periodic safety update reports single assessment (PSUSA) – review of PSUSA assessment report templates for nationally authorised products (NAPs) only

At the organisational, regulatory and methodological matters (ORGAM) meeting held on 30 March 2023, the EMA Secretariat in charge of the PSUR process presented to PRAC the revision of the PSUSA report template for NAPs only on how to reflect a direct healthcare professional communication (DHPC) recommendation as an outcome of a PSUSA procedure. PRAC agreed with the proposed revisions to the assessment report (AR) template and it was also agreed to apply the revisions to all PSUSA AR templates for all procedure types (CAP, mix CAP/NAP and NAPs only, as applicable). The revisions of the AR templates are for implementation with the procedures starting in May 2023.

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 on 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, 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 – annual report 2022

At the organisational matters, regulatory and methodological (ORGAM) meeting held on 30 March 2023, the EMA Secretariat presented the annual report related to EudraVigilance activity on the reporting of adverse drug reactions as well as an analysis on signal detection and signal outcomes for the year 2022.

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 medicinal products containing methotrexate for weekly administration: risk awareness and adherence

PRAC lead: Martin Huber, Nikica Mirošević Skvrce

The PRAC Sponsors (Martin Huber and Nikica Mirošević Skvrce) presented to PRAC the study report on the impact of EU label changes for methotrexate-containing medicinal products administered weekly which was commissioned by EMA under the remit of the PRAC Impact Strategy in context of referral procedure EMEA/H/A-31/1463. The study investigated risk awareness and adherence to risk minimisation measures introduced as an outcome of the referral to avoid dosing errors in patients incorrectly taking methotrexate-containing medicines daily instead of weekly. In line with the revised process for regulatory follow-up on impact research, the PRAC Sponsors' critical appraisal of the results was discussed, including the need for regulatory follow-up and stakeholder communication. PRAC agreed that there was no need for stakeholder communication at this point in time and that the impact study results should be followed up in the upcoming PSUR.

12.21. Others

12.21.1. IRIS platform – update on SharePoint functionality

At the organisational, regulatory and methodological matters (ORGAM) meeting held on 30 March 2023, the EMA Secretariat presented to PRAC a new IRIS functionality (IRIS SharePoint) where EMA and PRAC members/alternates can collaborate on certain documents. PRAC will receive a further communication on the timelines before starting using this new functionality.

12.21.2. Pharmacovigilance business team – activities and work plan for 2023

The EMA Secretariat presented to PRAC the Pharmacovigilance business team mandate, a summary of the activities performed in 2022, as well as the draft work plan for 2023. PRAC members are welcomed to send their comments on the workplan by 31 March 2023.

13. Any other business

None

14. Annex I – Signals assessment and prioritisation[26]

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[27].

14.1. New signals detected from EU spontaneous reporting systems

14.1.1. Dupilumab – DUPIXENT (CAP)

Applicant: Sanofi Winthrop Industrie

PRAC Rapporteur: Kimmo Jaakkola

Scope: Signal of weight decreased, abnormal loss of weight, cachexia, body mass index decreased

EPITT 19897 – New signal

Lead Member State(s): FI

14.1.2. Nusinersen – SPINRAZA (CAP)

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of arachnoiditis

EPITT 19896 – New signal

Lead Member State(s): SE

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).

[26] 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

[27] 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

15.1.1. Dabigatran etexilate - EMEA/H/C/006023

Scope: Prevention of venous thromboembolic events

15.1.2. Sugammadex - EMEA/H/C/006083

Scope: Reversal of neuromuscular blockade induced by rocuronium or vecuronium in adults

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. Dasabuvir - EXVIERA (CAP) - EMEA/H/C/003837/WS2430/0056; ombitasvir, paritaprevir, ritonavir - VIEKIRAX (CAP) - EMEA/H/C/003839/WS2430/0068

Applicant(s): AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Submission of an updated RMP version 7.1 for Viekirax and Exviera to include the completion of studies B16-959, B20-146, M14-423 (TOPAZ-I) and M14-222 (TOPAZ-II), following the outcome of EMEA/H/C/PSR/J/0038, EMEA/H/C/WS2216 and EMEA/H/C/WS2304, respectively. The MAH proposes to remove the emergence and recurrence of hepatocellular carcinoma as potential risks and update the related pharmacovigilance activities and other sections of the RMPs

15.2.2. Dexamethasone - OZURDEX (CAP) - EMEA/H/C/001140/II/0044

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Submission of an updated Annex II and RMP version 11 in order to remove additional risk minimisation measure: Patient guide, audio CD (where required)

15.2.3. Elasomeran - SPIKEVAX (CAP) - EMEA/H/C/005791/II/0085/G

Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Grouped application comprising of : 1) submission of RMP version 6.0 to add Spikevax bivalent Original / Omicron BA.4-5 vaccine (mRNA-1273.222), to update studies mRNA-1273-P904, mRNA-1273-P905 and mRNA-1273-P910 in the Pharmacovigilance Plan to include exposure to Spikevax bivalent vaccines, to update the INN to elasomeran/davesomeran, and to reclassify studies mRNA-1273-P205 from category 2 to category 3 studies in the Pharmacovigilance Plan; 2) submission of the final clinical study report (CSR) from study mRNA-1273-P201, a Phase 2a, Randomised, Observer-Blind, Placebo-Controlled, Dose-Confirmation Study to Evaluate the Safety, Reactogenicity, and Immunogenicity of mRNA-1273 SARS-CoV-2 Vaccine in Adults ⩾= 18 Years listed as a category 3 study including addition of clinical trial exposure data for part C of the study

mRNA-1273-P201

15.2.4. Elosulfase alfa - VIMIZIM (CAP) - EMEA/H/C/002779/II/0040, Orphan

Applicant: BioMarin International Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Submission of an updated RMP version 6.0 in order to correct the objectives of Morquio A registry study (MARS) in RMP to be consistent with version 6 of the protocol and to update the "m ethod used to calculate exposure" due to GDPR restrictions following the assessment of procedures PSA/S/0062 and PSUSA/00010218/202102

15.2.5. Glycopyrronium - SIALANAR (CAP) - EMEA/H/C/003883/II/0026

Applicant: Proveca Pharma Limited

PRAC Rapporteur: Zane Neikena

Scope: Submission of an updated RMP version 3.1 in order to remove study PRO/GLY/004: a drug utilisation study (DUS) to assess the efficacy of risk minimisation measures for Sialanar

15.2.6. Miglustat - ZAVESCA (CAP) - EMEA/H/C/000435/II/0076

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Mari Thorn

Scope: Submission of an updated RMP version 15.1 in order to remove risks in line with GVP module V revision 2. The MAH has also taken the opportunity to introduce minor changes, such as update of the post marketing exposure data and alignment with the latest Company EU-RMP Template

15.2.7. Obeticholic acid - OCALIVA (CAP) - EMEA/H/C/004093/II/0039, Orphan

Applicant: Advanz Pharma Limited

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Submission of an updated RMP version 2.0 in order to change to EU Qualified Person for Pharmacovigilance (QPPV), update the list of safety concerns and include study data for 747-302 and 747-401

15.2.8. Palivizumab - SYNAGIS (CAP) - EMEA/H/C/000257/II/0131

Applicant: AstraZeneca AB

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Submission of an updated RMP version 2.0 in order to remove from the list of safety concerns "Anaphylaxis, Anaphylactic shock, and Hypersensitivity" and "Medication error of mixing lyophilised and liquid palivizumab before injection". In addition, the MAH took the opportunity to apply the revised template

15.2.9. Sacubitril, valsartan - ENTRESTO (CAP) - EMEA/H/C/004062/WS2434/0049; NEPARVIS (CAP) - EMEA/H/C/004343/WS2434/0047

Applicant(s): Novartis Europharm Limited

PRAC Rapporteur: Anette Kirstine Stark

Scope: Submission of an updated RMP version 5.0 for Ernestro and its duplicate marketing authorisation Neparvis to update the milestones for MEA 002 (study CLCZ696B2014) and MEA 004 (study CLCZ696B2015) from 31 December 2022 to 30 June 2024

15.2.10. Smallpox vaccine (live modified vaccinia virus Ankara) - IMVANEX (CAP) - EMEA/H/C/002596/II/0081

Applicant: Bavarian Nordic A/S

PRAC Rapporteur: Gabriele Maurer

Scope: Submission of an updated RMP version 9.1 in order to update the safety specifications in line with extension of the indication to "active immunisation against smallpox, monkeypox and disease caused by vaccinia virus in adults", update the missing information from the list of safety concerns, differentiate routine pharmacovigilance activities and additional pharmacovigilance activities, addition of non-BN (Bavarian Nordic) sponsored clinical study SEMVAc to additional pharmacovigilance activities and deletion of paediatric study POX-MVA-035 upon request by PRAC following the assessment of procedure EMEA/H/C/002596/II/0076 concluded at PRAC in July 2022

15.2.11. Tacrolimus - ADVAGRAF (CAP) - EMEA/H/C/000712/WS2402/0069; MODIGRAF (CAP) - EMEA/H/C/000954/WS2402/0045

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

PRAC Rapporteur: Ronan Grimes

Scope: Submission of an updated RMP (version 4) to reflect the new Transplant Pregnancy Registry International (TPRI) final study submission milestone, related to procedure EMEA/H/C/000712/MEA030 and EMEA/H/C/000954/MEA022 (Study F506-PV-0001), from 21 December 2021 to 30 June 2023

15.2.12. Zanubrutinib - BRUKINSA (CAP) - EMEA/H/C/004978/II/0008

Applicant: BeiGene Ireland Ltd

PRAC Rapporteur: Menno van der Elst

Scope: Submission of the updated RMP (Version 3.0) in order to include changes on the dates of submission of information for the ongoing study BGB-3111-LTE1

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. Abatacept - ORENCIA (CAP) - EMEA/H/C/000701/II/0152

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Kimmo Jaakkola

Scope: Extension of indication to include the prophylaxis of acute Graft versus Host Disease (aGvHD) in the adult and paediatric population for Orencia, based on final results from studies IM101311 - Abatacept Combined With a Calcineurin Inhibitor and Methotrexate for Graft Versus Host Disease Prophylaxis and IM101841 - Overall Survival In 7/8 HLA-Matched Hematopoietic Stem Cell Transplantation Patients Treated With Abatacept Combined With A Calcineurin Inhibitor And Methotrexate - An Analysis Of The Center For International Blood And Marrow Transplant Research (Cibmtr) database. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and Labelling are updated in accordance. Version 28.0 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the product information

15.3.2. Alpelisib - PIQRAY (CAP) - EMEA/H/C/004804/II/0018

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Menno van der Elst

Scope: Update of sections 4.5 and 5.2 of the SmPC in order to update drug-drug interaction information, based on final results from study BYL719A2111; this is a phase 1, open-label, fixed-sequence, two-period drug-drug interaction (DDI) study evaluating the PK probe substrates for CYP3A4, CYP2B6, CYP2C8, CYP2C9, and CYP2C19 when administered either alone or in combination with repeated doses of alpelisib. The Annex II and package leaflet are updated accordingly. The RMP version 6.0 has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the product information

15.3.3. Apalutamide - ERLEADA (CAP) - EMEA/H/C/004452/X/0028/G

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Tiphaine Vaillant

Scope: Grouped application consisting of: 1) Extension application to add a new strength (240 mg) film-coated tablets. The RMP (version 6.1) has also been submitted; 2) Update of the SmPC/PL for Erleada 60 mg to align with the SmPC/PL proposed for the registration of the new Erleada film-coated tablet strength, 240 mg. The package leaflet for Erleada 60 mg is proposed to be updated to ensure consistency. In addition, few minor revisions are proposed to the SmPC for Erleada 60 mg, to align the SmPC proposed for the 240 mg strength: Sections 5.1 and 5.2: Orthographic corrections; Section 6.5: Further details on the description of the current packaging have been added, this change does not result from a change to the container; Section 6.6: The title of the section has been aligned with QRD template

