15 September 2023
EMA/PRAC/397811/2023
Human Medicines Division

Pharmacovigilance Risk Assessment Committee (PRAC)

Minutes of PRAC meeting on 03-06 July 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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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.

The Chair announced the start of the Spanish presidency of the Council of the European Union (EU).

1.2. Agenda of the meeting on 03-06 July 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 05-08 June 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 05-08 June 2023 were published on the EMA website on 04 September 2023 (EMA/PRAC/337931/2023).

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

None

3.3. Procedures for finalisation

None

3.4. Re-examination procedures[1]

None

3.5. Others

None

4. Signals assessment and prioritisation[2]

4.1. New signals detected from EU spontaneous reporting systems

See also Annex I 14.1.

4.1.1. Insulin degludec, liraglutide - XULTOPHY (CAP); liraglutide – SAXENDA (CAP), VICTOZA (CAP); Semaglutide – OZEMPIC (CAP), RYBELSUS (CAP), WEGOVY (CAP)

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Menno van der Elst

Scope: Signal of suicidal ideation and self-injurious ideation

EPITT 19946 – New signal

[1] Re-examination of PRAC recommendation under Article 32 of Directive 2001/83/EC

[2] 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

Background

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

During routine signal detection activities, a signal of suicidal ideation and self-injurious ideation was identified by the Icelandic Medicines Agency (IMA), based on 2 cases for liraglutide and 1 case for semaglutide retrieved from national databases, and on 108 cases for liraglutide and 62 cases for semaglutide retrieved from EudraVigilance. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by PRAC.

Discussion

Having considered the available evidence from case reports in EudraVigilance, PRAC agreed to extend the signal to the class of glucagon-like peptide-1 receptor agonists (GLP-1 RA).

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

Summary of recommendation(s)

- The MAHs for Saxenda, Victoza and Xultophy, liraglutide-containing products, for Ozempic, Rybelsus and Wegovy, semaglutide-containing products, as well as for Bydureon and Byetta, exenatide-containing products, for Trulicity (dulaglutide), Lyxumia (lixisenatide) and for Suliqua (insuline glargine/lixisenatide) should submit to EMA, within 60 days, a cumulative review of cases of depression and suicide/self-injury, including data from literature, clinical trials and post-marketing setting and discuss the need to update the product information/RMP as warranted.
- PRAC will assess the cumulative review within a 90-day timetable.

4.1.2. Insulin degludec, liraglutide - XULTOPHY (CAP); liraglutide – SAXENDA (CAP), VICTOZA (CAP)

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Menno van der Elst

Scope: Signal of drug-induced liver injury

EPITT 19949 – New signal

Background

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

During routine signal detection activities, a signal of drug-induced liver injury (DILI) was identified by EMA, based on 64 cases retrieved from EudraVigilance (MedDRA PTs: DILI, hepatitis, hepatitis autoimmune, hepatitis acute, hepatitis toxic) as well as on 1 case identified in the literature. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by PRAC.

Discussion

Having considered the available evidence from case reports in EudraVigilance and literature, PRAC agreed that the signal warranted further investigation and agreed to request further information from the MAH.

Summary of recommendation(s)

- In the next PSUR[3], the MAH for Saxenda, Victoza and Xultophy (liraglutide-containing products) should submit to EMA a cumulative review of cases of DILI, hepatitis, hepatitis autoimmune, hepatitis acute and hepatitis toxic, including data from literature, spontaneous reports and clinical trials, as well as a discussion on possible biological plausibility and mechanism of this association. The MAH should discuss the need for any amendment to the product information and/ or the risk management plan (RMP).

4.2. New signals detected from other sources

See Annex I 14.2.

4.3. Signals follow-up and prioritisation

4.3.1. Olaparib - LYNPARZA (CAP) - EMEA/H/C/003726/SDA 021.1

Applicant: AstraZeneca AB

PRAC Rapporteur: Amelia Cupelli

Scope: Signal of hepatocellular damage and hepatitis (HLT)

EPITT 19846 – Follow-up to March 2023

Background

For background information, see PRAC minutes November 2022[4] and PRAC minutes March 2023.

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

Discussion

Having considered the available evidence in EudraVigilance, the literature, nonclinical and clinical studies, PRAC agreed that there is sufficient evidence and that an update of the product information is warranted.

Summary of recommendation(s)

- The MAH for Lynparza (olaparib) should submit to EMA, within 60 days, a variation to amend[5] the product information.

For the full PRAC recommendation, see EMA/PRAC/294541/2023 published on 31 July 2023 on the EMA website.

[3] Data lock point 31/12/2023
[4] Held 24-27 October 2022
[5] Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly.

4.4. Variation procedure(s) resulting from signal evaluation

None

5. Risk management plans (RMPs)

5.1. Medicines in the pre-authorisation phase

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

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

See also Annex I 15.1.

5.1.1. Lebrikizumab - - EMEA/H/C/005894

Scope: Treatment of moderate-to-severe atopic dermatitis in adults and adolescents

5.1.2. Natalizumab - - EMEA/H/C/005752

Scope: Treatment of active relapsing remitting multiple sclerosis (RRMS)

5.1.3. Palopegteriparatide - - EMEA/H/C/005934, Orphan

Applicant: Ascendis Pharma Bone Diseases A/S

Scope: Parathyroid replacement therapy indicated for the treatment of hypoparathyroidism in adults

5.1.4. Pegzilarginase - - EMEA/H/C/005484, Orphan

Applicant: Immedica Pharma AB

Scope: Treatment of hyperargininemia

5.1.5. Rezafungin - - EMEA/H/C/005900, Orphan

Applicant: Mundipharma GmbH

Scope: Treatment of invasive candidiasis

5.1.6. Trastuzumab duocarmazine - - EMEA/H/C/005654

Scope: Treatment of HER2 (Human Epidermal Growth Factor Receptor 2)-positive metastatic breast cancer

5.1.7. Vamorolone - - EMEA/H/C/005679, Orphan

Applicant: Santhera Pharmaceuticals (Deutschland) GmbH

Scope: Treatment of Duchenne muscular dystrophy (DMD)

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

See also Annex I 15.2.

5.2.1. 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

Background

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

PRAC is evaluating a type II variation procedure for Zavesca, a centrally authorised medicine containing miglustat, to update the RMP to remove risks in line with GVP module V revision 2. PRAC is responsible for adopting an outcome based on the assessment report from the PRAC Rapporteur, to be further considered at the level of CHMP, responsible for adopting an opinion on this variation. For further background, see PRAC minutes March 2023.

S**ummary of advice**

- The RMP version 15.1 for Zavesca (miglustat) in the context of the variation under evaluation by PRAC is considered acceptable, however satisfactory responses to the request for supplementary information (RSI) should be submitted.
- PRAC considered that, based on the data submitted by the MAH, the product information (PI) should be amended to add a warning concerning Crohn's disease cases reported in Niemann–Pick type C (NP-C) disease patients treated with Zavesca in post-marketing setting. In addition, PRAC considered that the PI should be updated in order to better highlight the risk of reduced growth in the paediatric population.

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

See Annex I 15.3.

6. Periodic safety update reports (PSURs)

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

See also Annex I 16.1.

6.1.1. Aflibercept[6] - EYLEA (CAP) - PSUSA/00010020/202211

Applicant: Bayer AG

PRAC Rapporteur: Nathalie Gault

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 Eylea, a centrally authorised medicine containing aflibercept (ophthalmological indications only) and issued a recommendation on its marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Eylea (aflibercept) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated in order to amend the existing information on breastfeeding based on available data from literature and reported cases, even though the level of recommendation regarding breastfeeding do not change. Therefore, the current terms of the marketing authorisation(s) should be varied[7].
- In the next PSUR, the MAH should discuss the risk of renal impairment following treatment with aflibercept and provide a cumulative review of cases of renal impairment, including an analysis of the literature on vascular endothelial growth factor (VEGF) inhibitors. In addition, the MAH should provide reviews of cases of hypersensitivity reactions including severe cutaneous hypersensitivity reactions, skin, subcutaneous, musculoskeletal and connective tissue disorders, as well as intraocular inflammation including data from literature.

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. Artesunate - ARTESUNATE AMIVAS (CAP) - PSUSA/00010958/202212

Applicant: Amivas Ireland Ltd

[6] Ophthalmological indication(s) only
[7] Update of SmPC section 4.6. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion.

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

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

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Artesunate Amivas, a centrally authorised medicine containing artesunate 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 Artesunate Amivas (artesunate) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include immune haemolytic anaemia as an undesirable effect with a frequency 'not known' and to amend the warning on post-artesunate delayed haemolysis (PADH). In addition, the product information should be updated to add electrocardiogram QT prolonged as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[8].
- In the next PSUR, the MAH should provide a review of cases of reproductive toxicity (especially in the first trimester) and of Torsade de Pointes.

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.

6.1.3. Blinatumomab - BLINCYTO (CAP) - PSUSA/00010460/202212

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Jana Lukacisinova

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 Blincyto, a centrally authorised medicine containing blinatumomab 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 Blincyto (blinatumomab) in the approved indication(s) remains unchanged.

[8] 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 current terms of the marketing authorisation(s) should be maintained.
- The MAH should submit to EMA, within 6 months, a variation to provide a cumulative review of cases of immune effector cell-associated neurotoxicity syndrome (ICANS), including a proposal for update of the product information and of the RMP, as warranted. In addition, the MAH should discuss on the further need of maintaining the existing educational materials in place (Physician educational material, Pharmacist educational material, Nurse educational material).

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. Coronavirus (COVID-19) vaccine (ChAdOx1-S [recombinant]) - VAXZEVRIA (CAP) - PSUSA/00010912/202212

Applicant: AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

Background

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

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Vaxzevria, a centrally authorised medicine containing COVID-19 vaccine (ChAdOx1-S [recombinant]) and issued a recommendation on its marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Vaxzevria (COVID-19 vaccine (ChAdOx1-S [recombinant])) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include venous thromboembolism 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[9].
- In the next PSUR, the MAH should provide an updated cumulative review of cases of thrombosis with thrombocytopenia syndrome (TTS) after booster dose and discuss the need to update product information. In addition, the MAH should provide a review of cases of dermatomyositis and of severe cutaneous adverse reactions (SCARs), including data from literature. Furthermore, the MAH should provide a cumulative review of cases of erythema multiforme from all available sources, including a causality assessment, and discuss the need for an update of the product information and/or the RMP.

[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.

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. Efgartigimod alfa - VYVGART (CAP) - PSUSA/00011014/202212

Applicant: Argenx

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 Vyvgart, a centrally authorised medicine containing efgartigimod alfa 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 Vyvgart (efgartigimod alfa) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include details on risk minimisation measures to manage infusion and hypersensitivity-related reactions, and to add anaphylactic reaction as a warning and as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[10].
- In the next PSUR, the MAH should provide a review of cases of inappropriate schedule of product administration and any reported associated harm. The MAH should continue to monitor cases of hypersensitivity reactions and infusion reactions, in particular severe hypersensitivity reactions and anaphylactic reactions and discuss any new or cumulative data which may further characterise these risks, focusing especially on the temporality of severe hypersensitivity and anaphylactic reactions.

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. Elasomeran (Spikevax), elasomeran, imelasomeran (Spikevax bivalent Original/Omicron BA.1), elasomeran, davesomeran (Spikevax bivalent Original/Omicron BA.4-5) - SPIKEVAX (CAP) - PSUSA/00010897/202212 (with RMP)

Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

[10] Update of SmPC sections 4.2, 4.4, 4.8 and 6.6. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion.

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 Spikevax, a centrally authorised medicine containing either elasomeran, elasomeran/imelasomeran or elasomeran/davesomeran and issued a recommendation on its marketing authorisation(s). RMP version 7.0 was submitted by the MAH as part of this procedure.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Spikevax in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the warning regarding myocarditis and pericarditis, as well as the warning regarding the use in immunocompromised patients. In addition, the product information should be updated to add mechanical urticaria as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[11].
- In addition, PRAC recommended an update of the list of safety concerns in the RMP by removing the following safety concerns: vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD) as important potential risk and use in immunocompromised subjects, interaction with other vaccines, use in frail subjects with unstable health conditions and co-morbidities (e.g. chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders) and use in subjects with autoimmune or inflammatory disorders as missing information.
- In the next PSUR, the MAH should provide a review of cases of IgA nephropathy, as well as of cases of arrhythmia with a positive rechallenge including an individually justified WHO-UMC causality categorisation and cases of arrhythmia in vaccinees <18 years in the relevant subpopulation analysis.

The next two PSURs (DLP June 2023 and DLP December 2023) should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC. The frequency of submission of the subsequent PSURs should be changed from 6-monthly to yearly and the list of Union reference dates (EURD list) will be updated accordingly.

6.1.7. Tozinameran (COMIRNATY), tozinameran, riltozinameran (COMIRNATY Original/Omicron BA.1), tozinameran, famtozinameran (COMIRNATY Original/Omicron BA.4-5) - COMIRNATY (CAP) - PSUSA/00010898/202212

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

[11] 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.

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 Comirnaty, a centrally authorised medicine containing either tozinameran, tozinameran/riltozinameran or tozinameran, famtozinameran 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 Comirnaty in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the warning regarding myocarditis and pericarditis. Therefore, the current terms of the marketing authorisation(s) should be varied[12].
- In the next PSUR, the MAH should present a review of positive rechallenge cases of dyspnoea, palpitations and tachycardia/heart rate increase with a duration of the events not considered stress/anxiety-related reactions, including cases with a time to onset of less than 2 days and discuss whether an update of the product information is warranted.

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

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

See Annex I 16.2.

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

See also Annex I 16.3.

6.3.1. Apomorphine (NAP) - PSUSA/00000227/202211

Applicant(s): various

PRAC Lead: Marie Louise Schougaard Christiansen

Scope: Evaluation of a PSUSA procedure

Background

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

Apomorphine is a dopamine receptor agonist indicated for the treatment of motor fluctuations (on-off phenomenon) in patients with Parkinson's disease that are insufficiently controlled by an oral antiparkinsonian treatment.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing apomorphine 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 apomorphine-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add 'increased risk of hypotension and loss of consciousness with concomitant use of ondansetron' as contraindication. Therefore, the current terms of the marketing authorisation(s) should be varied[13].
- In the next PSUR, the MAHs of apomorphine-containing products should provide a cumulative review of cases of constipation, including data from literature, clinical trials and from post-marketing setting and discuss the need for an update of the product 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.

6.3.2. Flurbiprofen (NAP) - PSUSA/00001450/202211

Applicant(s): various

PRAC Lead: Valentina Di Giovanni

Scope: Evaluation of a PSUSA procedure

Background

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

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

Summary of recommendation(s) and conclusions

[13] Update of SmPC sections 4.3 and 4.5. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position.

- Based on the review of the data on safety and efficacy, the benefit-risk balance of flurbiprofen-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information of all flurbiprofen-containing products with systemic use, oromucosal formulations and transdermal patches should be updated to include a warning regarding the recommendation to use the lowest effective dose for the shortest duration necessary to relieve symptoms, as flurbiprofen can mask symptoms of infection, with consequent delay in the initiation of appropriate treatment and worsening of the infection. In addition, the product information of all flurbiprofen products with oromucosal formulations and transdermal patches should be updated to include a contraindication and a warning on the risk of topical flurbiprofen use in pregnancy. Therefore, the current terms of the marketing authorisation(s) should be varied[14].

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

6.3.3. Lamotrigine (NAP) - PSUSA/00001825/202211

Applicant(s): various

PRAC Lead: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

Background

Lamotrigine is a phenyltriazine derivative indicated for the treatment of epilepsy in children and adults, as well as for the treatment of bipolar disorder in adults, subject to certain conditions.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing lamotrigine 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 lamotrigine-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add a warning regarding association of HLA-B*1502 allele in individuals of Asian origin and risk of developing Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) following treatment with lamotrigine. In addition, the product information should be updated to add 'motor and/or phonic tics' under the existing undesirable effect 'tics' and to add 'pseudolymphoma' as an undesirable effect with a frequency 'not known'. Furthermore, the product information should be updated to amend the existing information on the overdose and include information regarding the use of intravenous lipid therapy for the

[14] Update of SmPC sections 4.2, 4.3, 4.4 and 4.6. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position.

treatment of cardiotoxicity. Therefore, the current terms of the marketing authorisation(s) should be varied[15].

- In the next PSUR, the originator/brand leader MAH GlaxoSmithKline should provide a cumulative review from literature of cases of skin cancer, including squamous cell carcinoma (SCC). In addition, the same MAH should provide a cumulative review of cases of associations between HLA alleles and lamotrigine induced severe cutaneous adverse reactions (SCARs) in general and specific skin reaction including SJS/TEN, maculopapular exanthema (MPE), drug rash with eosinophilia and systemic symptoms (DRESS) and discuss whether an update of the product information is warranted.

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

6.4. Follow-up to PSUR/PSUSA procedures

See also Annex I 16.4.

6.4.1. Nirmatrelvir, ritonavir - PAXLOVID (CAP) - EMEA/H/C/005973/LEG 017.2

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Martin Huber

Scope: Submission of a justification for not submitting a variation regarding an update of the Paxlovid product information to add myalgia as an adverse drug reaction

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 a safety review for myalgia covering safety data from ongoing early access worldwide and literature data for the above-mentioned medicine(s) (REC 017.1), PRAC requested the MAH to submit a variation to update the product information to add myalgia as an undesirable effect. The responses were assessed by the Rapporteur for further PRAC advice. For further background, see PRAC minutes February 2023.

Summary of advice/conclusion(s)

- Based on the available data and the Rapporteur's assessment, including responses submitted by the MAH, PRAC did not agree with the MAH's justification for not submitting a variation to update the product information.
- The MAH should submit to EMA, within 30 days, a variation to amend the product information to add myalgia as an undesirable effect with a frequency 'uncommon'.

6.5. Variation procedure(s) resulting from PSUSA evaluation

See Annex I 16.5.

[15] Update of SmPC sections 4.4, 4.8 and 4.9. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position.

6.6. Expedited summary safety reviews[16]

None

7. Post-authorisation safety studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)[17]

See also Annex I 17.1.

7.1.1. Axicabtagene ciloleucel - YESCARTA (CAP) - EMEA/H/C/PSA/S/0102.2

Applicant: Kite Pharma EU B.V., ATMP[18]

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Substantial amendment to a protocol for a long-term, non-interventional study of recipients of Yescarta for treatment of relapsed or refractory Diffuse Large B-cell Lymphoma and Primary Mediastinal B-cell Lymphoma [MAH's further response to PSA/S/0102]

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 joint PRAC/CAT recommendation on the need for MAHs' of CAR-T cell-based therapies to redesign their long-term safety and efficacy post-marketing follow-up studies to incorporate alternative data sources for aggregate reporting to EBMT (see PRAC minutes May 2022), the MAH for Yescarta (axicabtagene ciloleucel) submitted to EMA a feasibility assessment of the PRAC/CAT recommendation for the protocol KT-EU-471-0117 (listed as category 1 study in the RMP): a non-interventional PASS to assess the safety profile including long term safety in patients with B-lymphocyte malignancies treated with axicabtagene ciloleucel in the post marketing setting for review by PRAC. For further background, see PRAC minutes February 2023 and PRAC minutes June 2023.

Endorsement/Refusal of the protocol

- Based on the feasibility assessment, the MAH considered that no update of the study protocol is warranted. Having considered the MAH's responses, PRAC objected to the MAH's proposal, as the Committee considered that the design of the study did not fulfil the study objectives at this stage.
- The MAH should provide an update of the protocol to incorporate CIBMTR (Center for International Blood and Marrow Transplant Research) as a data source in the PASS, including a statistical analysis plan (SAP).
- The MAH should submit a revised PASS protocol by 14 August 2023 to EMA. A 60 days-assessment timetable will be followed.

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

7.2. Protocols of PASS non-imposed in the marketing authorisation(s)[19]

See Annex I 17.2.

7.3. Results of PASS imposed in the marketing authorisation(s)[20]

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

Applicant: Nordic Group BV (Trasylol)

PRAC Rapporteur: Jean-Michel Dogné

Scope: Submission of the final report from the Nordic Aprotinin Patient Registry to record utilisation information on patients at cardiac surgery centres

Background

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

In line with the conclusions reached in 2013 of the referral procedure under Article 31 of Directive 2001/83/EC (EMEA/H/A-1267) conducted by CHMP for antifibrinolytics containing aprotinin, aminocaproic acid and tranexamic acid, the MAH for Trasylol (aprotinin) was required to conduct a registry in order to monitor the pattern of use of aprotinin. The MAH for Trasylol (aprotinin) submitted to EMA the final results of the study entitled: 'Nordic Aprotinin Patient Registry (NAPaR): a multicentre, non-interventional PASS with active surveillance via patient exposure registry' enrolling patients undergoing cardiac surgery on cardiopulmonary bypass and exposed to aprotinin at all centres in EU. PRAC is responsible for issuing a recommendation on the final study results including the assessment of the MAH's responses to requests for supplementary information (RSI). For further background, see PRAC minutes April 2021, PRAC minutes September 2021[21], PRAC minutes February 2022, PRAC minutes October 2022[22] and PRAC minutes February 2023.