15.3.4. Atezolizumab - TECENTRIQ (CAP) - EMEA/H/C/004143/X/0076

Applicant: Roche Registration GmbH

PRAC Rapporteur: Inês Ribeiro-Vaz

Scope: Extension application to introduce a new pharmaceutical form (solution for injection) associated with a new strength (1875 mg) and new route of administration (subcutaneous use). The RMP (version 24.0) is updated in accordance

15.3.5. Baricitinib - OLUMIANT (CAP) - EMEA/H/C/004085/II/0037

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Extension of indication to include the treatment of paediatric patients (from 2 years of age and older) with moderate to severe atopic dermatitis for OLUMIANT, based on the final results from study I4V-MC-JAIP; this is a Phase III, multicentre, randomised, double blind, placebo controlled, parallel-group, outpatient study evaluating the pharmacokinetics, efficacy, and safety of baricitinib in paediatric patients with moderate-to-severe atopic dermatitis. As a consequence sections 4.1, 4.2, 4.4, 4.5, 4.8, 4.9, 5.1, 5.2 of the SmPC are updated. The package leaflet has been updated accordingly. Version 17.1 of the RMP has also been submitted

15.3.6. Bimekizumab - BIMZELX (CAP) - EMEA/H/C/005316/II/0010

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Extension of indication to include treatment of adults with active axial spondyloarthritis (axSpA), including non-radiographic axial spondyloarthritis (nr-axSpA) and ankylosing spondylitis (AS, radiographic axial spondyloarthritis), based on interim results from two interventional and controlled phase III clinical studies: AS0010 (BE MOBILE 1) and AS0011 (BE MOBILE 2), which provide evidence of the efficacy and safety of bimekizumab in axSpA (nr-axSpA and AS), both compared to placebo treatment. Further supportive data is provided by the results of a phase 2a exploratory study (AS0013), a phase 2b, dose-ranging study (AS0008) and its ongoing follow-on phase 2b open-label extension (OLE) study (AS0009). As a consequence, sections 4.1, 4.2, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet is updated in accordance. Version 1.2 of the RMP has also been submitted. Furthermore, the product information is brought in line with the latest QRD template version 10.2 rev.1

15.3.7. Bimekizumab - BIMZELX (CAP) - EMEA/H/C/005316/II/0011

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Extension of indication to include treatment of active psoriatic arthritis in adults patients who have had an inadequate response or who have been intolerant to one or more DMARDs for Bimzelx (bimekizumab), based on interim results of a Phase III study in biological DMARD naïve study participants (PA0010; BE OPTIMAL) and the final results of the Phase III study in study participants who are inadequate responders (inadequate response or intolerant) to ⩽2 prior TNF inhibitors (PA0011; BE COMPLETE). Both Phase III studies are interventional studies aimed to evaluate the efficacy and safety of bimekizumab. For PA0010, the Initial Treatment Period was placebo- and no inferential active reference (adalimumab)-controlled, while PA0011 was placebo-controlled. Further supportive data

comprise the results of a Phase 1 study (PA0007), a Phase 2b dose-finding study (PA0008) and a Phase 2 open label extension study (PA0009). A Phase 3 open-label extension study is currently ongoing (PA0012). As a consequence, sections 4.1, 4.2, 4.5, 4.8, 5.1 and 5.2 to the SmPC have been updated. The package leaflet is updated in accordance. Version 1.1 of the RMP has also been submitted. Furthermore, the product information is brought in line with the latest QRD template version 10.2 rev.1. As part of the application the MAH is requesting a 1-year extension of the market protection

15.3.8. Brolucizumab - BEOVU (CAP) - EMEA/H/C/004913/II/0018

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Gabriele Maurer

Scope: Update of sections 4.2 and 5.1 of the SmPC in order to introduce an alternative posology regimen for wet age-related macular degeneration and update information based on modelling and simulation studies; the package leaflet is updated accordingly. The RMP version 9.0 has also been submitted

15.3.9. Budesonide, formoterol fumarate dihydrate - BUDESONIDE/FORMOTEROL TEVA PHARMA B.V. (CAP) - EMEA/H/C/004882/II/0012/G

Applicant: Teva Pharma B.V.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Grouped variations consisting of: 1) To replace the multidose dry powder inhaler to be used for the delivery of a combination of Budesonide/Formoterol fumarate dihydrate inhalation powder, as well as detect, record, store and transfer inhaler usage information to a mobile application (App); the inhaler is an integrated part of the primary packaging of the medicinal product; 2) To change the name of the medicinal product 3) To update sections 4.2 and 4.4 of the SmPC to reorganise the flow of information within these sections (as approved for DuoResp Spiromax EMEA/H/C/002348), following assessment of the same change for the reference product Symbicort Turbohaler; 4) other quality variations

15.3.10. Carglumic acid - CARBAGLU (CAP) - EMEA/H/C/000461/II/0045

Applicant: Recordati Rare Diseases

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Update of sections 4.2, 4.4 and 5.2 of the SmPC in order to include a proposed dose adjustment for patients with impaired renal function based on final results from study RCD-P0-027; this is a Phase I, multicentre, open-label, parallel-group adaptive pharmacokinetic single dose study of oral Carbaglu in subjects with normal and varying degrees of impaired renal function. The package leaflet is updated accordingly. The RMP version 2.2 has also been submitted. In addition, the MAH took the opportunity to implement editorial changes in Annex II and Labelling, and to bring the product information in line with the latest QRD template version 10.3

15.3.11. Durvalumab - IMFINZI (CAP) - EMEA/H/C/004771/II/0057

Applicant: AstraZeneca AB

PRAC Rapporteur: David Olsen

Scope: Extension of indication to include treatment of adults with unresectable hepatocellular carcinoma (uHCC), based on final results from study D419CC00002 (HIMALAYA); this was a randomised, open-label, multicentre phase III study of durvalumab and tremelimumab as first-line treatment in patients with unresectable hepatocellular carcinoma (HIMALAYA). As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The package leaflet is updated in accordance. Version 9, Succession 1 of the RMP has also been submitted. In addition, the product information is brought in line with the latest QRD template version 10.3

15.3.12. Edoxaban - LIXIANA (CAP) - EMEA/H/C/002629/WS2409/0042; ROTEAS (CAP) - EMEA/H/C/004339/WS2409/0029

Applicant(s): Daiichi Sankyo Europe GmbH

PRAC Rapporteur: Nathalie Gault

Scope: Update of sections 4.2, 4.8, 5.1 and 5.2 of the SmPC with available paediatric data based on final results from study DU176b-D-U312; this is a phase 3, open-label, randomised, multicentre, controlled trial to evaluate the pharmacokinetics and pharmacodynamics of edoxaban and to compare the efficacy and safety of edoxaban with standard-of-care anticoagulant therapy in paediatric subjects from birth to less than 18 years of age with confirmed venous thromboembolism (VTE). The package leaflet and Labelling are updated accordingly. The RMP version 15.0 has also been submitted. In addition, the MAH took the opportunity to implement editorial changes in the SmPC and to bring the product information in line with the latest QRD template version 10.3

15.3.13. Efgartigimod alfa - VYVGART (CAP) - EMEA/H/C/005849/X/0003, Orphan

Applicant: Argenx

PRAC Rapporteur: Rhea Fitzgerald

Scope: Extension application to introduce a new pharmaceutical form (solution for injection) associated with a new strength (1000 mg) and a new route of administration (subcutaneous use)

15.3.14. Empagliflozin - JARDIANCE (CAP) - EMEA/H/C/002677/II/0074

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Extension of indication to include treatment of chronic kidney disease (CKD) for JARDIANCE, based on final results from study EMPA-KIDNEY (1245-0137) listed as a category 3 study in the RMP; this is a Phase III, multicentre international randomised parallel group double-blind placebo controlled clinical trial of empagliflozin once daily to assess cardio-renal outcomes in patients with chronic kidney disease. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet is updated in accordance. Version 19.0 of the RMP has also been submitted. Furthermore, the product information is brought in line with the latest QRD template version 10.3

15.3.15. Enfortumab vedotin - PADCEV (CAP) - EMEA/H/C/005392/II/0007

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Eva Jirsová

Scope: Update of sections 4.2, 4.4 and 4.8 of the SmPC in order to introduce new posology recommendations in case of pneumonitis/interstitial lung disease (ILD), add a new warning on 'pneumonitis/ILD' and add it to the list of adverse drug reactions (ADRs) with frequency not known. 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 PI

15.3.16. Human fibrinogen, human thrombin - EVICEL (CAP) - EMEA/H/C/000898/II/0099

Applicant: Omrix Biopharmaceuticals N. V.

PRAC Rapporteur: Gabriele Maurer

Scope: Update of sections 4.8 and 5.1 of the SmPC in order to update the frequency of adverse drug reactions (ADRs), add Pseudomeningocele to the list of ADRs with frequency uncommon and to update efficacy and safety information on paediatric population, following P46/0030 based on the final results from paediatric clinical study BIOS-13-006. This is a Prospective Randomised Controlled Study Evaluating the Safety and Efficacy of EVICEL used for Suture- Line Sealing in Dura-Mater Closure during Paediatric Neurosurgical Cranial Procedures. The package leaflet is updated accordingly. Editorial changes are proposed to sections of the product information. In addition, the MAH took the opportunity to bring the product information in line with the latest QRD template version 10.3. The RMP version 15 has also been submitted

15.3.17. Lanadelumab - TAKHZYRO (CAP) - EMEA/H/C/004806/X/0034/G, Orphan

Applicant: Takeda Pharmaceuticals International AG Ireland Branch

PRAC Rapporteur: Kirsti Villikka

Scope: Grouped application consisting of: 1) Extension application to add a new strength of 150 mg for lanadelumab solution for injection in pre-filled syringe and to extend the indication to include paediatric use (2 to <12 years). The new indication is only applicable to the new 150 mg strength presentations. The RMP (version 3.0) is updated in accordance; 2) A type IB variation (C.I.z) to update section 7 of the package leaflet (PL) for the 300 mg in 2 ml pre-filled syringe (EU/1/18/1340/004-006) in line with the proposed package leaflet for the 150 mg in 1 ml pre-filled syringe (new strength). In addition, the MAH has requested an extension of the Orphan Market Exclusivity from 10 to 12 years

15.3.18. Lisocabtagene maraleucel - BREYANZI (CAP) - EMEA/H/C/004731/II/0014

Applicant: Bristol-Myers Squibb Pharma EEIG, ATMP[28]

PRAC Rapporteur: Gabriele Maurer

Scope: Update of section 5.1 of the SmPC in order to update efficacy information based on final results from studies 017001 and JCAR-017-BCM-001 listed as obligations in the Annex

[28] Advanced therapy medicinal product

II. These studies aimed to further characterise the long-term efficacy and safety of Breyanzi in patients treated with relapsed or refractory DLBCL, PMBCL, FL3B after two or more lines of systemic therapy. Study 017001 is a phase 1, open-label, single-arm, multicohort, multicentre, seamless design trial, while study JCAR-017-BCM-001 is a phase 2, open-label, single-arm, multicohort, multicentre trial. The Annex II is updated accordingly. The RMP version 3.0 has also been submitted

15.3.19. Melphalan flufenamide - PEPAXTI (CAP) - EMEA/H/C/005681/II/0002

Applicant: Oncopeptides AB

PRAC Rapporteur: Martin Huber

Scope: Extension of indication to include treatment of patients with Multiple Myeloma who have received at least two prior lines of therapies for PEPAXTI, based on final results from study OP-103 OCEAN; this is a randomised, open-label phase III study in patients with relapsed or refractory multiple myeloma following two to four lines of prior therapies and who were refractory to lenalidomide and the last line of therapy. As a consequence, sections 4.1, 4.4, 4.8 and 5.1 of the SmPC are updated. The package leaflet is updated in accordance. Version 1.1 of the RMP has also been submitted. In addition, the MAH took the opportunity to implement editorial changes in the SmPC