Summary of recommendation(s) and conclusions

- Based on the review of the final report of the registry study, the MAH's responses to the RSI and the Rapporteur's assessment, PRAC considered that the benefit-risk balance of aprotinin-containing products remains unchanged.
- Nevertheless, PRAC recommended changes to the conditions of the marketing authorisation(s) of medicinal products containing the active substance intravenous aprotinin concerned by the PASS final report. As a consequence, the product information should be amended in order to reflect the study results. In addition, the MAH should submit, within 6 months, to the National Competent Authorities (NCAs), the content and format of the educational programme aiming at reducing off-label use of intravenous aprotinin and educating healthcare professionals about its key risks and how to ensure adequate anticoagulation during its use. In addition, PRAC agreed on the key elements of the educational material for healthcare professionals (accompanied by a cover letter, where applicable). Moreover, the MAH should submit to the NCAs, within 6 months, an updated RMP, including an assessment of the effectiveness of the additional risk

[19] 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
[20] In accordance with Article 107p-q of Directive 2001/83/EC
[21] Held on 30 August-2 September 2021
[22] Held on 26-29 September 2022

minimisation measures. Therefore, the current terms of the marketing authorisation(s) should be varied[23].

7.3.2. Valproate[24] (NAP) - EMEA/H/N/PSR/J/0043

Applicant: Sanofi-Aventis Recherche & Développement

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Final study report for a retrospective observational study to investigate the association between paternal exposure to valproate and the risk of congenital anomalies and neurodevelopmental disorders including autism in offspring

Background

Further to the conclusions dated 2018 of the referral procedure under Article 31 of Directive 2001/83/EC (EMEA/H/A-31/1454) conducted by PRAC for valproate-containing medicines, the MAHs were required as a condition to the marketing authorisation(s) (Annex IV) to conduct a retrospective observational study to investigate the association between paternal exposure to valproate and the risk of congenital anomalies and neurodevelopmental disorders including autism in offspring. The MAH Sanofi-Aventis Recherche & Développement, on behalf of a consortium, submitted to EMA the final results of the study. See PRAC minutes May 2023 and PRAC minutes June 2023.

Following the revised list of questions (LoQ) adopted in June 2023, the MAH Sanofi-Aventis Recherche & Développement submitted a letter to EMA and PRAC, dated 23 June 2023, where it was confirmed that the (quality) issues detected in the Danish dataset had been investigated and confirmed as not impacting the DK (final) study results previously submitted. The issues detected in the Norwegian dataset were not yet resolved. The MAH also informed that only part of the questions raised by PRAC could be answered as per the timetable adopted in June.

Summary of recommendation(s) and conclusions

- Based on the PRAC Rapporteur's assessment and the information provided by the MAH, PRAC adopted a revised list of questions (LoQ) and an updated timetable for this procedure.
- The MAH should provide responses on the study results and additional analyses, as well as corrected analyses, as soon as possible, having resolved the issues with the Norwegian dataset.

Post meeting note: See EMA press release on data on paternal exposure to valproate published on 16 August 2023.

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

See also Annex I 17.4.

[23] Update of SmPC sections 4.2, 4.4, 4.5, 4.8 and 5.1. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of an opinion.
[24] Valproic acid, sodium valproate, valproate pivoxil, valproate semisodium, valpriomide, valproate bismuth, calcium valproate, valproate magnesium
[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

7.4.1. 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

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 Entyvio (vedolizumab), the MAH conducted a non-imposed non-interventional PASS (listed as category 3 study in the RMP) comparing vedolizumab to other biologic agents in patients with ulcerative colitis or Crohn's disease. The Rapporteur assessed the MAH's final study report in addition to the MAH's answers to the request for supplementary information (RSI). For further background, see PRAC minutes October 2022[26], PRAC minutes March 2023.

Summary of advice

- Based on the available data, the MAH's responses to the RSI and the Rapporteur's review, PRAC considered that the ongoing variation assessing the final study report can be advised for approval. It includes amendments to the product information on malignancies, to add *Clostridium difficile* infection as an undesirable effect with a frequency 'common', as well as to update the frequency of other undesirable effects such as herpes zoster, infusion site reaction (including: infusion site pain and infusion site irritation), and infusion related reaction in order to reflect the results of the study. Moreover, all the risks from the list of safety concerns in the RMP were removed, except the 'long term safety' as missing information. Finally, PRAC agreed with the removal of the patient alert card and physician's educational material as additional risk minimisation measures from Annex II-D.

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

See Annex I 17.5.

7.6. Others

None

7.7. New Scientific Advice

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

[26] Held 26-29 September 2022

7.8. Ongoing Scientific Advice

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

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

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

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

8.1. Annual reassessments of the marketing authorisation

See Annex I 18.1.

8.2. Conditional renewals of the marketing authorisation

See Annex I 18.2.

8.3. Renewals of the marketing authorisation

See Annex I 18.3.

9. Product related pharmacovigilance inspections

9.1. List of planned pharmacovigilance inspections

None

9.2. Ongoing or concluded pharmacovigilance inspections

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

9.3. Others

None

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

10.1. Safety related variations of the marketing authorisation

None

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

None

10.3. Other requests

None

10.4. Scientific Advice

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

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

11.1. Safety related variations of the marketing authorisation

11.1.1. Amino acid combinations, glucose, triglyceride combinations[27], with or without electrolytes, mineral compounds[28] [29] (NAP) - SE/H/918/02-04/II/51

Applicant(s): Baxter Medical AB

PRAC Lead: Ulla Wändel Liminga

Scope: PRAC consultation on a type II national variation addressing the potential risks associated with the formation of 'yellow globules' in the lipid emulsion need to be further assessed, given the potential seriousness of this finding as per conclusions of the PSUSA procedure (PSUSA/00010190/202112) concluded in September 2022[30], on request of Sweden

Background

Amino acid combinations/glucose/triglyceride combinations/with or without electrolytes/mineral compounds are indicated for parenteral nutrition in paediatric patients when oral or enteral nutrition is not possible, insufficient or contraindicated.

In the context of the evaluation of a type II variation procedure on the potential risks associated with the formation of 'yellow globules' in the lipid emulsion as per conclusions of the PSUSA procedure (PSUSA/00010190/202112) concluded in September 2022, Sweden requested PRAC advice on its assessment.

Summary of advice

- Based on the review of the available information, PRAC expressed different views on the need for an update of the product information to include the need for using inline filters in order to minimise the risk of potential clinical consequences related to particulate matter in intravenous solution. Although some members agreed that the use of filters is

[27] E.g. olive oil, soya bean oil, fish oil
[28] Intravenous (I.V.) application only
[29] Nationally authorised product Numeta only
[30] Held 29 August-1 September 2022

part of routine clinical practice, and an update of the product information might not be warranted, others considered that the use of 1.2 micron filter is an adequate measure to further minimise this risk, taking into account the vulnerable population exposed to the particulate matter (newborns, including prematures) and that it is reasonable to reflect this recommendation in the product information, so that health care professionals are given advice about the use of the Numeta products. However, PRAC agreed that updating the product information for Numeta does not automatically call for similar actions for other lipid containing parenteral nutrition products and that each product should be assessed on a case-by-case basis. Finally, PRAC agreed there is no need to issue a DHPC to communicate on the recommendation to use a filter when administering Numeta (amino acid combinations/glucose/triglyceride combinations/with or without electrolytes/mineral compounds).

11.2. Other requests

None

12. Organisational, regulatory and methodological matters

12.1. Mandate and organisation of PRAC

12.1.1. PRAC membership

The Chair announced that Marie Louise Schougaard Christiansen is the new member for Denmark, replacing Anette Kirstine Stark whose mandate ended on 09 June 2023.

12.1.2. Vote by proxy

None

12.1.3. Scientific Committee Meetings – alternating face-to-face and virtual meetings schedule for 2024

The EMA Secretariat presented to PRAC the alternating face-to-face and virtual meetings schedule for 2024. PRAC noted the information.

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. Health threats and EMA Emergency Task Force (ETF) activities - update

The EMA Secretariat provided PRAC with an update on the characteristics of the post-COVID-19 condition, COVID-19 outcomes for paediatric population, as well as study results on effectiveness of COVID-19 mRNA vaccines' (booster dose and adapted mRNA vaccines) against the new Omicron subvariants. The EMA Secretariat also updated PRAC on the safety and efficacy of vaccines under development intended for prevention of influenza virus infection and ZIKA virus infection.

12.5. Cooperation with International Regulators

None

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

None

12.7. PRAC work plan

None

12.8. Planning and reporting

12.8.1. Marketing authorisation applications (MAA) forecast for 2023 – planning update dated Q2 2023

The EMA Secretariat presented for information to PRAC a quarterly updated report on marketing authorisation applications (MAA) planned for submission (the business 'pipeline'). For previous update, see PRAC minutes April 2023.

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

The EMA Secretariat presented the ongoing activities of the Granularity and Periodicity Advisory Group (GPAG) in the context of the implementation of the new EURD tool. PRAC noted the information.

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 July 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 July 2023, the updated EURD list was adopted by CHMP and CMDh at their upcoming 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. Periodic Safety Update Reports Single Assessment (PSUSA) – proactive publication of PRAC assessment reports for COVID-19 vaccines

The EMA Secretariat presented to PRAC the EMA initiative to publish PSURs and PRAC assessment reports for COVID-19 vaccines following PSUSA procedures, in order to further increase the transparency of safety information to the public and stakeholders. The EMA Secretariat also presented an overview of the activities to be performed in the context of the publication process. PRAC supported the initiative.

12.11. Signal management

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

PRAC lead: Menno van der Elst

PRAC was updated on the ongoing activities and the progress from the SMART working group meeting on Methods held on 14 June 2023, such as an update on EurEKA, including an outline on the benefits and challenges of implementing a database of adverse drug reactions using the current product information, as well as an update on the work on the Vigibase Pregnancy algorithm.

12.11.2. Signal management – List of substances subject to worksharing

The EMA Secretariat presented to PRAC a brief background about the List of active substances subject to worksharing for signal management, as well as the proposed plan for the next update and publication of a consolidated list based on Article 57 and EudraVigilance reporting data. PRAC noted the information.

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

12.14. Risk management plans and effectiveness of risk minimisations

12.14.1. Risk management systems

None

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

None

12.15. Post-authorisation safety studies (PASS)

12.15.1. Post-authorisation Safety Studies – imposed PASS

None

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

None

12.16. Community procedures

12.16.1. Referral procedures for safety reasons

None

12.17. Renewals, conditional renewals, annual reassessments

None

12.18. Risk communication and transparency

12.18.1. Public participation in pharmacovigilance

None

12.18.2. Safety communication

None

12.19. Continuous pharmacovigilance

12.19.1. Incident management

None

12.20. Impact of pharmacovigilance activities

12.20.1. Impact of EU label changes and regulatory communication on SARS-CoV-2 adenovirus vector vaccines in context of thrombosis with thrombocytopenia syndrome (TTS): risk awareness and adherence - PRAC Sponsor's critical appraisal

PRAC lead: Jean-Michel Dogné

PRAC discussed the results of the survey study 'Impact of EU label changes and regulatory communication on SARS-CoV-2 adenovirus vector vaccines in context of thrombosis with thrombocytopenia syndrome (TTS): risk awareness and adherence' (EUPAS44970) commissioned under the remit of the PRAC Strategy on measuring the impact of pharmacovigilance activities following recommendations in 2021 to learned societies and healthcare professionals for assessing people with signs and symptoms of TTS following vaccination with COVID-19 adenovirus vector vaccines in context of referral EMEA/H/A-

5(3)/1507. The study concluded that there was variability in the countries studied as regards the implementation of EMA recommendations in national vaccination policies. Healthcare professional awareness about the risk of TTS was high with preference for national guidelines as source of risk information about COVID-19 vaccines. Public knowledge about TTS resulted in less willingness to be vaccinated with COVID-19 adenovirus vector vaccines. PRAC noted that the study was subject to several methodological limitations which precluded the ability to draw conclusions on the impact of the 2021 recommendations for COVID-19 adenovirus vector vaccines.

12.20.2. Strategy on measuring the impact of pharmacovigilance – PRAC interest group (IG) Impact – revision of the process for prioritisation and follow-up of impact research, including regulatory toolbox (rev.2)

The EMA secretariat presented to PRAC the proposed revised process for prioritisation and regulatory follow-up of impact research commissioned under the remit of the PRAC Strategy on measuring the impact of pharmacovigilance activities (revision 2). For further background on the previous revision of the process, please see PRAC minutes February 2023. The main changes envisaged by this revision are related to further clarification on the roles and responsibilities for impact research via DARWIN EU® pathway, as well as to the implementation of a regulatory toolbox to support PRAC Sponsor/PRAC Rapporteur in identifying the appropriate framework for regulatory follow-up.

PRAC members were invited to send their comments on the revised process by 28 July 2023.

12.21. Others

12.21.1. International Conference on Harmonisation (ICH) E2D(R1) guideline - Post-approval safety data management: definitions and standards for expedited reporting – update on the revision process

The EMA secretariat presented to PRAC an update on the revision process of the ICH E2D (R1) guideline, including feedback on the Expert Working Group (EWG) meeting held on 10-13 June 2023 in Vancouver, Canada. Ahead of the release for public consultation planned for October 2023. PRAC members were invited to comment on the draft guideline, by 31 July 2023. Further updates on the revision of the guideline will be provided to PRAC in due course.

12.21.2. Guideline on risk assessment of medicinal products on human reproduction and lactation: from data to labelling – concept paper on revision of the guideline

PRAC lead: Ulla Wändel Liminga, Eva Jirsová, Hedvig Nordeng

The EMA secretariat presented to PRAC the scope of the guideline, along with the rationale for starting the revision of this guideline, as well as the ongoing activities and the next steps to be performed in order to finalise the document. The revision of the 'Guideline on risk assessment of medicinal products on human reproduction and lactation: from data to labelling' (EMEA/CHMP/203927/2005) is included in both PRAC and CHMP workplans for 2023.

Post-meeting note: PRAC members were invited to express their interest in joining the drafting group. The aim of the drafting group is to discuss and finalise the concept paper in

view of the public consultation.

12.21.3. Good Pharmacovigilance Practice (GVP) – mid-year update 2023

PRAC lead: Sabine Straus

PRAC was provided with an overview of the status of the activities on GVP updates included in the PRAC workplan for 2023. In addition, the EMA Secretariat presented a list of ongoing and planned activities on various GVP modules updates, together with their proposed timelines. The EMA secretariat will keep PRAC informed about the status on GVP updates. PRAC noted the information.

12.21.4. EMA-funded study on anticonvulsants in pregnancy

In line with EMA strategy on drug safety in pregnancy and breastfeeding, the EMA secretariat presented to PRAC a proposal to conduct a study with the aim to generate an overview of anticonvulsant utilisation patterns in pregnancy and exposure *in utero.* PRAC will be kept informed about the development of this project.

12.21.5. PRAC Assessors trainings - EU NTC Learning & Development (L&D) toolkit and remuneration for training development/delivery

PRAC lead: Martin Huber, Sabine Straus

The EMA secretariat presented to PRAC an update on the organisation of training sessions for pharmacovigilance assessors aiming to replace the yearly training and on the schedule for the next sessions. The EMA secretariat also provided on overview of the new EU NTC L&D toolkit, covering information regarding the development of curriculum frameworks, as well as design, development and evaluation of training courses, and informed the Committee about the possibility of remuneration for training development and delivery, based on the criteria in place. PRAC noted the information.

13. Any other business

None

14. Annex I – Signals assessment and prioritisation[31]

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[32].

[31] 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

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

14.1. New signals detected from EU spontaneous reporting systems

14.1.1. Axicabtagene Ciloleucel – YESCARTA (CAP)

Applicant: Kite Pharma EU B.V., ATMP[33]

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Signal of progressive multifocal leukoencephalopathy (PML)

EPITT 19940 – New signal

Lead Member State(s): DK

14.1.2. Ixazomib – NINLARO (CAP)

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of angioedema and anaphylactic reaction

EPITT 19950 – New signal

Lead Member State(s): SE

14.2. New signals detected from other sources

14.2.1. Dabrafenib - TAFINLAR (CAP); Trametinib - MEKINIST (CAP)

Applicant: Novartis Europharm Limited

PRAC Rapporteur: David Olsen

Scope: Signal of peripheral neuropathy

EPITT 19947 – New signal

Lead Member State(s): NO

14.2.2. Encorafenib – BRAFTOVI (CAP); Binimetinib – MEKTOVI (CAP)

Applicant: Pierre Fabre Medicament

PRAC Rapporteur: Inês Ribeiro-Vaz

Scope: Signal of tumour lysis syndrome

EPITT 19941 – New signal

Lead Member State(s): PT

[33] Advanced therapy medicinal product

15. Annex I – Risk management plans

15.1. Medicines in the pre-authorisation phase

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

15.1.1. Leniolisib - - EMEA/H/C/005927, Orphan

Applicant: Pharming Technologies B.V.

Scope: Treatment of activated phosphoinositide 3-kinase delta syndrome (APDS)

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. Abiraterone acetate - ZYTIGA (CAP) - EMEA/H/C/002321/II/0072

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Submission of an updated RMP version 15.1 in order to align with Good Pharmacovigilance Practices Module V, Revision 2

15.2.2. Anakinra - KINERET (CAP) - EMEA/H/C/000363/II/0090

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Submission of an updated RMP version 6.2 in order to add DRESS as an important potential risk as well as the removal of the additional risk minimization measures for serious infections, following the assessment of procedure PSUSA/00000209/202205. Annexes II and IV are updated in accordance

15.2.3. Benralizumab - FASENRA (CAP) - EMEA/H/C/004433/II/0049/G

Applicant: AstraZeneca AB

PRAC Rapporteur: David Olsen

Scope: Grouped application consisting of: 1) Submission of an updated RMP version 5 in order to remove the safety concern of missing information on use in pregnant and lactating women. Consequently, the MAH proposes to remove study D3250R00026 as an additional pharmacovigilance activity, and to remove the commitment to conduct additional pharmacovigilance for the use of benralizumab in pregnant and lactating women with

severe eosinophilic asthma; 2) Submission of an updated RMP version 5 in order to remove the safety concern of important potential risk of serious infections

15.2.4. Esomeprazole - NEXIUM CONTROL (CAP) - EMEA/H/C/002618/II/0038

Applicant: GlaxoSmithKline Dungarvan Ltd

PRAC Rapporteur: Rugile Pilviniene

Scope: Submission of an updated RMP version 2.0 in order to update the list of safety concerns to meet the definition of important risk and missing information provided in GVP Module V Rev. 2

15.2.5. Insulin glargine - LANTUS (CAP) - EMEA/H/C/000284/WS2491/0127; TOUJEO (CAP) - EMEA/H/C/000309/WS2491/0122

Applicant: Sanofi-Aventis Deutschland GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Submission of an updated RMP version 7.0 of Toujeo and Lantus following removal of the "Medication error due to non-compliance with instructions to use a new needle for each injection: wrong dose injected due to blocked needle" from the list of safety concerns (EMEA/H/C/000309/II/0105/G), to: remove the follow-up questionnaire for the topic "Medication error due to non-compliance with instructions to use a new needle for each injection: wrong dose injected due to blocked needle" from routine pharmacovigilance activities (Part III); remove the suspected blockage of needle questionnaire (Annex 4);- update with the revised data lock point (DLP) (Part II)

15.2.6. Somatropin - NUTROPINAQ (CAP) - EMEA/H/C/000315/II/0077

Applicant: Ipsen Pharma

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Submission of an updated RMP version 4.0 in order to remove some of the safety concerns in compliance with GVP Module V Revision 2. In addition, the MAH took the opportunity to add data from final clinical study report of International Cooperative Growth Study (iNCGS) registry (non-interventional study) and exposure and safety information

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

Applicant: Takeda Pharmaceuticals International AG Ireland Branch

PRAC Rapporteur: Martin Huber

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

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

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

15.3.1. Anifrolumab - SAPHNELO (CAP) - EMEA/H/C/004975/II/0007

Applicant: AstraZeneca AB

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Update of sections 4.4, 4.8, 5.1 and 5.2 of the SmPC based on final results from study D3461C00009 listed as an additional pharmacovigilance activity in the RMP; this is a multicentre, randomised, double-blind, placebo-controlled Phase III extension study to characterise the long-term safety and tolerability of anifrolumab in adult subjects with active systemic lupus erythematosus. In addition, the MAH took the opportunity to implement minor changes to sections 4.2 and 6.6 of the SmPC and to the package leaflet

15.3.2. Atezolizumab - TECENTRIQ (CAP) - EMEA/H/C/004143/II/0078

Applicant: Roche Registration GmbH

PRAC Rapporteur: Inês Ribeiro-Vaz

Scope: Update of section 5.1 of the SmPC in order to include the final overall survival (OS) analysis results based on final results from study WO30070 listed as a PAES in the Annex II to fulfil ANX/PAE 003; this is a Phase III, multicenter, randomised, placebo-controlled study of atezolizumab as monotherapy and in combination with platinum-based chemotherapy in patients with untreated locally advanced or metastatic urothelial carcinoma. The RMP version 27 has also been submitted. In addition, the MAH took the opportunity to update Annex II of the SmPC

15.3.3. 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

15.3.4. 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

15.3.5. Baricitinib - OLUMIANT (CAP) - EMEA/H/C/004085/X/0035/G

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Extension application to introduce a new strength (1 mg film-coated tablet), grouped with a type II variation (C.I.6.a) in order to extend the indication to include treatment, as monotherapy or in combination with conventional synthetic disease modifying antirheumatic drugs (DMARDs), of active juvenile idiopathic arthritis (JIA) in patients 2 years of age and older who have had an inadequate response or intolerance to one or more prior conventional synthetic or biologic DMARDs, based on final results from the pivotal study JAHV (I4V-MC-JAHV); this is a multicentre, double-blind, randomised, placebo-controlled, medication-withdrawal Phase 3 study in children from 2 years to less than 18 years of age with JIA who have had an inadequate response or intolerance to treatment with at least 1 conventional DMARD (cDMARD) or biological (bDMARD). 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 15.1 of the RMP has also been submitted

15.3.6. Burosumab - CRYSVITA (CAP) - EMEA/H/C/004275/II/0035/G, Orphan

Applicant: Kyowa Kirin Holdings B.V.