15.3.20. Midostaurin - RYDAPT (CAP) - EMEA/H/C/004095/II/0028, Orphan

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Inês Ribeiro-Vaz

Scope: Update of sections 4.2 and 5.2 of the SmPC in order to update efficacy and safety information in elderly patients based on final results from study CPKC412A2408 - An open-label, multicentre, Phase IIIb study to assess the safety and efficacy of midostaurin (PKC412) in patients 18 years of age or older with newly diagnosed FLT3-mutated acute myeloid leukaemia who are eligible for "7+3" or "5+2" chemotherapy, listed as a PAES in the Annex II. The RMP version 8.0 has also been submitted

15.3.21. Naltrexone hydrochloride, bupropion hydrochloride - MYSIMBA (CAP) - EMEA/H/C/003687/II/0056

Applicant: Orexigen Therapeutics Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: Submission of an updated study design and a protocol synopsis for study CVOT-2 (listed as a category 1 study in Annex II-D (ANX/001.7)): a multicentre, randomised, double-blind, placebo-controlled phase 4 study to assess the effect of naltrexone extended release (ER)/bupropion ER on the occurrence of major adverse cardiovascular events (MACE) in overweight and obese subjects with cardiovascular disease, as requested by CHMP in the conclusions of procedure ANX 001.6 adopted in April 2021. Annex II and the RMP (version 13) are updated accordingly

15.3.22. Nonacog beta pegol - REFIXIA (CAP) - EMEA/H/C/004178/II/0032

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Gabriele Maurer

Scope: Extension of indication to include treatment and prophylaxis of bleeding in children below 12 years of age with haemophilia B including previously untreated patients for REFIXIA, based on interim results from studies NN7999-3774 and NN7999-3895. NN7999-3774 is a multicentre, open-label, non-controlled study evaluating the safety, efficacy and pharmacokinetics of nonacog beta pegol in previously treated children with haemophilia B, while NN7999-3895 is a multicentre, open-label, single-arm, non-controlled trial evaluating the safety and efficacy of nonacog beta pegol in previously untreated patients with haemophilia B. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The package leaflet is updated accordingly. Version 5.0 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the product information

15.3.23. Obinutuzumab - GAZYVARO (CAP) - EMEA/H/C/002799/II/0052, Orphan

Applicant: Roche Registration GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension of indication to include the pre-treatment to reduce the risk of cytokine release syndrome (CRS) induced by glofitamab for Gazyvaro, based on results from study NP30179; this is a multicentre, open-label, Phase I/II study evaluating the safety, efficacy, tolerability and pharmacokinetics of escalating doses of glofitamab as a single agent and in combination with obinutuzumab administered after a fixed, single dose pre-treatment of Gazyvaro in patients with relapsed/refractory B-cell NHL. As a consequence, sections 4.1, 4.2, 4.4, 5.1, 5.3 and 6.6 of the SmPC are updated. The package leaflet is updated in accordance. Version 10.0 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the package leaflet. Furthermore, the product information is brought in line with the latest QRD template version

15.3.24. Ocrelizumab - OCREVUS (CAP) - EMEA/H/C/004043/II/0034/G

Applicant: Roche Registration GmbH

PRAC Rapporteur: Gabriele Maurer

Scope: Grouped variations consisting of: 1) submission of the final report from study BN29739 (VELOCE) listed as a category 3 study in the RMP. This is a phase 3b, multicentre, randomised, parallel-group, open-label study to evaluate the effectiveness of vaccinations in patients with relapsing forms of multiple sclerosis (RMS) undergoing treatment with ocrelizumab; 2) submission of the final report from studies MA30005 (CASTING) and MN30035 (CHORDS). These are prospective, multicentre, international, interventional, open-label phase 3b studies to assess the efficacy and safety of ocrelizumab in patients with relapsing multiple sclerosis who have a suboptimal response to an adequate course of disease-modifying treatment. The RMP version 8.0 has also been submitted

15.3.25. Odevixibat - BYLVAY (CAP) - EMEA/H/C/004691/II/0011, Orphan

Applicant: Albireo

PRAC Rapporteur: Adam Przybylkowski

Scope: Extension of indication to include treatment of cholestasis and pruritus in Alagille syndrome (ALGS) in patients from birth and older for BYLVAY, based on final results from Study A4250-012 and interim results from Study A4250-015. Study A4250-012 is a 24-week, randomised, double-blind, placebo-controlled Phase III study conducted in 52 patients with a genetically confirmed diagnosis of ALGS and presence of pruritus and high serum bile acid levels at baseline. Study A4250-015 is an ongoing 72-week open-label extension trial for patients who completed Study A4250-012 and evaluates the long-term safety and efficacy of Bylvay in patients with ALGS. As a consequence, sections 4.1, 4.2, 4.8, 5.1, and 5.2 of the SmPC are updated. The package leaflet is updated in accordance. Version 2.1 of the RMP has also been submitted

15.3.26. Olipudase alfa - XENPOZYME (CAP) - EMEA/H/C/004850/II/0001/G, Orphan

Applicant: Genzyme Europe BV

PRAC Rapporteur: Martin Huber

Scope: Grouped variations consisting of: 1) update sections 4.6 of the SmPC in order to include a recommendation to conduct a pregnancy test for women of childbearing potential (WOCP) prior to treatment initiation based on embryo-foetal study in mice (study TER0694). In addition, the MAH proposes an update of section 5.3 of the SmPC based on a re-calculation of exposure margins for the embryo-foetal study. MAH also proposes to align the SmPC with the updated Company Core Data Sheet (CCDS); 2) update sections 4.6 and 5.3 of the SmPC in order to include data in lactating mice based on final results from study MSSM-1120 - Evaluation of Olipudase alfa Transfer Into Milk of Lactating Mice. The package leaflet is updated accordingly. The RMP version 2.0 has also been submitted

15.3.27. Oritavancin - TENKASI (CAP) - EMEA/H/C/003785/II/0037

Applicant: Menarini International Operations Luxembourg S.A.

PRAC Rapporteur: Adam Przybylkowski

Scope: Extension of indication to include treatment of paediatric population, aged between 3 months and less than 18 years for Tenkasi (oritavancin) 400 mg based on interim results from study TMC-ORI-11-01; this is a multicentre, open-label, dose-finding study of oritavancin single dose infusion in paediatric subjects less than 18 years of age with suspected or confirmed bacterial infections. The purpose of this Phase 1 study is to evaluate the safety, tolerability and PK of oritavancin in paediatric subjects and determine the optimal dose for a Phase 2 trial in paediatric subjects with acute bacterial skin structure infections (ABSSSI). As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated. The package leaflet is updated in accordance. Version 5.0 of the RMP has also been submitted. In addition, MAH is also taking this opportunity to update the contact details of the local representatives in the package leaflet. Furthermore, the product information is brought in line with the latest QRD template version 10.2 rev 1

15.3.28. Pandemic influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) - FOCLIVIA (CAP) - EMEA/H/C/001208/II/0081

Applicant: Seqirus S.r.l

PRAC Rapporteur: Amelia Cupelli

Scope: Extension of indication to include children from 6 months to less than 18 years of age for Foclivia, based on final results from study V87_30; this is a phase 2, randomised, observer-blind, multicentre study to evaluate the immunogenicity and safety of several doses of antigen and MF59 adjuvant content in a monovalent H5N1 pandemic influenza vaccine in healthy paediatric subjects 6 months to less than 9 years of age. As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The package leaflet is updated accordingly. Version 4.9 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the product information and to bring it in line with the latest QRD template

15.3.29. Parathyroid hormone - NATPAR (CAP) - EMEA/H/C/003861/II/0042, Orphan

Applicant: Takeda Pharmaceuticals International AG

PRAC Rapporteur: Rhea Fitzgerald

Scope: Submission of the updated protocol from study SHP634-403 listed as a specific obligation in the Annex II of the product information with twice-daily (BID) as the proposed alternative dosing regimen to be evaluated. This is a randomised, 2-Arm, double-blind, phase 4 study to evaluate once daily (QD) versus twice daily (BID) administration of recombinant human parathyroid hormone (rhPTH[1-84]; NATPARA) for the treatment of adults with hypoparathyroidism (HPT). Annex II and the RMP (submitted version 3.4) are updated accordingly

15.3.30. Patiromer - VELTASSA (CAP) - EMEA/H/C/004180/X/0031/G

Applicant: Vifor Fresenius Medical Care Renal Pharma France

PRAC Rapporteur: Kirsti Villikka

Scope: Extension application to introduce a new strength (1 g powder for oral suspension), grouped with a type II variation (C.I.6.a) in order to extend the indication to include treatment of population from 6 to 18 years old for Veltassa based on final results from paediatric study RLY5016-206P (EMERALD); this is a phase 2, open-label, multiple dose study to evaluate the pharmacodynamic effects, safety, and tolerability of patiromer for oral suspension in children and adolescents 2 to less than 18 years of age with chronic kidney disease and hyperkalaemia. As a consequence, sections 1, 2, 4.1, 4.2, 4.8, 4.9, 5.1 and 6.5 of the SmPC are updated. The package leaflet and Labelling are updated in accordance. Version 2 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce editorial changes

15.3.31. Pneumococcal polysaccharide conjugate vaccine (20-valent, adsorbed) - APEXXNAR (CAP) - EMEA/H/C/005451/II/0012

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Jean-Michel Dogné

Scope: Extension of indication to include infants, children and adolescents from 6 weeks to less than 18 years of age for the prevention of invasive disease, pneumonia and acute otitis media caused by Streptococcus pneumoniae, based on final results from studies B7471003, B7471011, B7471012, B7471013 and B7471014. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8 and 5.1 of the SmPC are updated. The package leaflet is updated in accordance.

Version 3.0 of the RMP has also been submitted

15.3.32. Polatuzumab vedotin - POLIVY (CAP) - EMEA/H/C/004870/II/0020, Orphan

Applicant: Roche Registration GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of the updated final overall survival (OS) CSR for study GO39942 - A Phase III, multicentre, randomised, double-blind, placebo-controlled trial comparing the efficacy and safety of polatuzumab vedotin in combination with R-CHP versus R-CHOPin previously untreated patients with DLBCL (POLARIX) listed as a Category 3 study in the RMP. This submission will address the missing information of "long-term safety" in patients treated with polatuzumab vedotin. An updated RMP version 4.0 has also been submitted to remove the commitment for this study along with the missing information of "long-term safety

15.3.33. Pralsetinib - GAVRETO (CAP) - EMEA/H/C/005413/II/0012

Applicant: Roche Registration GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of sections 4.2, 4.4 and 4.5 of the SmPC in order to amend posology recommendations, warnings and drug-drug interaction information regarding the co-administration with CYP3A4 inhibitors, P-gp inhibitors and CYP3A4 inducers based on final results from the DDI study GP43162, listed as a category 3 study in the RMP, as well as results from the physiologically based pharmacokinetic (PBPK) analyses summarised in the PBPK Report 1120689. Study GP43162 is a phase 1, open-label, fixed-sequence study to evaluate the effect of a single dose of cyclosporine on the single dose pharmacokinetics of pralsetinib in healthy subjects. The RMP version 1.6 has also been submitted

15.3.34. Sacituzumab govitecan - TRODELVY (CAP) - EMEA/H/C/005182/II/0020

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication to include treatment of adult patients with unresectable or metastatic hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer who have received endocrine-based therapy and at least two additional systemic therapies in the metastatic setting, based on final results from study IMMU-132-09 (TROPiCS-02); this is an open-label, randomised, multicentre phase 3 study of sacituzumab govitecan (IMMU-132) versus treatment of physician's choice (TPC) in subjects with hormonal receptor-positive (HR+) human epidermal growth factor receptor 2 (HER2) negative metastatic breast cancer (mBC) who have failed at least two prior chemotherapy regimens. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated. The package leaflet is updated in accordance. Version 2.1 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the product information and to update the list of local representatives in the package leaflet

15.3.35. Selpercatinib - RETSEVMO (CAP) - EMEA/H/C/005375/II/0021

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication to include the treatment of adults and adolescents 12 years and older with advanced RET fusion-positive thyroid cancer in the first-line setting for RETSEVMO based on interim data from studies LIBRETTO-001 (LOXO-RET-17001) and LIBRETTO-121; LIBRETTO-001 is an open-label, multicentre, global Phase 1/2 study of selpercatinib in patients with RET-altered advanced solid tumors. LIBRETTO-121 is a Phase 1/2 study of selpercatinib in paediatric patients with advanced RET-altered solid or primary central nervous system tumours. As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The package leaflet is updated in accordance. Version 3.2 of the RMP has also been submitted

15.3.36. Selpercatinib - RETSEVMO (CAP) - EMEA/H/C/005375/II/0022

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication to include the treatment of adults with advanced or metastatic RET fusion-positive solid tumours with disease progression on or after prior systemic therapies or who have no satisfactory therapeutic options, based on interim data from study LIBRETTO-001 (LOXO-RET-17001); LIBRETTO-001 is an open-label, multicentre, global Phase 1/2 study of selpercatinib in in adult and adolescent patients with advanced RET-altered tumours. As a consequence, sections 4.1, 4.2 and 5.1 of the SmPC are updated. The package leaflet is updated in accordance. Version 3.1 of the RMP has also been submitted. In addition, the MAH took the opportunity to implement editorial changes to the SmPC

15.3.37. Sotorasib - LUMYKRAS (CAP) - EMEA/H/C/005522/II/0007

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Update of sections 4.2 and 5.2 of the SmPC in order to update recommendations for patients with moderate to severe hepatic impairment following final results from study 20200362 listed as a category 3 PASS study in the EU RMP; this is a Phase I clinical study to evaluate the pharmacokinetics (PK) of a single oral dose of sotorasib administered in subjects with moderate or severe hepatic impairment compared with subjects who have normal hepatic function. The EU RMP version 1.0 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

15.3.38. Tafasitamab - MINJUVI (CAP) - EMEA/H/C/005436/II/0008, Orphan

Applicant: Incyte Biosciences Distribution B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of section 4.4 of the SmPC in order to add a new warning on Progressive

Multifocal Leukoencephalopathy (PML) based on post-marketing data; the package leaflet is updated accordingly. The RMP version 2.0 has also been submitted. In addition, the MAH took the opportunity to implement editorial changes in the SmPC and to bring the product information in line with the latest QRD template version 10.3

15.3.39. Teriflunomide - AUBAGIO (CAP) - EMEA/H/C/002514/II/0042

Applicant: Sanofi Winthrop Industrie

PRAC Rapporteur: Martin Huber

Scope: Submission of the final report from study EFC11759 listed as a category 3 study in the RMP. This is a two-year, multicentre, randomised, double-blind, placebo-controlled, parallel group trial to evaluate efficacy, safety, tolerability and pharmacokinetics of teriflunomide administered orally once daily in paediatric patients with relapsing forms of multiple sclerosis (MS) followed by an open-label extension. The RMP version 8.0 has also been submitted

15.3.40. Tralokinumab - ADTRALZA (CAP) - EMEA/H/C/005255/X/0007

Applicant: LEO Pharma A/S

PRAC Rapporteur: Kimmo Jaakkola

Scope: Extension application to add a new strength of 300 mg (150 mg/ml) tralokinumab solution for injection in pre-filled pen for subcutaneous administration. The RMP (version 1.1) is updated accordingly

15.3.41. Trastuzumab deruxtecan - ENHERTU (CAP) - EMEA/H/C/005124/II/0027

Applicant: Daiichi Sankyo Europe GmbH

PRAC Rapporteur: Inês Ribeiro-Vaz

Scope: Extension of indication to include the indication treatment of non-small cell lung cancer for Enhertu (trastuzumab deruxtecan), based on results from study DS8201-A-U204 (DESTINY-Lung01) and study DS8201-A-U206 (DESTINY-Lung02). Study DESTINY-Lung01 is a phase 2, multicentre, open-label, 2-cohort study of trastuzumab deruxtecan (DS-8201a), an anti-HER2 antibody drug conjugate (ADC), for HER2-over-expressing or -mutated, unresectable and/or metastatic non-small cell lung cancer (NSCLC) conducted at sites in Japan, the United States and Europe. Study DESTINY-Lung02 is an ongoing phase 2, multicentre, randomised study to evaluate the safety and efficacy of trastuzumab deruxtecan in subjects with HER2-mutated metastatic non-small cell lung cancer, conducted in North America, Europe and Asia-Pacific. As a consequence, sections 4.1, 4.2, 4.8, 5.1, and 5.2 of the SmPC are updated. The package leaflet is updated in accordance. Version 2.2 of the RMP has also been submitted

15.3.42. Tucatinib - TUKYSA (CAP) - EMEA/H/C/005263/II/0010

Applicant: Seagen B.V.

PRAC Rapporteur: Jean-Michel Dogné

Scope: Submission of the final report from study SGNTUC-017 (MOUNTAINEER) listed as a

category 3 study in the RMP. This is a Phase 2, Open Label Study of Tucatinib Combined with Trastuzumab in Patients with HER2+ Metastatic Colorectal Cancer. Primary objective is to determine the antitumor activity of tucatinib given in combination with trastuzumab. The RMP version 1.1 has also been submitted

15.3.43. Vosoritide - VOXZOGO (CAP) - EMEA/H/C/005475/II/0006, Orphan

Applicant: BioMarin International Limited

PRAC Rapporteur: Zane Neikena

Scope: Extension of indication to include treatment of children less than 2 years of age for Voxzogo, based on final results from the category 1 study BMN 111-206 and interim results from its open-label extension study 111-208. 111-206 is a phase 2 randomised, double-blind, placebo-controlled, multicentre study to assess the safety and efficacy of BMN 111 in infants and young children with achondroplasia. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Annex II and package leaflet are updated in accordance. Version 3.0 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the product information

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. Agalsidase beta - FABRAZYME (CAP) - PSUSA/00000070/202207

Applicant: Genzyme Europe BV

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

16.1.2. Anifrolumab - SAPHNELO (CAP) - PSUSA/00010980/202207

Applicant: AstraZeneca AB

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

16.1.3. Asenapine - SYCREST (CAP) - PSUSA/00000256/202208

Applicant: N.V. Organon

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.1.4. Ataluren - TRANSLARNA (CAP) - PSUSA/00010274/202207

Applicant: PTC Therapeutics International Limited

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

16.1.5. Avalglucosidase alfa - NEXVIADYME (CAP) - PSUSA/00011002/202208

Applicant: Genzyme Europe BV

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

16.1.6. Baricitinib - OLUMIANT (CAP) - PSUSA/00010578/202208

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.7. Bempedoic acid - NILEMDO (CAP); bempedoic acid, ezetimibe - NUSTENDI (CAP) - PSUSA/00010841/202208

Applicant(s): Daiichi Sankyo Europe GmbH

PRAC Rapporteur: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

16.1.8. Bimekizumab - BIMZELX (CAP) - PSUSA/00010953/202208

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

16.1.9. Brentuximab vedotin - (CAP) - PSUSA/00010039/202208 (with RMP)

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.10. Bulevirtide - HEPCLUDEX (CAP) - PSUSA/00010873/202207

Applicant: Gilead Sciences Ireland Unlimited Company

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.11. Burosumab - CRYSVITA (CAP) - PSUSA/00010669/202208

Applicant: Kyowa Kirin Holdings B.V.

PRAC Rapporteur: Gabriele Maurer

Scope: Evaluation of a PSUSA procedure

16.1.12. Caplacizumab - CABLIVI (CAP) - PSUSA/00010713/202208

Applicant: Ablynx NV

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.1.13. Ciltacabtagene autoleucel - CARVYKTI (CAP) - PSUSA/00011000/202208

Applicant: Janssen-Cilag International NV, ATMP[29]

PRAC Rapporteur: Jo Robays

Scope: Evaluation of a PSUSA procedure

16.1.14. Coronavirus (COVID-19) vaccine (inactivated, adjuvanted, adsorbed) - COVID-19 VACCINE (INACTIVATED, ADJUVANTED) VALNEVA (CAP) - PSUSA/00011001/202208

Applicant: Valneva Austria GmbH

PRAC Rapporteur: Gabriele Maurer

Scope: Evaluation of a PSUSA procedure

16.1.15. Darolutamide - NUBEQA (CAP) - PSUSA/00010843/202207

Applicant: Bayer AG

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.1.16. Daunorubicin, cytarabine - VYXEOS LIPOSOMAL (CAP) - PSUSA/00010701/202208

Applicant: Jazz Pharmaceuticals Ireland Limited

PRAC Rapporteur: Inês Ribeiro-Vaz

[29] Advanced therapy medicinal product

Scope: Evaluation of a PSUSA procedure

16.1.17. Defatted powder of Arachis hypogaea L., semen (peanuts) - PALFORZIA (CAP) - PSUSA/00010902/202207

Applicant: Aimmune Therapeutics Ireland Limited

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

16.1.18. Difelikefalin - KAPRUVIA (CAP) - PSUSA/00010995/202208

Applicant: Vifor Fresenius Medical Care Renal Pharma France

PRAC Rapporteur: Mari Thorn

Scope: Evaluation of a PSUSA procedure

16.1.19. Doravirine - PIFELTRO (CAP) - PSUSA/00010729/202208 (with RMP)

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.1.20. Doravirine, lamivudine, tenofovir disoproxil - DELSTRIGO (CAP) - PSUSA/00010731/202208 (with RMP)

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.1.21. Dronedarone - MULTAQ (CAP) - PSUSA/00001180/202207

Applicant: Sanofi Winthrop Industrie

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.22. Eptinezumab - VYEPTI (CAP) - PSUSA/00010966/202208

Applicant: H. Lundbeck A/S

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

16.1.23. Eravacycline - XERAVA (CAP) - PSUSA/00010718/202208

Applicant: Paion Deutschland GmbH

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.24. Evinacumab - EVKEEZA (CAP) - PSUSA/00010945/202208

Applicant: Ultragenyx Germany GmbH

PRAC Rapporteur: Mari Thorn

Scope: Evaluation of a PSUSA procedure

16.1.25. Ex vivo expanded autologous human corneal epithelial cells containing stem cells - HOLOCLAR (CAP) - PSUSA/00010352/202208

Applicant: Holostem Terapie Avanzate s.r.l., ATMP[30]

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

16.1.26. Fedratinib - INREBIC (CAP) - PSUSA/00010909/202208

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Sonja Hrabcik

Scope: Evaluation of a PSUSA procedure

16.1.27. Fostemsavir - RUKOBIA (CAP) - PSUSA/00010911/202208

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

16.1.28. Hydrocortisone31 32 - ALKINDI (CAP) - PSUSA/00010674/202208

Applicant: Diurnal Europe BV

PRAC Rapporteur: Mari Thorn

Scope: Evaluation of a PSUSA procedure

16.1.29. Imlifidase - IDEFIRIX (CAP) - PSUSA/00010870/202208

Applicant: Hansa Biopharma AB

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

[30] Advanced therapy medicinal product
[31] Centrally authorised product(s)
[32] Indication for adrenal insufficiency in paediatric patients only

16.1.30. Influenza vaccine (intranasal, live attenuated) - FLUENZ TETRA (CAP) - PSUSA/00001742/202208

Applicant: AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

16.1.31. Ioflupane (123I) - DATSCAN (CAP) - PSUSA/00001767/202207

Applicant: GE Healthcare B.V.