PRAC Rapporteur: Gabriele Maurer

Scope: Grouped variation consisting of: 1) Addition of prefilled syringe presentation for the 10 mg strength; addition of prefilled syringe presentation for the 20 mg strength; addition of prefilled syringe presentation for the 30 mg strength; 2) other quality variations

15.3.7. Denosumab - PROLIA (CAP) - EMEA/H/C/001120/II/0098

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Mari Thorn

Scope: Update of sections 4.2, 4.4, 5.1 and 5.2 in order to update efficacy, pharmacokinetic and safety information for paediatric population following the assessment of P46/043 and P46/044 based on final results from study 20130173, listed as a category 3 study in the RMP and study 20170534. Study 20130173 was a prospective, multicentre, open-label, single-arm phase 3 study to evaluate the safety, efficacy, and PK of denosumab in children 2 to 17 years of age with osteogenesis imperfecta (OI). Study 20170534 was an open-label, prospective, extension study of Study 20130173. The RMP version 31 has also been submitted. In addition, the MAH took this opportunity to introduce minor editorial changes

15.3.8. Dolutegravir, lamivudine - DOVATO (CAP) - EMEA/H/C/004909/II/0040/G

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: David Olsen

Scope: Submission of the final reports from study 204861 (GEMINI-1) and study 205543 (GEMINI-2) listed as category 3 studies in the RMP; these are phase 3, randomised, double-blind, multicentre, parallel group, non-inferiority studies evaluating the efficacy, safety and tolerability of dolutegravir plus lamivudine compared to dolutegravir plus

tenofovir/emtricitabine in HIV-1-infected treatment-naïve adults. The RMP version 4.0 has also been submitted

15.3.9. Dostarlimab - JEMPERLI (CAP) - EMEA/H/C/005204/II/0023

Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Inês Ribeiro-Vaz

Scope: Extension of indication to include in combination with platinum-containing chemotherapy the treatment of adult patients with mismatch repair deficient (dMMR)/ microsatellite instability-high (MSI-H) primary advanced or recurrent endometrial cancer (EC) and who are candidates for systemic therapy, based on results from study 213361 (RUBY) Part 1, listed as a Specific Obligation in the Annex II; this is a phase 3, randomised, double-blind, multicenter study of dostarlimab (TSR-042) plus carboplatin-paclitaxel versus placebo plus carboplatin-paclitaxel in patients with recurrent or primary advanced endometrial cancer. 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 marketing authorisation holder (MAH) took the opportunity to introduce minor editorial changes to the product information. As part of the application, the MAH is requesting a 1-year extension of the market protection

15.3.10. Efgartigimod alfa - VYVGART (CAP) - EMEA/H/C/005849/II/0006, Orphan

Applicant: Argenx

PRAC Rapporteur: Rhea Fitzgerald

Scope: Update of sections 4.4 and 4.5 of the SmPC in order to amend an existing warning on use of vaccination and update drug-drug interaction information on vaccines based on final results from study ARGX-113-2102; this is a phase 1, randomised, open-label, placebo-controlled, parallel-group study to evaluate the immune response to PNEUMOVAX 23 in healthy participants receiving efgartigimod IV 10 mg/kg or placebo. The RMP version 1.2 has also been submitted. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet

15.3.11. 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)

15.3.12. Fluticasone furoate, vilanterol - RELVAR ELLIPTA (CAP) - EMEA/H/C/002673/WS2438/0061/G; REVINTY ELLIPTA (CAP) - EMEA/H/C/002745/WS2438/0058/G

Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Monica Martinez Redondo

Scope: Grouped application consisting of 1) Update sections 4.2 and 5.1 of the SmPC to include results from study HZA107116. This is a randomised, double-blind, parallel group, multicentre, stratified, study evaluating the efficacy and safety of once daily fluticasone furoate (FF)/vilanterol (VI) inhalation powder compared to once daily fluticasone furoate inhalation powder in the treatment of asthma in participants aged 5 to 17 years old (inclusive) currently uncontrolled on inhaled corticosteroids. The package leaflet and labelling are updated accordingly. The RMP version 12.0 has also been submitted. In addition, the MAH took the opportunity to implement editorial changes to the SmPC; 2) Submission of final report from Phase 2b study HZA106855 (FF dose ranging) which gives information regarding the dose selection for FF combination in study HZA107116; 3) Submission of final report from Phase 2b study HZA106853 (VI dose ranging) which gives information regarding the dose selection for VI combination in study HZA107116

15.3.13. Golimumab - SIMPONI (CAP) - EMEA/H/C/000992/II/0113

Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Mari Thorn

Scope: Submission of the final report from study CNTO148UCO1001 (PURSUIT PEDS PK) listed as a category 3 study in the RMP. This is a phase 1b open-label study to assess the safety and pharmacokinetics of subcutaneously administered golimumab, a human anti-TNFα antibody, in paediatric subjects with moderately to severely active ulcerative colitis. The RMP version 24.1 has also been submitted

15.3.14. Influenza vaccine (surface antigen, inactivated, adjuvanted) - FLUAD TETRA (CAP) - EMEA/H/C/004993/II/0043

Applicant: Seqirus Netherlands B.V.

PRAC Rapporteur: Jean-Michel Dogné

Scope: Extension of indication to include adults 50 years of age and older for Fluad Tetra, based on final results from study V118_23; this is a phase 3, randomised, observer-blind, controlled, multicenter, clinical study to evaluate immunogenicity and safety of an MF59-adjuvanted quadrivalent subunit inactivated influenza vaccine in comparison with a licensed quadrivalent influenza vaccine, in adults 50 to 64 years of age. As a consequence, sections 4.1, 4.8 and 5.1 of the SmPC are updated. The Labelling and package leaflet are updated in accordance. Version 2.9 of the RMP has also been submitted. In addition, the marketing authorisation holder (MAH) took the opportunity to introduce minor editorial changes to the product information

15.3.15. Ivacaftor - KALYDECO (CAP) - EMEA/H/C/002494/X/0114/G

Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Monica Martinez Redondo

Scope: Grouped applications consistin of: 1) Extension application to add a new strength (59.5 mg) of the granules pharmaceutical form grouped with a type II variation to support a new indication in a combination regimen with ivacaftor/tezacaftor/elexacaftor for the treatment of cystic fibrosis (CF) in paediatric patients aged 2 to less than 6 years who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator

(CFTR) gene (see section 5.1). The RMP (version 15.1) has also been submitted; 2) Type IB B.II.f.1.b - to extend the shelf-life of the granules pharmaceutical form of the finished product as packaged for sale from 3 to 4 years. The product information has been updated accordingly

15.3.16. Ivacaftor, tezacaftor, elexacaftor - KAFTRIO (CAP) - EMEA/H/C/005269/X/0033, Orphan

Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Martin Huber

Scope: Extension application to add a new pharmaceutical form (granules) associated with 2 new strengths (60 mg/40 mg/80 mg and 75 mg/50 mg/100 mg) to support a new indication in a combination regimen with ivacaftor for the treatment of cystic fibrosis (CF) in paediatric patients aged 2 to less than 6 years who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene (see section 5.1). The new indication is only applicable to the new granules pharmaceutical form. As a consequence of the line extension the product information for the film coated tablets is also updated to reflect the addition of a new pharmaceutical form. The RMP (version 6.2) 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. Maralixibat - LIVMARLI (CAP) - EMEA/H/C/005857/II/0003/G, Orphan

Applicant: Mirum Pharmaceuticals International B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Grouped variation consisting of: 1) Extension of indication to include treatment of Progressive Familial Intrahepatic Cholestasis (PFIC) in patients 2 months of age and older for LIVMARLI, based on results from studies MRX-502, LUM001-501, MRX-503, MRX-800 and MRX-801; MRX-502 is an international, multicenter, randomised, double-blind, placebo-controlled, parallel group Phase 3 study that evaluated the efficacy and safety of maralixibat in PFIC participants aged >12 months to <18 years on a proposed dosage of up to 600 µg/kg BID over 6 months. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and Annex II are updated in accordance. Version 2.0 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to introduce minor editorial changes; 2)

other quality variations

15.3.19. Natalizumab - TYSABRI (CAP) - EMEA/H/C/000603/II/0136

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Gabriele Maurer

Scope: Update of sections 4.2 and 4.4 of the SmPC to modify administration instructions and update educational guidance to enable the subcutaneous formulation to be administered outside a clinical setting by healthcare professionals based on the cumulative review of post marketing and clinical study data. The package leaflet and Annex IID are updated accordingly. The RMP version 29.1 has also been submitted. In addition, the MAH took this opportunity to introduce minor editorial changes

15.3.20. Nirmatrelvir, ritonavir - PAXLOVID (CAP) - EMEA/H/C/005973/II/0043/G

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Martin Huber

Scope: Grouped variations consisting of: 1) update of section 5.1 of the SmPC in order to include new virology updates; 2) update of sections 4.5 and 5.2 of the SmPC in order to update interaction information related to CYP2B6, MATE1 and OCT1. The RMP version 3.0 has also been submitted