PRAC Rapporteur: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

16.1.32. Lanadelumab - TAKHZYRO (CAP) - PSUSA/00010743/202208

Applicant: Takeda Pharmaceuticals International AG Ireland Branch

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

16.1.33. Lefamulin - XENLETA (CAP) - PSUSA/00010872/202208

Applicant: Nabriva Therapeutics Ireland DAC

PRAC Rapporteur: Eva Jirsová

Scope: Evaluation of a PSUSA procedure

16.1.34. Linaclotide - CONSTELLA (CAP) - PSUSA/00010025/202208

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.35. Lisocabtagene maraleucel - BREYANZI (CAP) - PSUSA/00010990/202208

Applicant: Bristol-Myers Squibb Pharma EEIG, ATMP[33]

PRAC Rapporteur: Gabriele Maurer

Scope: Evaluation of a PSUSA procedure

16.1.36. Lomitapide - LOJUXTA (CAP) - PSUSA/00010112/202207

Applicant: Amryt Pharmaceuticals DAC

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

[33] Advanced therapy medicinal product

16.1.37. Lonapegsomatropin - SKYTROFA (CAP) - PSUSA/00010969/202208

Applicant: Ascendis Pharma Endocrinology Division A/S

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.38. Mecasermin - INCRELEX (CAP) - PSUSA/00001942/202208

Applicant: Ipsen Pharma

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

16.1.39. Meropenem, vaborbactam - VABOREM (CAP) - PSUSA/00010727/202208

Applicant: Menarini International Operations Luxembourg S.A.

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

16.1.40. Panobinostat - FARYDAK (CAP) - PSUSA/00010409/202208

Applicant: Secura Bio Limited

PRAC Rapporteur: Sofia Trantza

Scope: Evaluation of a PSUSA procedure

16.1.41. Pegaspargase34 - ONCASPAR (CAP) - PSUSA/00010457/202207

Applicant: Les Laboratoires Servier

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.42. Pretomanid - DOVPRELA (CAP) - PSUSA/00010863/202208

Applicant: Mylan IRE Healthcare Limited

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

16.1.43. Regdanvimab - REGKIRONA (CAP) - PSUSA/00010964/202208 (with RMP)

Applicant: Celltrion Healthcare Hungary Kft.

PRAC Rapporteur: Valentina Di Giovanni

Scope: Evaluation of a PSUSA procedure

[34] Centrally authorised product(s) only

16.1.44. Rimegepant - VYDURA (CAP) - PSUSA/00010997/202208

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

16.1.45. Risdiplam - EVRYSDI (CAP) - PSUSA/00010925/202208

Applicant: Roche Registration GmbH

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.1.46. Risperidone35 - OKEDI (CAP) - PSUSA/00010985/202208

Applicant: Laboratorios Farmaceuticos Rovi S.A.

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.47. Romiplostim - NPLATE (CAP) - PSUSA/00002660/202207

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Monica Martinez Redondo

Scope: Evaluation of a PSUSA procedure

16.1.48. Rotavirus vaccine monovalent (live, oral) - ROTARIX (CAP) - PSUSA/00002665/202207

Applicant: GlaxoSmithKline Biologicals S.A.

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

16.1.49. Smallpox and monkeypox vaccine (live, modified vaccinia virus Ankara) - IMVANEX (CAP) - PSUSA/00010119/202207

Applicant: Bavarian Nordic A/S

PRAC Rapporteur: Gabriele Maurer

Scope: Evaluation of a PSUSA procedure

16.1.50. Somapacitan - SOGROYA (CAP) - PSUSA/00010920/202208

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Martin Huber

[35] Centrally authorised product(s) only

Scope: Evaluation of a PSUSA procedure

16.1.51. Sotrovimab - XEVUDY (CAP) - PSUSA/00010973/202208

Applicant: Glaxosmithkline Trading Services Limited

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

16.1.52. Tafasitamab - MINJUVI (CAP) - PSUSA/00010951/202207

Applicant: Incyte Biosciences Distribution B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.53. Teduglutide - REVESTIVE (CAP) - PSUSA/00009305/202208

Applicant: Takeda Pharmaceuticals International AG Ireland Branch

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Evaluation of a PSUSA procedure

16.1.54. Tocofersolan - VEDROP (CAP) - PSUSA/00002981/202207

Applicant: Recordati Rare Diseases

PRAC Rapporteur: Melinda Palfi

Scope: Evaluation of a PSUSA procedure

16.1.55. Upadacitinib - RINVOQ (CAP) - PSUSA/00010823/202208

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Evaluation of a PSUSA procedure

16.1.56. Vosoritide - VOXZOGO (CAP) - PSUSA/00010952/202208

Applicant: BioMarin International Limited

PRAC Rapporteur: Zane Neikena

Scope: Evaluation of a PSUSA procedure

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

16.2.1. Human protein C - CEPROTIN (CAP); NAP - PSUSA/00002563/202207

Applicant(s): Takeda Manufacturing Austria AG (Ceprotin), various

PRAC Rapporteur: Gabriele Maurer

Scope: Evaluation of a PSUSA procedure

16.2.2. Palonosetron - ALOXI (CAP); NAP - PSUSA/00002268/202207

Applicant(s): Helsinn Birex Pharmaceuticals Limited (Aloxi), various

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

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

16.3.1. Alprostadil[36] (NAP) - PSUSA/00000111/202207

Applicant(s): various

PRAC Lead: Eva Jirsová

Scope: Evaluation of a PSUSA procedure

16.3.2. Anastrozole (NAP) - PSUSA/00000210/202208

Applicant(s): various

PRAC Lead: Zane Neikena

Scope: Evaluation of a PSUSA procedure

16.3.3. Beclometasone, formoterol[37] (NAP) - PSUSA/00010068/202207

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.3.4. Cefadroxil (NAP) - PSUSA/00000584/202207

Applicant(s): various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.3.5. Clindamycin phosphate, tretinoin (NAP) - PSUSA/00010080/202207

Applicant(s): various

PRAC Lead: Anna Mareková

Scope: Evaluation of a PSUSA procedure

[36] Indicated in peripheral arterial occlusive diseases only
[37] For inhalation use only

16.3.6. Diclofenac, misoprostol (NAP) - PSUSA/00001040/202207

Applicant(s): various

PRAC Lead: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

16.3.7. Diphtheria, tetanus, poliomyelitis (inactivated) vaccine (adsorbed, reduced antigens(s) content) (NAP) - PSUSA/00001127/202208

Applicant(s): various

PRAC Lead: Gabriele Maurer

Scope: Evaluation of a PSUSA procedure

16.3.8. Enalapril, hydrochlorothiazide (NAP) - PSUSA/00001212/202207

Applicant(s): various

PRAC Lead: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

16.3.9. Ethinylestradiol, norethisterone (NAP) - PSUSA/00001312/202208

Applicant(s): various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.3.10. Fludarabine (NAP) - PSUSA/00001406/202208

Applicant(s): various

PRAC Lead: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

16.3.11. Fluvoxamine (NAP) - PSUSA/00001458/202207

Applicant(s): various

PRAC Lead: Rugilė Pilvinienė

Scope: Evaluation of a PSUSA procedure

16.3.12. Fosfomycin38 (NAP) - PSUSA/00010326/202207

Applicant(s): various

PRAC Lead: Nathalie Gault

Scope: Evaluation of a PSUSA procedure

[38] Oral formulation

16.3.13. Fosfomycin39 (NAP) - PSUSA/00010336/202207

Applicant(s): various

PRAC Lead: Nathalie Gault

Scope: Evaluation of a PSUSA procedure

16.3.14. Human coagulation factor IX (NAP) - PSUSA/00001617/202207

Applicant(s): various

PRAC Lead: Gabriele Maurer

Scope: Evaluation of a PSUSA procedure

16.3.15. Ketorolac40 (NAP) - PSUSA/00001810/202207

Applicant(s): various

PRAC Lead: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

16.3.16. Norethisterone (NAP) - PSUSA/00002188/202208

Applicant(s): various

PRAC Lead: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

16.3.17. Pilocarpine[41] (NAP) - PSUSA/00002409/202207

Applicant(s): various

PRAC Lead: Željana Margan Koletić

Scope: Evaluation of a PSUSA procedure

16.3.18. Pitavastatin (NAP) - PSUSA/00010502/202207

Applicant(s): various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.3.19. Poliovirus type 1, poliovirus type 2, poliovirus type 3 vaccine (oral, live, attenuated) (NAP) - PSUSA/00010801/202207

Applicant(s): various

PRAC Lead: Jean-Michel Dogné

[39] Intravenous (IV) formulation
[40] Ophtalmic formulation(s) only
[41] All formulations except ophthalmic

Scope: Evaluation of a PSUSA procedure

16.3.20. Triamcinolone[42] (NAP) - PSUSA/00003017/202207

Applicant(s): various

PRAC Lead: Inês Ribeiro-Vaz

Scope: Evaluation of a PSUSA procedure

16.3.21. Triazolam (NAP) - PSUSA/00003023/202207

Applicant(s): various

PRAC Lead: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

16.4. Follow-up to PSUR/PSUSA procedures

16.4.1. Dexmedetomidine - DEXDOR (CAP) - EMEA/H/C/002268/LEG 016.5

Applicant: Orion Corporation

PRAC Rapporteur: Ulla Wändel Liminga

Scope: From EMEA/H/C/002268/II/0035: proposal for additional pharmacovigilance activities to address the important potential risk of 'increased mortality in younger ICU patients''

16.5. Variation procedure(s) resulting from PSUSA evaluation

16.5.1. Nirmatrelvir, ritonavir - PAXLOVID (CAP) - EMEA/H/C/005973/II/0032

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Martin Huber

Scope: Update of section 4.8 of the SmPC in order to add 'hypertension' to the list of adverse drug reactions (ADRs) with frequency 'uncommon', following procedure EMEA/H/C/005973/LEG 006 (LEG assessed by PRAC), based on review of aggregated post-marketing data. The package leaflet is updated accordingly

16.6. Expedited summary safety reviews[43]

None

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

17. 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)[44]

17.1.1. Lenalidomide - REVLIMID (CAP) - EMEA/H/C/PSA/S/0093.1

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Tiphaine Vaillant

Scope: Substantial amendment to a protocol for a post-authorisation, non-interventional, retrospective, drug-utilisation study to describe the pattern of use of lenalidomide in patients with myelodysplastic syndromes (MDS) [MAH's response to PSA/S/0093]

17.1.2. Rurioctocog alfa pegol - ADYNOVI (CAP) - EMEA/H/C/PSA/S/0095.1

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Substantial amendment to a protocol for study: evaluation of long-term safety of ADYNOVI/ADYNOVATE (Antihaemophilic Factor [Recombinant] PEGylated, rurioctocog alfa pegol) in adults and adolescents ⩾12 years of age with haemophilia A [MAH's response to PSA/S/0095]

17.1.3. Velmanase alfa - LAMZEDE (CAP) - EMEA/H/C/PSA/S/0094.1

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Jan Neuhauser

Scope: Substantial amendment to a protocol for study: THE ALPHA-MANNOSIDOSIS REGISTRY: A multicentre, multi-country, non-interventional, prospective cohort, in alpha-mannosidosis patients to evaluate the long-term effectiveness and safety profile of treatment with Lamzede under conditions of routine clinical care and to characterize the entire alpha-mannosidosis population, including variability of clinical manifestation, progression and natural history [MAH's response to PSA/S/0094]

17.2. Protocols of PASS non-imposed in the marketing authorisation(s)[45]

17.2.1. Alemtuzumab - LEMTRADA (CAP) - EMEA/H/C/003718/MEA 007.13

Applicant: Sanofi Belgium

PRAC Rapporteur: Anette Kirstine Stark

[44] In accordance with Article 107n of Directive 2001/83/EC
[45] In accordance with Article 107m of Directive 2001/83/EC, supervised by PRAC in accordance with Article 61a (6) of Regulation (EC) No 726/2004

Scope: Revised PASS protocol for study OBS13434: a prospective, multicentre, observational, PASS to evaluate the long term safety profile of alemtuzumab treatment in patients with relapsing forms of multiple sclerosis (RMS)

17.2.2. Bimekizumab - BIMZELX (CAP) - EMEA/H/C/005316/MEA 002.2

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: MAH's response to MEA 002.1 [Submission of a revised protocol for study PS0038: a non-interventional cohort study on the safety of bimekizumab in patients with plaque psoriasis comparing the risk of safety outcomes of interest in bimekizumab exposed patients compared to patients exposed to other biologics] as per the request for supplementary information (RSI) adopted in November 2022

17.2.3. Bimekizumab - BIMZELX (CAP) - EMEA/H/C/005316/MEA 003.2

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: MAH's response to MEA 003.1 [Submission of a revised protocol for study PS0036: bimekizumab pregnancy exposure and outcome registry - an OTIS autoimmune diseases in pregnancy study] as per the request for supplementary information (RSI) adopted in November 2022. PASS Study no PS0036: Bimekizumab Pregnancy Exposure and Outcome Registry: An OTIS Autoimmune Diseases in Pregnancy Study (NINI PASS protocol)

17.2.4. Birch bark extract - FILSUVEZ (CAP) - EMEA/H/C/005035/MEA 001

Applicant: Amryt Pharmaceuticals DAC

PRAC Rapporteur: Zane Neikena

Scope: Submission of a protocol for Filsuvez Observational Safety and Effectiveness Evaluation Registry-based study in epidermolysis bullosa (EB) (FOStER-EB) [(AEB-21)] (listed as category 3 study in the RMP) to evaluate the long-term safety of Filsuvez amongst patients treated for EB in relation to the incidence, severity and relatedness of skin malignancies (including squamous cell carcinoma (SCC), basal cell carcinoma (BCC) and malignant melanoma (MM)), and use in patients with different skin types regarding ethnic origin

17.2.5. Coronavirus (COVID-19) vaccine (Ad26.COV2-S, recombinant) - JCOVDEN (CAP) - EMEA/H/C/005737/MEA 008.3

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of a protocol amendment for study VAC31518COV4003 (listed as category 3 study in the RMP): post-authorisation, observational study to assess the safety of Ad26.COV2.S using electronic health record (EHR) database(s) in Europe

17.2.6. Enfortumab vedotin - PADCEV (CAP) - EMEA/H/C/005392/MEA 003

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Eva Jirsová

Scope: Protocol for study 7465-PV-0002: PASS to evaluate patients understanding and awareness of the content of the patient card related to risks of skin reactions and patients behaviours to minimise the risks

17.2.7. Fentanyl - INSTANYL (CAP) - EMEA/H/C/000959/MEA 029.3

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Tiphaine Vaillant

Scope: Updated protocol for study study Instanyl-5002 (listed as a category 3 study in the RMP): a non-interventional study to assess the effectiveness of updated educational materials on prescribers' knowledge and behaviour with respect to risks associated with Instanyl (fentanyl) off-label use together with an interim report and the statistical analysis plan (SAP)

17.2.8. Filgotinib - JYSELECA (CAP) - EMEA/H/C/005113/MEA 016.2

Applicant: Galapagos N.V.

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: MAH's response to MEA 016.1 [revised protocol for study GLPG0634-CL-413: a non-interventional, PASS of filgotinib in patients with moderately to severely active ulcerative colitis (a European multi registry-based study)] as per the request for supplementary information (RSI) adopted in October 2022

17.2.9. Fremanezumab - AJOVY (CAP) - EMEA/H/C/004833/MEA 002.3

Applicant: TEVA GmbH

PRAC Rapporteur: Kirsti Villikka

Scope: Revised protocol for observational cohort study TV48125-MH-50037: a pregnancy registry assessing pregnancy outcomes in patients treated with Ajovy (fremanezumab)

17.2.10. Talimogene laherparepvec - IMLYGIC (CAP) - EMEA/H/C/002771/MEA 005.1

Applicant: Amgen Europe B.V., ATMP[46]

PRAC Rapporteur: Gabriele Maurer

Scope: MAH's response to MEA 001 [Substantial amendment to a protocol previously agreed within the initial application/marketing authorisation in 2015 for study 20130193 (listed as category 3 study in the RMP): a post-marketing, prospective cohort study of patients treated with talimogene laherparepvec in clinical practice to characterize the risk of herpetic illness among patients, close contacts, and healthcare providers; and long term safety in treated patients] as per the request for supplementary information (RSI) adopted

[46] Advanced therapy medicinal product

in March 2022

17.2.11. Tebentafusp - KIMMTRAK (CAP) - EMEA/H/C/004929/MEA 002.1

Applicant: Immunocore Ireland Limited

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to MEA 002 [Protocol for a physician's survey to evaluate the effectiveness of additional risk minimisation measure for (educational materials) cytokine release syndrome (CRS) associated with Kimmtrak administration] as per the request for supplementary information (RSI) adopted in September 2022

17.2.12. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/MEA 018.2

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Revised protocol for study A3921407: a post-authorisation active safety surveillance programme among patients treated with tofacitinib for polyarticular course juvenile idiopathic arthritis and juvenile PsA within the German Biologics in Pediatric Rheumatology Registry (BIKER) and within the Juvenile Arthritis Methotrexate/Biologics long-term Observation (JuMBO) Registry

17.2.13. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/MEA 019.2

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Revised protocol for study A3921408: a PASS surveillance programme among patients treated with tofacitinib for polyarticular course juvenile idiopathic arthritis and juvenile psoriatic arthritis (PsA) within the Swedish juvenile idiopatic arthritis (JIA) clinical registry

17.2.14. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/MEA 020.2

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Revised protocol for study A3921409: a PASS surveillance programme among patients treated with tofacitinib for polyarticular course juvenile idiopathic arthritis and juvenile psoriatic arthritis (PsA) within the UK juvenile idiopathic arthritis (JIA) biologics register

17.2.15. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/MEA 025

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Protocol for study No921403 (listed as category 3 study in the RMP): a PASS of the Utilisation and Prescribing Patterns of Xeljanz (tofacitinib) Using an Administrative

Healthcare Database in France: a descriptive drug utilisation study using real-world data collected from routine clinical care in France. The overall goal is to determine if there is evidence that prescribers in France are compliant with the recommendations and limitations for use described in the tofacitinib additional risk minimisation measures (aRMM) materials

17.2.16. Vutrisiran - AMVUTTRA (CAP) - EMEA/H/C/005852/MEA 002

Applicant: Alnylam Netherlands B.V.

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Third protocol amendment for study ALN-TTR02-013, ConTTRibute Study: global, prospective, observational, multicentre long-term study. This is a prospective, observational study that will provide a robust assessment of the long-term safety of Amvuttra in real-world clinical practice along with a comparator group being enrolled in ConTTRibute who follow local standard of care. ConTTRibute aims to document the natural history, clinical characteristics, and management of ATTR amyloidosis as part of routine clinical care. The study cohort will include patients with hATTR amyloidosis under care at the participating study site, as no exclusion criteria are intended with this observational cohort. Patients with hepatic impairment will be observed as part of the cohort. The study will also include data collection on the clinical consequences of vitamin A deficiency, including delayed symptoms, and pregnancy exposure and pregnancy and infant outcomes

17.3. Results of PASS imposed in the marketing authorisation(s)[47]

17.3.1. Chlormadinone acetate, ethinyl estradiol (NAP) - EMEA/H/N/PSR/J/0042

Applicant: Gedeon Richter Plc

PRAC Rapporteur: Martin Huber

Scope: Final study report for: risk of venous thromboembolism – The role of oral contraceptives – a case control study comparing levonorgestrel and chlormadinone acetate (CMA) to compare the VTE risk of combined oral contraceptives (COCs) containing CMA 2mg / ethinylestradiol (EE) 30 µg, compared to COCs containing levonorgestrel (LNG) 0.15mg, both combined with 30 µg ethinylestradiol (EE)

17.3.2. Roflumilast – DAXAS (CAP) - EMEA/H/C/PSR/S/0041

Applicant: AstraZeneca AB

PRAC Rapporteur: Monica Martinez Redondo

Scope: Final study report for a long-term post-marketing observational study of the safety of roflumilast

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

17.4. Results of PASS non-imposed in the marketing authorisation(s)[48]

17.4.1. Alglucosidase alfa - MYOZYME (CAP) - EMEA/H/C/000636/II/0093

Applicant: Genzyme Europe BV

PRAC Rapporteur: Nathalie Gault

Scope: Submission of the final non-interventional Pompe Registry Report 2022 (MEA 024 and MEA 025)

17.4.2. Delamanid - DELTYBA (CAP) - EMEA/H/C/002552/II/0061, Orphan

Applicant: Otsuka Novel Products GmbH

PRAC Rapporteur: Jo Robays

Scope: Update of sections 4.2 and 4.4 of the SmPC in order to update treatment duration based on final results from EU PASS (protocol no. 242-12-402), listed as a category 3 study in the RMP. This is a "A Multicentre, EU-wide, Non-Interventional Post-Authorisation Study to Assess the Safety and Usage of Delamanid in Routine Medical Practice in Multidrug-Resistant Tuberculosis (MDR-TB) Patients". This treatment registry was for monitoring and documenting Deltyba use in routine medical practice and aimed to assess compliance with the recommendations in the authorised product information when prescribed as part of an appropriate combination regimen (ACR) for the treatment of MDR-TB. The package leaflet is updated accordingly. The RMP version 4.2 has also been submitted. In addition, the MAH took the opportunity to update Annex II section D of the SmPC

17.4.3. Etelcalcetide - PARSABIV (CAP) - EMEA/H/C/003995/II/0021

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Valentina Di Giovanni

Scope: Submission of the final report from study 20170561 listed as a category 3 study in the RMP. This is an observational PASS to evaluate the potential association between Parsabiv and gastrointestinal bleeding

17.4.4. Gilteritinib - XOSPATA (CAP) - EMEA/H/C/004752/II/0012, Orphan

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Martin Huber

Scope: Submission of the final report from study 2215-PV-0001 - Evaluation of the effectiveness of the Xospata routine risk minimisation measures (RMMs) and an additional Risk Minimisation Measure (aRMM): A Cross sectional study among Healthcare Professionals to assess awareness and knowledge, listed as a category 3 study in the RMP. The RMP version 3.0 has also been submitted

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

17.4.5. Golimumab - SIMPONI (CAP) - EMEA/H/C/000992/II/0112

Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of the final report from study P04480 (RABBIT) listed as a category 3 study in the RMP. This is an observational prospective cohort study to evaluate the long-term safety of treatment with biologics in rheumatoid arthritis. The RMP version 23.3 has also been submitted

17.4.6. Nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/II/0127

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Martin Huber

Scope: Submission of the final report from the PASS CA209835: A registry study in patients who underwent post-nivolumab allogeneic haematopoetic stem-cell transplantation (HSCT). This study is listed as a Category 3 study in the RMP. An updated RMP version 31.0 has also been submitted

17.4.7. Sacubitril, valsartan - ENTRESTO (CAP) - EMEA/H/C/004062/WS2435/0048; NEPARVIS (CAP) - EMEA/H/C/004343/WS2435/0046

Applicant(s): Novartis Europharm Limited

PRAC Rapporteur: Anette Kirstine Stark

Scope: Submission of the final report from study CLCZ696B2013 listed as a category 3 study in the RMP. Study CLCZ696B2013 is a non-interventional, post-authorisation, database cohort study to assess the risk of serious angioedema in association with LCZ696 (sacubitril/valsartan; Entresto) use in Black patients with heart failure in the United States

17.4.8. Tezacaftor, ivacaftor - SYMKEVI (CAP) - EMEA/H/C/004682/II/0039, Orphan

Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Submission of the final report from PASS study VX17-661-117 listed as a category 3 study in the RMP. This is an observational study to evaluate the utilisation patterns and real-world effects of tezacaftor and ivacaftor combination therapy (TEZ/IVA) in patients with cystic fibrosis (CF). The RMP version 3.4 has also been submitted

17.4.9. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/II/0095

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: Submission of the final report from study PSOLAR (C0168Z03) (listed as a category 3 study in the RMP): a multicentre, open registry of patients with psoriasis who are candidates for systemic therapy including biologics: PSOLAR. The RMP (version 22.2) is updated accordingly