15.3.21. Nirsevimab - BEYFORTUS (CAP) - EMEA/H/C/005304/II/0005

Applicant: AstraZeneca AB

PRAC Rapporteur: Kimmo Jaakkola

Scope: Extension of indication to include treatment of children up to 24 months of age who remain vulnerable to severe Respiratory Syncytial Virus (RSV) disease through their second RSV season for BEYFORTUS, based on interim results from studies D5290C00005 and D5290C00008. Study D5290C00005 (MEDLEY) is a Phase II/III, randomised, double-blind, placebo-controlled study to evaluate the safety of Beyfortus in high-risk children. Study D5290C00008 (MUSIC) is a Phase II, open-label, uncontrolled, single-dose study to evaluate the safety and tolerability, pharmacokinetics, and occurrence of antidrug antibody for Beyfortus in immunocompromised children ≤ 24 Months of Age. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 of the SmPC are updated. The package leaflet is updated accordingly. Version 2.1 of the RMP has also been submitted. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet

15.3.22. Nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/II/0130

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Martin Huber

Scope: Extension of indication to include OPDIVO for the adjuvant treatment of adults and adolescents 12 years of age and older with stage IIB or IIC melanoma who have undergone complete resection, based on results from study CA20976K; This is a phase III, randomised, double-blind study of adjuvant immunotherapy with nivolumab versus placebo

after complete resection of stage IIB/C melanoma. 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 33.0 of the RMP has also been submitted

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 a multicenter, 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 non-Hodgkin's lymphoma (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. Olaparib - LYNPARZA (CAP) - EMEA/H/C/003726/II/0061

Applicant: AstraZeneca AB

PRAC Rapporteur: Amelia Cupelli

Scope: Update of sections 4.8 and 5.1 of the SmPC in order to update the overall survival and safety information following procedure H/C/003726/II/0048, based on the final results from study D081SC00001 (PROpel), listed as a PAES in the Annex II; this is a randomised, double-blind, placebo-controlled, multicentre phase III study of olaparib plus abiraterone relative to placebo plus abiraterone as first-line therapy in men with metastatic castration resistant prostate cancer; The RMP version 27 has also been submitted

15.3.25. Onasemnogene abeparvovec - ZOLGENSMA (CAP) - EMEA/H/C/004750/II/0040, Orphan

Applicant: Novartis Europharm Limited, ATMP[34]

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of sections 4.4 and 5.1 of the SmPC in order to add a new warning and precaution capturing the theoretical risk of tumorigenicity as a result of vector integration and to include a new statement indicating random instances of vector integration are possible; based on final results from studies 2220205 and 2220117, and literature. The package leaflet is updated accordingly. The RMP version 3 has also been submitted

[34] Advanced therapy medicinal product'

15.3.26. Pandemic influenza vaccine (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 pediatric 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

15.3.27. Pegcetacoplan - ASPAVELI (CAP) - EMEA/H/C/005553/II/0011, Orphan

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Kimmo Jaakkola

EMA resources: PL: Sotirios Michaleas; RMS: Sotirios Michaleas

Scope: Extension of indication to include treatment of adult patients with Paroxysmal Nocturnal Hemoglobinuria (PNH) not previously treated with a complement inhibitor for ASPAVELI, based on final results from study APL2-308. This is a Phase III, randomised, open-label, comparator-controlled study that enrolled adult patients with PNH who had not been treated with a complement inhibitor. 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 1.1 of the RMP has also been submitted

15.3.28. Pembrolizumab - KEYTRUDA (CAP) - EMEA/H/C/003820/II/0133

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication to include in combination with trastuzumab, fluoropyrimidine and platinum-containing chemotherapy for treatment of locally advanced unresectable or metastatic HER2- positive gastric or gastro-oesophageal junction adenocarcinoma for Keytruda, based on interim results from study KEYNOTE-811, an ongoing Phase 3, double-blind trial comparing trastuzumab plus chemotherapy and pembrolizumab with trastuzumab plus chemotherapy and placebo as first-line treatment in participants with HER2-positive advanced gastric or gastro-oesophageal junction adenocarcinoma. As a consequence, sections 4.1, 4.8, and 5.1 of the SmPC are updated. The package leaflet and Labelling are updated in accordance. Version 40.1 of the RMP has also been submitted

15.3.29. 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

15.3.30. Pneumococcal polysaccharide conjugate vaccine (20-valent, adsorbed) - APEXXNAR (CAP) - EMEA/H/C/005451/II/0016

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Jean-Michel Dogné

Scope: Submission of an updated RMP version 4 in order to update post-approval commitments. In addition, the MAH took the opportunity to update Annex II of the SmPC to expand the B4741015 PAES study protocol to sites in Europe and Israel for Apexxnar. B4741015 is a Phase 4 study using a test negative design to evaluate the effectiveness of Apexxnar against vaccine type radiologically confirmed community acquired pneumonia in adults ≥ 65 years of age

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

Applicant: Roche Registration GmbH

PRAC Rapporteur: Jan Neuhauser

Scope: Grouped variations consisting of: 1) extension of indication to include treatment of patients below 2 months of age based on interim results from pivotal study BN40703 (RAINBOWFISH): an ongoing phase 2 multicentre, open-label, and single-arm study designed to evaluate the efficacy, safety, tolerability, and pharmacokinetic/pharmacodynamic (PK/PD) of risdiplam in pre-symptomatic infants below 2 months of age who were genetically diagnosed with spinal muscular atrophy (SMA). As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. In addition, the MAH took the opportunity to make some editorial improvements in the product information; 2) update of Evrysdi (risdiplam) pack configuration with the addition of a new 1 mL oral syringe into the product carton allowing precise dosing of infants below 2 months of age. As a consequence, section 6.5 of the SmPC and the labelling are updated; 3) removal of a device: the spare unit of 12 mL oral syringe out of the two units currently provided in the product carton. As a consequence, section 6.5 of the SmPC and the labelling are updated. The package leaflet and the RMP (version 1.1) are updated in accordance

15.3.32. 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 rearranged during transfection (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

15.3.33. 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 rearranged during transfection (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

15.3.34. Siponimod - MAYZENT (CAP) - EMEA/H/C/004712/II/0020

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Update of sections 4.4 and 4.8 of the SmPC in order to add "Progressive multifocal leukoencephalopathy (PML)" to the list of adverse drug reactions (ADRs) with frequency "not known" based on post-marketing data. The Annex II (Physician's Checklist), and package leaflet are updated accordingly. The RMP version 6.0 has also been submitted. In addition, the MAH took the opportunity to update the text regarding herpes viral infection in the package leaflet in alignment with the currently approved SmPC

15.3.35. 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

15.3.36. Teclistamab - TECVAYLI (CAP) - EMEA/H/C/005865/II/0006

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Jana Lukacisinova

Scope: Update of sections 4.2, 5.1 and 5.2 of the SmPC in order to update the posology recommendations to include the possibility of bi-weekly dosing, based on interim results from study 64007957MMY1001 (MajesTEC-1); this is a phase 1/2, single-arm, open-label, multicenter study of teclistamab administered as monotherapy to adult subjects with relapsed or refractory multiple myeloma. The package leaflet is updated accordingly. The RMP version 2.1 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 and update the list of local representatives in the package leaflet

15.3.37. Teriflunomide - TERIFLUNOMIDE ACCORD (CAP) - EMEA/H/C/005960/X/0002

Applicant: Accord Healthcare S.L.U.

PRAC Rapporteur: Martin Huber

Scope: Extension application to add a new strength of 7 mg film-coated tablets. The bioequivalence study data were submitted

15.3.38. Tixagevimab, cilgavimab - EVUSHELD (CAP) - EMEA/H/C/005788/II/0009/G

Applicant: AstraZeneca AB

PRAC Rapporteur: Kimmo Jaakkola

Scope: Grouped application consisting of: 1) Update of sections 4.4, 4.8 and 5.1 of the SmPC in order to update efficacy and safety information based on final results from study TACKLE (D8851C00001); 2) Update of sections 4.4, 4.8, 5.1 and 5.2 of the SmPC in order to update efficacy and safety information based on final results from studies PROVENT (D8850C00002) and STORM CHASER (D8850C00003). The RMP version 4.1 has also been submitted

15.3.39. 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

15.3.40. Trastuzumab deruxtecan - ENHERTU (CAP) - EMEA/H/C/005124/II/0031

Applicant: Daiichi Sankyo Europe GmbH

PRAC Rapporteur: Inês Ribeiro-Vaz

Scope: Update of sections 4.8, 5.1 and 5.2 of the SmPC in order to update safety, efficacy and pharmacokinetic information based on data from study DS8201-A-U301 and study DS8201-A-U302. Study U301was a Phase 3, randomised, 2-arm, open-label, multicenter study designed to compare the safety and efficacy of T-DXd vs TPC in HER2-positive, unresectable and/or metastatic BC subjects who were resistant or refractory to T-DM1. Study U302 was a Phase 3, multicenter, randomised, open-label, 2-arm, active-controlled study in subjects with unresectable and/or metastatic HER2-positive (IHC 3+ or ISH-positive) BC previously treated with trastuzumab plus taxane in the advanced/metastatic setting or who had progressed within 6 months after neoadjuvant or adjuvant treatment involving a regimen including trastuzumab plus taxane. The package leaflet and Annex II are updated accordingly. The updated RMP version 4.1 has also been submitted

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. Angiotensin II - GIAPREZA (CAP) - PSUSA/00010785/202212

Applicant: Paion Deutschland GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.2. Atidarsagene autotemcel - LIBMELDY (CAP) - PSUSA/00010899/202212

Applicant: Orchard Therapeutics (Netherlands) B.V., ATMP[35]

PRAC Rapporteur: Gabriele Maurer

Scope: Evaluation of a PSUSA procedure

[35] Advanced therapy medicinal product

16.1.3. Autologous CD34+ enriched cell fraction that contains CD34+ cells transduced with retroviral vector that encodes for the human ADA cDNA sequence - STRIMVELIS (CAP) - PSUSA/00010505/202211

Applicant: Orchard Therapeutics (Netherlands) B.V., ATMP[36]

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.4. Berotralstat - ORLADEYO (CAP) - PSUSA/00010930/202212

Applicant: BioCryst Ireland Limited

PRAC Rapporteur: Julia Pallos

Scope: Evaluation of a PSUSA procedure

16.1.5. Budesonide[37] - KINPEYGO (CAP) - PSUSA/00011007/202212

Applicant: STADA Arzneimittel AG

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Evaluation of a PSUSA procedure

16.1.6. Buprenorphine[38] - SIXMO (CAP) - PSUSA/00010778/202211

Applicant: L. Molteni & C. dei Fratelli Alitti Societa di Esercizio S.p.A.

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.7. Coronavirus (COVID-19) vaccine (recombinant, adjuvanted) - NUVAXOVID (CAP) - PSUSA/00010972/202212

Applicant: Novavax CZ, a.s.

PRAC Rapporteur: Gabriele Maurer

Scope: Evaluation of a PSUSA procedure

16.1.8. Dengue tetravalent vaccine (live, attenuated) - DENGVAXIA (CAP) - PSUSA/00010740/202212

Applicant: Sanofi Pasteur

PRAC Rapporteur: Sonja Hrabcik

Scope: Evaluation of a PSUSA procedure

[36] Advanced therapy medicinal product
[37] For centrally authorised products indicated for primary immunoglobulin A nephropathy only
[38] Implant(s) only

16.1.9. Eladocagene exuparvovec - UPSTAZA (CAP) - PSUSA/00011004/202212

Applicant: PTC Therapeutics International Limited, ATMP[39]

PRAC Rapporteur: Gabriele Maurer

Scope: Evaluation of a PSUSA procedure

16.1.10. Enfortumab vedotin - PADCEV (CAP) - PSUSA/00010989/202212

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Eva Jirsová

Scope: Evaluation of a PSUSA procedure

16.1.11. Entrectinib - ROZLYTREK (CAP) - PSUSA/00010874/202212

Applicant: Roche Registration GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.12. Fenfluramine - FINTEPLA (CAP) - PSUSA/00010907/202212

Applicant: UCB Pharma SA

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.13. Formoterol fumarate dihydrate, glycopyrronium bromide, budesonide - RILTRAVA AEROSPHERE (CAP); TRIXEO AEROSPHERE (CAP) - PSUSA/00010908/202212

Applicant: AstraZeneca AB

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.1.14. Human papillomavirus vaccine (rDNA) - 2-valent - CERVARIX (CAP) - PSUSA/00009175/202211

Applicant: GlaxoSmithkline Biologicals SA

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

16.1.15. Hydroxocobalamin[40] - CYANOKIT (CAP) - PSUSA/00010228/202211

Applicant: SERB SA

PRAC Rapporteur: Nathalie Gault

[39] Advanced therapy medicinal product
[40] Only for product(s) for chemical poisoning

Scope: Evaluation of a PSUSA procedure

16.1.16. Indacaterol - HIROBRIZ BREEZHALER (CAP); ONBREZ BREEZHALER (CAP); OSLIF BREEZHALER (CAP) - PSUSA/00001730/202211

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Evaluation of a PSUSA procedure

16.1.17. Inebilizumab - UPLIZNA (CAP) - PSUSA/00010996/202212

Applicant: Horizon Therapeutics Ireland DAC

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.1.18. Inotuzumab ozogamicin - BESPONSA (CAP) - PSUSA/00010659/202212

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Gabriele Maurer

Scope: Evaluation of a PSUSA procedure

16.1.19. Larotrectinib - VITRAKVI (CAP) - PSUSA/00010799/202211

Applicant: Bayer AG

PRAC Rapporteur: Rugile Pilviniene

Scope: Evaluation of a PSUSA procedure

16.1.20. Latanoprost, netarsudil - ROCLANDA (CAP) - PSUSA/00010905/202212

Applicant: Santen Oy

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.21. Levodopa - INBRIJA (CAP) - PSUSA/00107800/202212

Applicant: Acorda Therapeutics Ireland Limited

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Evaluation of a PSUSA procedure

16.1.22. Luspatercept - REBLOZYL (CAP) - PSUSA/00010860/202212

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Jo Robays

Scope: Evaluation of a PSUSA procedure

16.1.23. Lutetium (^{177}Lu) oxodotreotide - LUTATHERA (CAP) - PSUSA/00010643/202212

Applicant: Advanced Accelerator Applications

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.24. Lutropin alfa - LUVERIS (CAP) - PSUSA/00001918/202211

Applicant: Merck Europe B.V.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Evaluation of a PSUSA procedure

16.1.25. Mexiletine[41] - NAMUSCLA (CAP) - PSUSA/00010738/202212

Applicant: Lupin Europe GmbH

PRAC Rapporteur: Eva Jirsová

Scope: Evaluation of a PSUSA procedure

16.1.26. Mosunetuzumab - LUNSUMIO (CAP) - PSUSA/00010999/202212

Applicant: Roche Registration GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.27. Obeticholic acid - OCALIVA (CAP) - PSUSA/00010555/202211

Applicant: Advanz Pharma Limited

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

16.1.28. Olaparib - LYNPARZA (CAP) - PSUSA/00010322/202212

Applicant: AstraZeneca AB

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.1.29. Pegvisomant - SOMAVERT (CAP) - PSUSA/00002328/202211

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Nathalie Gault

Scope: Evaluation of a PSUSA procedure

[41] Centrally authorised product(s) only

16.1.30. Pertuzumab, trastuzumab - PHESGO (CAP) - PSUSA/00010906/202212

Applicant: Roche Registration GmbH

PRAC Rapporteur: Gabriele Maurer

Scope: Evaluation of a PSUSA procedure

16.1.31. Pneumococcal polysaccharide conjugate vaccine (20-valent, adsorbed) - APEXXNAR (CAP) - PSUSA/00010981/202212

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

16.1.32. Relugolix, estradiol, norethisterone acetate - RYEQO (CAP) - PSUSA/00010942/202211

Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.33. Roxadustat - EVRENZO (CAP) - PSUSA/00010955/202212

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Anna Mareková

Scope: Evaluation of a PSUSA procedure

16.1.34. Rucaparib - RUBRACA (CAP) - PSUSA/00010694/202212

Applicant: Zr Pharma& GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.35. Satralizumab - ENSPRYNG (CAP) - PSUSA/00010944/202211

Applicant: Roche Registration GmbH

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.1.36. Sotorasib - LUMYKRAS (CAP) - PSUSA/00010970/202211

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Evaluation of a PSUSA procedure

16.1.37. Tagraxofusp - ELZONRIS (CAP) - PSUSA/00010896/202212

Applicant: Stemline Therapeutics B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.38. Tezepelumab - TEZSPIRE (CAP) - PSUSA/00011015/202212

Applicant: AstraZeneca AB

PRAC Rapporteur: Eva Jirsová

Scope: Evaluation of a PSUSA procedure

16.1.39. Tirbanibulin - KLISYRI (CAP) - PSUSA/00010943/202212

Applicant: Almirall, S.A.

PRAC Rapporteur: Anna Mareková

Scope: Evaluation of a PSUSA procedure

16.1.40. Tralokinumab - ADTRALZA (CAP) - PSUSA/00010937/202212

Applicant: LEO Pharma A/S

PRAC Rapporteur: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

16.1.41. Trastuzumab deruxtecan - ENHERTU (CAP) - PSUSA/00010894/202212

Applicant: Daiichi Sankyo Europe GmbH

PRAC Rapporteur: Inês Ribeiro-Vaz

Scope: Evaluation of a PSUSA procedure

16.1.42. Turoctocog alfa pegol - ESPEROCT (CAP) - PSUSA/00010782/202212

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Gabriele Maurer

Scope: Evaluation of a PSUSA procedure

16.1.43. Vutrisiran - AMVUTTRA (CAP) - PSUSA/00011021/202212

Applicant: Alnylam Netherlands B.V.

PRAC Rapporteur: Liana Gross-Martirosyan

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. Acetylsalicylic acid, clopidogrel, clopidogrel - CLOPIDOGREL ZENTIVA (CAP); DUOPLAVIN (CAP); ISCOVER (CAP); PLAVIX (CAP); NAP - PSUSA/00000820/202211

Applicant(s): Zentiva k.s. (Clopidogrel Zentiva), Sanofi Winthrop Industrie (DuoPlavin, Iscover, Plavix), various

PRAC Rapporteur: Inês Ribeiro-Vaz

Scope: Evaluation of a PSUSA procedure

16.2.2. Docetaxel - TAXOTERE (CAP); NAP - PSUSA/00001152/202211

Applicant(s): Sanofi Mature IP (Taxotere), various

PRAC Rapporteur: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

16.2.3. Edotreotide - SOMAKIT TOC (CAP); NAP - PSUSA/00010552/202212

Applicant(s): Advanced Accelerator Applications (SomaKit TOC), various

PRAC Rapporteur: Eamon O'Murchu

Scope: Evaluation of a PSUSA procedure

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

16.3.1. Alfuzosin (NAP) - PSUSA/00000084/202211

Applicant(s): various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.3.2. Amlodipine (NAP), indapamide, amlodipine (NAP), indapamide (NAP), perindopril (NAP) - PSUSA/00010358/202211

Applicant(s): various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.3.3. Bacillus clausii multi-antibioresistant spores (NAP) - PSUSA/00000284/202211

Applicant(s): various

PRAC Lead: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.3.4. Bambuterol (NAP) - PSUSA/00000295/202212

Applicant(s): various

PRAC Lead: Jana Lukačišinová

Scope: Evaluation of a PSUSA procedure

16.3.5. Bromperidol (NAP) - PSUSA/00000439/202211

Applicant(s): various

PRAC Lead: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

16.3.6. Brotizolam (NAP) - PSUSA/00000444/202212

Applicant(s): various

PRAC Lead: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.3.7. Caffeine, ergotamine (NAP) - PSUSA/00000485/202211

Applicant(s): various

PRAC Lead: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

16.3.8. Cetirizine (NAP) - PSUSA/00000628/202211

Applicant(s): various

PRAC Lead: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

16.3.9. Dienogest (NAP) - PSUSA/00003167/202212

Applicant(s): various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.3.10. Dutasteride (NAP), dutasteride, tamsulosine (NAP) - PSUSA/00010506/202211

Applicant(s): various

PRAC Lead: Melinda Palfi

Scope: Evaluation of a PSUSA procedure

16.3.11. Econazole (NAP), econazole nitrate, triamcinolone acetonide (NAP), econazole nitrate, zinc oxide (NAP) - PSUSA/00001195/202211

Applicant(s): various

PRAC Lead: Melinda Palfi

Scope: Evaluation of a PSUSA procedure

16.3.12. Horse-derived anti-T lymphocyte immunoglobulin for human use (NAP) - PSUSA/00010433/202211

Applicant(s): various

PRAC Lead: Zane Neikena

Scope: Evaluation of a PSUSA procedure

16.3.13. Hydroxycarbamide[42] (NAP) - PSUSA/00009182/202212

Applicant(s): various

PRAC Lead: Nikica Mirošević Skvrce

Scope: Evaluation of a PSUSA procedure

16.3.14. Idarubicin (NAP) - PSUSA/00001720/202211

Applicant(s): various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.3.15. Inactivated leptospire vaccine (NAP) - PSUSA/00010813/202211