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

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Adam Przybylkowski

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

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

17.5.1. Cabotegravir - VOCABRIA (CAP) - EMEA/H/C/004976/MEA 005.3

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Martin Huber

Scope: Interim report for study 215163 (listed as category 3 study in the RMP): a study on pregnancy and neonatal outcomes following prenatal exposure to cabotegravir long acting (CAB LA) – data from the European Pregnancy and Paediatric human immunodeficiency virus (HIV) Cohort Collaboration (EPPICC)

17.5.2. Cabotegravir - VOCABRIA (CAP) - EMEA/H/C/004976/MEA 006.3

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Martin Huber

Scope: Interim report for study 215325 (listed as category 3 study in the RMP): a study on pregnancy and neonatal outcomes following prenatal exposure to cabotegravir – data from the Antiretroviral Pregnancy Registry (APR)

17.5.3. Cinacalcet - MIMPARA (CAP) - EMEA/H/C/000570/MEA 035.6

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Mari Thorn

Scope: Third interim report for study 20180204: a registry study to evaluate the incidence and risk of hypocalcaemia in paediatric patients treated with cinacalcet with secondary hyperparathyroidism receiving maintenance dialysis within the International Pediatric Dialysis Network (IPDN) registry

17.5.4. Coronavirus (COVID-19) vaccine (Ad26.COV2-S, recombinant) - JCOVDEN (CAP) - EMEA/H/C/005737/MEA 008.2

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: From Initial MAA: Post-authorisation, observational study (VAC31518COV4003) to assess the safety of Ad26.COV2.S using electronic health record (EHR) database(s) in

Europe

17.5.5. Deferasirox - EXJADE (CAP) - EMEA/H/C/000670/ANX 038.14

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Tiphaine Vaillant

Scope: Ninth annual interim report for study CICL670E2422: an observational, multicentre cohort study to evaluate the long-term exposure and safety of deferasirox in the treatment of paediatric non-transfusion dependent thalassaemia patients over 10 years old for whom deferoxamine is contraindicated or inadequate]

17.5.6. Eculizumab - SOLIRIS (CAP) - EMEA/H/C/000791/MEA 053.5

Applicant: Alexion Europe SAS

PRAC Rapporteur: Monica Martinez Redondo

Scope: Biennial interim report for study M07-001: a prospective registry for an observational, multicentre, multinational study of patients with paroxysmal nocturnal haemoglobinuria (PNH)

17.5.7. Ertugliflozin - STEGLATRO (CAP) - EMEA/H/C/004315/MEA 002.5

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Second interim report for study MK8835-062: a PASS to assess the risk of diabetic ketoacidosis among type 2 diabetes mellitus patients (T2DM) treated with ertugliflozin compared to patients treated with other antihyperglycemic agents

17.5.8. Ertugliflozin, metformin hydrochloride - SEGLUROMET (CAP) - EMEA/H/C/004314/MEA 002.5

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Second interim report for study MK-8835-062: a PASS to assess the risk of diabetic ketoacidosis (DKA) among type 2 diabetes mellitus (T2DM) patients treated with ertugliflozin compared to patients treated with other antihyperglycemic agents

17.5.9. Ertugliflozin, sitagliptin - STEGLUJAN (CAP) - EMEA/H/C/004313/MEA 002.5

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Second interim report for study MK-8835-062: a PASS to assess the risk of diabetic ketoacidosis (DKA) among type 2 diabetes mellitus (T2DM) patients treated with ertugliflozin compared to patients treated with other antihyperglycemic

17.5.10. Fingolimod - GILENYA (CAP) - EMEA/H/C/002202/MEA 038.5

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Tiphaine Vaillant

Scope: Third interim report for study CFTY720D2311: a two-year, double-blind, randomised, multicentre, active-controlled core phase study to evaluate the safety and efficacy of fingolimod administered orally once daily versus interferon β-1a intramuscular (IM) once weekly in paediatric patients with multiple sclerosis with five-year fingolimod extension phase

17.5.11. Galcanezumab - EMGALITY (CAP) - EMEA/H/C/004648/MEA 002.1

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Kirsti Villikka

Scope: Interim report for study I5Q-MC-B003: Observational Cohort Study of Exposure to Galcanezumab during Pregnancy among Women with Migraine

17.5.12. Golimumab - SIMPONI (CAP) - EMEA/H/C/000992/MEA 033.6

Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Fourth anual progress report for study MK-8259-050: an observational PASS for golimumab in the treatment of poly-articular juvenile idiopathic arthritis (pJIA) using the German Biologics JIA registry (BiKeR)

17.5.13. Human papillomavirus vaccine [types 16, 18] (recombinant, adjuvanted, adsorbed) - CERVARIX (CAP) - EMEA/H/C/000721/II/0117

Applicant: GlaxoSmithkline Biologicals SA

PRAC Rapporteur: Jean-Michel Dogné

Scope: Submission of the interim report for study EPI-HPV-099 (217743): an observational, retrospective database post-authorisation safety study (PASS) assessing trends and changes over time in incidence of anal cancer and feasibility for a case-control study in European countries that introduced Cervarix in their National Immunisation Programme. The study was set up to address the missing information on the impact and effectiveness of Cervarix against anal lesions and cancer in the Cervarix RMP. The RMP version 26 has also been submitted

17.5.14. Ivacaftor, tezacaftor, elexacaftor - KAFTRIO (CAP) - EMEA/H/C/005269/MEA 002.5

Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Martin Huber

Scope: Second annual interim report for study VX20-445-120: Real-World Effects and Utilisation Patterns of Elexacaftor, Tezacaftor, and Ivacaftor Combination Therapy (ELX/TEZ/IVA) in Patients with Cystic Fibrosis (CF)

17.5.15. Naldemedine - RIZMOIC (CAP) - EMEA/H/C/004256/MEA 001.4

Applicant: Shionogi B.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: First progress report for an observational PASS of patients with chronic opioid use for non-cancer and cancer pain who have opioid-induced constipation (OIC)

17.5.16. Nonacog beta pegol - REFIXIA (CAP) - EMEA/H/C/004178/LEG 006.3

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Gabriele Maurer

Scope: Fourth yearly progress report for PASS NN7999-4031 (Paradigm 8): a non-interventional study in male haemophilia B patients receiving nonacog beta pegol (N9-GP) prophylaxis treatment to investigate the potential effects of polyethylene glycol (PEG) accumulation in the choroid plexus of the brain and other tissues/organs

17.5.17. Ofatumumab - KESIMPTA (CAP) - EMEA/H/C/005410/MEA 002.3

Applicant: Novartis Ireland Limited

PRAC Rapporteur: Amelia Cupelli

Scope: First annual interim report for study COMB157G2407] category 3 study listed in the RMP version 2.0: evaluation of pregnancy and infant outcomes in Kesimpta patients using Pregnancy outcomes Intensive Monitoring (PRIM) data – The Kesimpta-PRIM study

17.5.18. Plasmodium falciparum and hepatitis B vaccine (recombinant, adjuvanted) - MOSQUIRIX (Art 5849) - EMEA/H/W/002300/MEA 003.8

Applicant: GlaxoSmithkline Biologicals SA

PRAC Rapporteur: Jean-Michel Dogné

Scope: Seventh progress report for study EPI-MAL-003: Estimate the incidence of protocol-defined potential adverse events of special interest (AESI) and other adverse events leading to hospitalisation or death, in children vaccinated with RTS,S/AS01E enrolled during the EPI-MAL-003 study

17.5.19. Teduglutide - REVESTIVE (CAP) - EMEA/H/C/002345/ANX 003.9

Applicant: Takeda Pharmaceuticals International AG Ireland Branch

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Fourth interim report for study TED-R-13-002: an international short bowel syndrome registry - a prospective, long-term observational cohort study of patients with short bowel syndrome

[49] 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

17.5.20. Tildrakizumab - ILUMETRI (CAP) - EMEA/H/C/004514/MEA 003.6

Applicant: Almirall S.A

PRAC Rapporteur: Adam Przybylkowski

Scope: Third annual progress report for study M14745-40 (Tildrakizumab PASS in European Psoriasis Registry): To collect long-term safety data in particular relating to event of special interest (important potential risks and pregnancy related outcomes) for tildrakizumab. (Malignancies, MACEs, Serious infections, SIBH, Hypersensitivity, IBD, Safety in pregnant and lactating women). To further characterise the long-term safety profile of tildrakizumab in the treatment of psoriasis under conditions of routine clinical care

17.5.21. Tisagenlecleucel - KYMRIAH (CAP) - EMEA/H/C/004090/ANX 003.10

Applicant: Novartis Europharm Limited, ATMP[50]

PRAC Rapporteur: Gabriele Maurer

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

17.5.22. Tozinameran - COMIRNATY (CAP) - EMEA/H/C/005735/MEA 041.2

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Justification for not submitting an interim study report for study C4591036 (former paediatric heart network study): a safety surveillance study of myocarditis and myopericarditis associated with Comirnaty (tozinameran) in persons less than 21 years of age to characterize the clinical course, risk factors, long-term sequelae, and quality of life in children and young adults under 21 years with acute post-vaccine myocarditis, including a protocol amendment

17.6. Others

17.6.1. Tacrolimus - ADVAGRAF (CAP) - EMEA/H/C/000712/MEA 032.3

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Ronan Grimes

Scope: MAH's response to MEA 032.2 [submission of a critical analysis of the feasibility of using alternative data sources to complement the Transplantation Pregnancy Registry International (TPRI) study outcomes on pregnancy and breastfeeding] as per the request for supplementary information (RSI) adopted in October 2022

[50] Advanced therapy medicinal product

17.6.2. Tacrolimus - MODIGRAF (CAP) - EMEA/H/C/000954/MEA 024.3

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Mari Thorn

Scope: MAH's response to MEA 032.2 [submission of a critical analysis of the feasibility of using alternative data sources to complement the Transplantation Pregnancy Registry International (TPRI) study outcomes on pregnancy and breastfeeding] as per the request for supplementary information (RSI) adopted in October 2022

17.6.3. Tozinameran - COMIRNATY (CAP) - EMEA/H/C/005735/MEA 047.2

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Initial statistical analysis plan (SAP) for study C4591038 (listed as a category 3 study in the RMP): a post conditional approval active surveillance study among individuals in Europe receiving the Pfizer BioNTech coronavirus disease 2019 (COVID-19) vaccine to investigate natural history of post-vaccination myocarditis and pericarditis

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 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. Defibrotide - DEFITELIO (CAP) - EMEA/H/C/002393/S/0060 (without RMP)

Applicant: Gentium S.r.l.

PRAC Rapporteur: Mari Thorn

Scope: Annual reassessment of the marketing authorisation

18.1.2. Susoctocog alfa - OBIZUR (CAP) - EMEA/H/C/002792/S/0050 (without RMP)

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Gabriele Maurer

Scope: Annual reassessment of the marketing authorisation

18.2. Conditional renewals of the marketing authorisation

18.2.1. Budesonide - KINPEYGO (CAP) - EMEA/H/C/005653/R/0003 (without RMP)

Applicant: STADA Arzneimittel AG

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Conditional renewal of the marketing authorisation

18.2.2. Entrectinib - ROZLYTREK (CAP) - EMEA/H/C/004936/R/0015 (without RMP)

Applicant: Roche Registration GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Conditional renewal of the marketing authorisation

18.2.3. Volanesorsen - WAYLIVRA (CAP) - EMEA/H/C/004538/R/0022 (without RMP)

Applicant: Akcea Therapeutics Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: Conditional renewal of the marketing authorisation

18.3. Renewals of the marketing authorisation

18.3.1. Abemaciclib - VERZENIOS (CAP) - EMEA/H/C/004302/R/0025 (without RMP)

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Inês Ribeiro-Vaz

Scope: 5-year renewal of the marketing authorisation

18.3.2. Adalimumab - HULIO (CAP) - EMEA/H/C/004429/R/0041 (without RMP)

Applicant: Viatris Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: 5-year renewal of the marketing authorisation

18.3.3. Brexpiprazole - RXULTI (CAP) - EMEA/H/C/003841/R/0014 (with RMP)

Applicant: Otsuka Pharmaceutical Netherlands B.V.

PRAC Rapporteur: Lucia Kuráková

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. Defibrotide - DEFITELIO (CAP) - EMEA/H/C/002393/R/0061 (with RMP)

Applicant: Gentium S.r.l.

PRAC Rapporteur: Mari Thorn

Scope: 5-year renewal of the marketing authorisation

18.3.6. Lomitapide - LOJUXTA (CAP) - EMEA/H/C/002578/R/0054 (without RMP)

Applicant: Amryt Pharmaceuticals DAC

PRAC Rapporteur: Menno van der Elst

Scope: 5-year renewal of the marketing authorisation

18.3.7. Melatonin - SLENYTO (CAP) - EMEA/H/C/004425/R/0021 (with RMP)

Applicant: RAD Neurim Pharmaceuticals EEC SARL

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: 5-year renewal of the marketing authorisation

18.3.8. Neratinib - NERLYNX (CAP) - EMEA/H/C/004030/R/0031 (with RMP)

Applicant: Pierre Fabre Medicament

PRAC Rapporteur: Menno van der Elst

Scope: 5-year renewal of the marketing authorisation

18.3.9. Pegfilgrastim - PELGRAZ (CAP) - EMEA/H/C/003961/R/0040 (with RMP)

Applicant: Accord Healthcare S.L.U.

PRAC Rapporteur: Menno van der Elst

Scope: 5-year renewal of the marketing authorisation

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

Applicant: AstraZeneca AB

PRAC Rapporteur: Ulla Wändel Liminga

Scope: 5-year renewal of the marketing authorisation

18.3.11. Tezacaftor, ivacaftor - SYMKEVI (CAP) - EMEA/H/C/004682/R/0038 (with RMP)

Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: 5-year renewal of the marketing authorisation

18.3.12. Tildrakizumab - ILUMETRI (CAP) - EMEA/H/C/004514/R/0042 (with RMP)

Applicant: Almirall S.A

PRAC Rapporteur: Adam Przybylkowski

Scope: 5-year renewal of the marketing authorisation

18.3.13. Vestronidase alfa - MEPSEVII (CAP) - EMEA/H/C/004438/R/0033 (without RMP)

Applicant: Ultragenyx Germany GmbH

PRAC Rapporteur: Maria del Pilar Rayon

Scope: 5-year renewal of the marketing authorisation

18.3.14. Vigabatrin - KIGABEQ (CAP) - EMEA/H/C/004534/R/0012 (with RMP)

Applicant: ORPHELIA Pharma SAS

PRAC Rapporteur: Kirsti Villikka

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 13-16 March 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 [a,b]	Member	Austria	No interests declared	
Sonja Hrabcik [a]	Alternate	Austria	No interests declared	
Jean-Michel Dogné [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	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Željana Margan Koletić [a]	Alternate	Croatia	No interests declared	
Elena Kaisis [a]	Member	Cyprus	No interests declared	
Panagiotis Psaras [a]	Alternate	Cyprus	No interests declared	
Eva Jirsová [a,b]	Member	Czechia	No interests declared	
Jana Lukacisinova [a,b]	Alternate	Czechia	No interests declared	
Anette Stark [a,b]	Member	Denmark	No interests declared	
Marie Louise Schougaard Christiansen [a,b]	Alternate	Denmark	No interests declared	
Maia Uusküla [a]	Member	Estonia	No interests declared	
Kroot Aab [a]	Alternate	Estonia	No interests declared	
Kirsti Villikka [a,b]	Member	Finland	No interests declared	
Kimmo Jaakkola [a,b]	Alternate	Finland	No interests declared	
Tiphaine Vaillant [a]	Member	France	No interests declared	
Nathalie Gault [a,b]	Alternate	France	No interests declared	
Martin Huber [a,b]	Member (Vice-Chair)	Germany	No interests declared	
Gabriele Maurer [a]	Alternate	Germany	No participation in final deliberations and voting on:	17.4.6. Nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/II/0127
Sofia 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	15.3.1. Abatacept - ORENCIA (CAP) -

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			deliberations and voting on:	EMEA/H/C/000701/II/0152 15.3.18. Lisocabtagene maraleucel - BREYANZI (CAP) - EMEA/H/C/004731/II/0014 16.1.26. Fedratinib - INREBIC (CAP) - PSUSA/00010909/202208 16.1.35. Lisocabtagene maraleucel - BREYANZI (CAP) - PSUSA/00010990/202208 17.1.1. Lenalidomide - REVLIMID (CAP) - EMEA/H/C/PSA/S/0093.1 17.4.6. Nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/II/0127
Melinda Palfi [a,b]	Alternate	Hungary	No interests declared	
Guðrún Stefánsdóttir [b]	Member	Iceland	No participation in final deliberations and voting on:	15.3.37. Sotorasib - LUMYKRAS (CAP) - EMEA/H/C/005522/II/0007 16.1.47. Romiplostim - NPLATE (CAP) - PSUSA/00002660/202207

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				17.2.10. Talimogene laherparepvec - IMLYGIC (CAP) - EMEA/H/C/002771/MEA 005.1 17.4.3. Etelcalcetide - PARSABIV (CAP) - EMEA/H/C/003995/II/0021 17.5.3. Cinacalcet - MIMPARA (CAP) - EMEA/H/C/000570/MEA 035.6
Gudrun Thengilsdottir [a]	Alternate	Iceland	No restrictions applicable to this meeting	
Ronan Grimes [a]	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	
Nadine Petitpain [a,b]	Member	Luxembourg	No restrictions applicable to this meeting	
John Joseph Borg [a,b]	Member (CHMP member)	Malta	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Menno van der Elst [a,b]	Member	Netherlands	No interests declared	
Liana Gross-Martirosyan [a,b]	Alternate	Netherlands	No interests declared	
David Olsen [a,b]	Member	Norway	No participation in final deliberations and voting on:	16.1.15. Darolutamide - NUBEQA (CAP) - PSUSA/00010843/202207 16.3.16. Norethisterone (NAP) - PSUSA/00002188/2
Karen Pernille Harg [a,b]	Alternate	Norway	No interests declared	
Katarzyna Ziolkowska [a,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	
Irina Sandu [a]	Alternate	Romania	No interests declared	
Anna Mareková [a,b]	Member	Slovakia	No interests declared	
Lucia Kuráková [a]	Alternate	Slovakia	No interests declared	
Polona Golmajer [b]	Member	Slovenia	No interests declared	
Milena Radoha-Bergoc [a,b]	Alternate	Slovenia	No restrictions applicable to this meeting	
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]	Member	Sweden	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Mari Thorn [a,b]	Alternate	Sweden	No interests declared	
Annalisa Capuano [a]	Member	Independent scientific expert	No interests declared	
Milou Daniel Drici [a]	Member	Independent scientific expert	No interests declared	
Maria Teresa Herdeiro [a,b]	Member	Independent scientific expert	No interests declared	
Patricia McGettigan [a]	Member	Independent scientific expert	No interests declared	
Hedvig Nordeng [a,b]	Member	Independent scientific expert	No interests declared	
Tania Schink [a]	Member	Independent scientific expert	No participation in final deliberations and voting on:	15.3.12. Edoxaban - LIXIANA (CAP) - EMEA/H/C/002629/WS2409/0042; ROTEAS (CAP) - EMEA/H/C/004339/WS2409/0029 17.3.2. Roflumilast – DAXAS (CAP) - EMEA/H/C/PSR/S/0041
Roberto Frontini [a,b]	Member	Healthcare Professionals' Representative	No restrictions applicable to this meeting	
Salvatore Messana [a]	Alternate	Healthcare Professionals' Representative	No interests declared	
Declan Noone [a]	Member	Patients' Organisation Representative	No interests declared	
Marko Korenjak [a]	Alternate	Patients' Organisation Representative	No participation in discussion, final deliberations	16.1.38. Mecasermin - INCRELEX (CAP) - PSUSA/00001942/202208

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			and voting on:	
Christelle Bizimungu [a]	Expert	Belgium	No restrictions applicable to this meeting	
Laurence de Fays [a]	Expert	Belgium	No interests declared	
Jamila Hamdani [a]	Expert	Belgium	No interests declared	
Piyush Jain [a]	Expert	Belgium	No interests declared	
Fabrice Moore [a]	Expert	Belgium	No interests declared	
Veerle Verlinden [a]	Expert	Belgium	No interests declared	
Françoise Wuillaume [a]	Expert	Belgium	No interests declared	
Petra Vackova [a]	Expert	Czech Republic	No interests declared	
Alexander Braathen [a]	Expert	Denmark	No interests declared	
Hanna Belcik Christensen [a]	Expert	Denmark	No restrictions applicable to this meeting	
Marianne Hald Clemmensen [a]	Expert	Denmark	No restrictions applicable to this meeting	
Karin Erneholm [a]	Expert	Denmark	No restrictions applicable to this meeting	
Kirsten Egebjerg Juul [b]	Expert	Denmark	No interests declared	
Kristina Laursen [a]	Expert	Denmark	No interests declared	
Line Michan [a]	Expert	Denmark	No interests declared	
Annette Cleveland Nielsen [a]	Expert	Denmark	No restrictions	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			applicable to this meeting	
Helle Gerda Olsen [a]	Expert	Denmark	No interests declared	
Aynur Sert [a]	Expert	Denmark	No interests declared	
Ditte Søgaard [a]	Expert	Denmark	No restrictions applicable to this meeting	
Emma Stadsbjerg [a]	Expert	Denmark	No interest declared	
Chau Minh Tran [a]	Expert	Denmark	No interest declared	
Caroline Marie Voss [a,b]	Expert	Denmark	No interests declared	
Julia Maslovskaja [a]	Expert	Estonia	No interests declared	
Serge Bakchine [a]	Expert	France	No restrictions against giving the SAG report for topiramate	
Thomas Berbain [a]	Expert	France	No interests declared	
Camille De-Kervasdoue [a]	Expert	France	No interests declared	
Vincent Gazin [a]	Expert	France	No interests declared	
Mathilde Geynet [a]	Expert	France	No interests declared	
Dina Habib-Hanawy [a]	Expert	France	No restrictions applicable to this meeting	
Stephanie Hueber [a]	Expert	France	No interests declared	
Marie-Caroline Pesquidous [a]	Expert	France	No restrictions applicable to this meeting	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Anne Kleinau [a]	Expert	Germany	No interests declared	
Dennis Lex [a,b]	Expert	Germany	No interests declared	
Dirk Mentzer [b]	Expert	Germany	No interests declared	
Vivien Molitor [a]	Expert	Germany	No interests declared	
Karin Seifert [a]	Expert	Germany	No interests declared	
Gareth Bowen [a]	Expert	Ireland	No interests declared	
Emer Maloney [a]	Expert	Ireland	No interests declared	
Eamon O'Murchu [a]	Expert	Ireland	No interests declared	
Biance Mulder [a]	Expert	Netherlands	No interests declared	
Gunnar Rimul [a]	Expert	Norway	No interests declared	
Carla Torre [a]	Expert	Portugal	No interests declared	
Natividad Galiana Llorca [a]	Expert	Spain	No restrictions applicable to this meeting	
Consuelo Mejías [a]	Expert	Spain	No interests declared	
Charlotte Backman [a,b]	Expert	Sweden	No interests declared	
Karin Hellgren [a]	Expert	Sweden	No interests declared	
Karin Nylén [a]	Expert	Sweden	No interests declared	
A representative from the European Commission attended the meeting				
Meeting run with support from relevant EMA staff				

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

20. Annex III - List of acronyms and abbreviations

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

21. Explanatory notes

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

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

(Items 2 and 3 of the PRAC minutes)

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

Signals assessment and prioritisation

(Item 4 of the PRAC minutes)

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

Risk Management Plans (RMPs)

(Item 5 of the PRAC minutes)

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

Assessment of Periodic Safety Update Reports (PSURs)

(Item 6 of the PRAC minutes)

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

Post-authorisation Safety Studies (PASS)

(Item 7 of the PRAC minutes)

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

Product related pharmacovigilance inspections
(Item 9 of the PRAC minutes)

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

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