Applicant(s): various

PRAC Lead: Nathalie Gault

Scope: Evaluation of a PSUSA procedure

16.3.16. Levocabastine (NAP) - PSUSA/00001849/202211

Applicant(s): various

PRAC Lead: Marie Louise Schougaard Christiansen

Scope: Evaluation of a PSUSA procedure

16.3.17. Mizolastine (NAP) - PSUSA/00002078/202211

Applicant(s): various

PRAC Lead: Jana Lukačišinová

[42] Except for centrally authorised product

Scope: Evaluation of a PSUSA procedure

16.3.18. Naltrexone (NAP) - PSUSA/00002117/202211

Applicant(s): various

PRAC Lead: Eamon O'Murchu

Scope: Evaluation of a PSUSA procedure

16.3.19. Propofol (NAP) - PSUSA/00002555/202211

Applicant(s): various

PRAC Lead: Karen Pernille Harg

Scope: Evaluation of a PSUSA procedure

16.3.20. Rosuvastatin (NAP) - PSUSA/00002664/202211

Applicant(s): various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.3.21. Sodium fluoride (^{18}F) (NAP) - PSUSA/00010706/202211

Applicant(s): various

PRAC Lead: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

16.3.22. Yellow fever vaccine (live) (NAP) - PSUSA/00003135/202212

Applicant(s): various

PRAC Lead: Gabriele Maurer

Scope: Evaluation of a PSUSA procedure

16.4. Follow-up to PSUR/PSUSA procedures

16.4.1. Coronavirus (COVID-19) vaccine (ChAdOx1-S [recombinant]) - VAXZEVRIA (CAP) - EMEA/H/C/005675/LEG 115

Applicant: AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

Scope: Submission of a cumulative review of cases of myocarditis, including a causality assessment according to WHO-UMC criteria for cases with Brighton Collaboration Classification (BCC) case definition level 1, 2 or 3, a discussion on the O/E analysis for myocarditis based on EU/UK data and on Australian data, with stratifications by risk window (7, 14, 21, 42 days), age group, gender and dose, together with a literature review, as per conclusions of the PSUSA/00010916/202208 adopted in April 2023

16.5. Variation procedure(s) resulting from PSUSA evaluation

16.5.1. Fondaparinux sodium - ARIXTRA (CAP) - EMEA/H/C/000403/II/0087

Applicant: Mylan Ire Healthcare Limited

PRAC Rapporteur: Mari Thorn

Scope: To update section 4.8 of the SmPC to update the ADR table following the assessment of PSUSA (EMEA/H/C/PSUSA/00001467/202112). The package leaflet is updated accordingly

16.6. Expedited summary safety reviews[43]

None

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

Based on the assessment of the following PASS protocol(s), result(s), interim result(s) or feasibility study(ies), and following endorsement of the comments received, PRAC adopted the conclusion of the Rapporteurs on their assessment for the medicines listed below without further plenary discussion.

17.1. Protocols of PASS imposed in the marketing authorisation(s)[44]

17.1.1. Lenalidomide - REVLIMID (CAP) - EMEA/H/C/PSA/S/0093.2

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Tiphaine Vaillant

Scope: Substantial amendment to a protocol for a post-autorisation, 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/0093.1]

17.1.2. Valproate[45] (NAP) – EMEA/H/N/PSP/J/0074.7

Applicant: Sanofi-Aventis Recherche & Développement

PRAC Rapporteur : Jean-Michel Dogné

Scope: Responses to the RSI of the 2nd Interim report: Observational study to evaluate and identify the best practices for switching of valproate in clinical practice

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

17.2. Protocols of PASS non-imposed in the marketing authorisation(s)[46]

17.2.1. Baricitinib - OLUMIANT (CAP) - EMEA/H/C/004085/MEA 015

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Submission of a protocol for study I4V-MC-B025: Rheumatologist and Dermatologist Survey to Assess the Effectiveness of the Risk Minimisation Measures (RMM) for Olumiant (baricitinib), a JAK1/2 Inhibitor

17.2.2. Baricitinib - OLUMIANT (CAP) - EMEA/H/C/004085/MEA 016

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Submission of a protocol for study I4V-MC-B038: Baricitinib Drug Utilisation Study: Assessment of Effectiveness of New Recommendations for Use Based on Secondary Data Sources in France, Germany, The Netherlands, and Sweden. This study aims to assess the utilisation of baricitinib in patients with RA, AA, or AD with respect to the new recommendations further to the completion of the Pharmacovigilance article 20 in the aRMMs (DHPC, Healthcare Professional educational materials, and Patient Alert Card)

17.2.3. Coronavirus (COVID-19) vaccine (recombinant, adjuvanted) - NUVAXOVID (CAP) - EMEA/H/C/005808/MEA 004.3

Applicant: Novavax CZ, a.s.

PRAC Rapporteur: Gabriele Maurer

Scope: Submission of an updated protocol (version 3.0) and statistical analysis plan (v 1.0) for study 2019nCoV-402

17.2.4. Daridorexant - QUVIVIQ (CAP) - EMEA/H/C/005634/MEA 003

Applicant: Idorsia Pharmaceuticals Deutschland GmbH

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Submission of a pregnancy registry protocol ID-078A403 to compare the maternal, foetal, and infant outcomes of women exposed to daridorexant during pregnancy to an unexposed control population

17.2.5. Efgartigimod alfa - VYVGART (CAP) - EMEA/H/C/005849/MEA 002.1

Applicant: Argenx

PRAC Rapporteur: Rhea Fitzgerald

Scope: MAH's response to MEA 002 [Submission of a protocol for a PASS to characterise the risks and missing information outlined in the risk management plan including serious

[46] 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

infections, use of live/attenuated vaccines, use with monoclonal antibodies, long-term safety and use in immunocompromised patients and evaluate whether there are specific and/or unexpected patterns of adverse events] as per the request for supplementary information (RSI) adopted in February 2023

17.2.6. Efgartigimod alfa - VYVGART (CAP) - EMEA/H/C/005849/MEA 004.1

Applicant: Argenx

PRAC Rapporteur: Rhea Fitzgerald

Scope: MAH's response to MEA 004 [Submission of a protocol for a PASS to characterise the missing information use in pregnant woman outlined in the risk management plan] as per the request for supplementary information (RSI) adopted in February 2023

17.2.7. Fremanezumab - AJOVY (CAP) - EMEA/H/C/004833/MEA 003.3

Applicant: TEVA GmbH

PRAC Rapporteur: Kirsti Villikka

Scope: Submission of a protocol amendment 4.0 for study TV48125-MH-50038: Assessment of Pregnancy Outcomes in Patients Treated with AJOVY (Fremanezumab): Pregnancy Database Study

17.2.8. Nirmatrelvir, ritonavir - PAXLOVID (CAP) - EMEA/H/C/005973/MEA 008.1

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Martin Huber

Scope: Submission of a protocol amendment 2 for studyC4671037: use and safety of Paxlovid in pregnant and breastfeeding women

17.2.9. Nirmatrelvir, ritonavir - PAXLOVID (CAP) - EMEA/H/C/005973/MEA 009.2

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Martin Huber

Scope: MAH's response and Revised Protocol for Study C4671047 (amendment 1) - use and safety of Paxlovid among patients with moderate or severe hepatic or renal impairment as per request for supplementary information (RSI) adopted in February 2023

17.2.10. Pegvaliase - PALYNZIQ (CAP) - EMEA/H/C/004744/MEA 005.6

Applicant: BioMarin International Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Submission of a revised protocol for study 165-504: a global, multicentre study to assess maternal, foetal and infant outcomes of exposure to Palynziq (pegvaliase) during pregnancy and breastfeeding as per request for supplementary information (RSI) adopted in February 2023

17.2.11. Romosozumab - EVENITY (CAP) - EMEA/H/C/004465/MEA 001.6

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Tiphaine Vaillant

Scope: Submission of a protocol amendment for study OP0005: a European non-interventional PASS to study the adherence to the risk minimisation measures (RMMs) in the product information by estimating the compliance with contraindications and target indication(s) amongst incident romosozumab users, and analysing the utilisation pattern using the EU-adverse drug reactions (EU-ADR) Alliance

17.2.12. Romosozumab - EVENITY (CAP) - EMEA/H/C/004465/MEA 002.6

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Tiphaine Vaillant

Scope: Submission of a protocol amendment for study OP0004: European non-interventional PASS to evaluate potential differences in terms of serious cardiovascular adverse events between romosozumab and currently available therapies used in comparable patients in real-world conditions using the EU-adverse drug reactions (EU-ADR) Alliance

17.2.13. Romosozumab - EVENITY (CAP) - EMEA/H/C/004465/MEA 003.4

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Tiphaine Vaillant

Scope: Submission of a protocol amendment for study OP0006: evaluate potential differences in terms of serious infection between romosozumab and currently available therapies used in comparable patients in real-world conditions using the EU-adverse drug reactions (EU-ADR) Alliance

17.2.14. Talimogene laherparepvec - IMLYGIC (CAP) - EMEA/H/C/002771/MEA 005.2

Applicant: Amgen Europe B.V., ATMP[47]

PRAC Rapporteur: Gabriele Maurer

Scope: MAH's response to MEA 005.1 [Submission of a protocol amendment for study 20130193: 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 in March 2023

17.2.15. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/MEA 017.3

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Submission of a protocol amendment v4.0 for study A3921352: an active

[47] Advanced therapy medicinal product

surveillance, post-authorisation study to characterize the safety of tofacitinib in patients with moderately to severely active ulcerative colitis in the real-world setting using data from the United Registries for Clinical Assessment and Research (UR-CARE) in the European Union (EU)

17.2.16. Upadacitinib - RINVOQ (CAP) - EMEA/H/C/004760/MEA 014.3

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: MAH's response to MEA 014.2 [protocol for study P21-824: a study of growth and development in adolescents with atopic dermatitis who receive upadacitinib] as per request for supplementary information (RSI) adopted in January 2023

17.3. Results of PASS imposed in the marketing authorisation(s)[48]

None

17.4. Results of PASS non-imposed in the marketing authorisation(s)[49]

17.4.1. Agalsidase alfa - REPLAGAL (CAP) - EMEA/H/C/000369/II/0126

Applicant: Takeda Pharmaceuticals International AG Ireland Branch

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Submission of the final report from the Fabry Outcome Survey (FOS) registry study. The FOS (Fabry Outcome Survey) was a prospective, multicenter, observational, open-ended disease registry designed to document the clinical outcome over time of patients with Fabry disease, irrespective of their treatment

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

[48] In accordance with Article 107p-q of Directive 2001/83/EC
[49] 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

17.4.3. Eribulin - HALAVEN (CAP) - EMEA/H/C/002084/II/0067

Applicant: Eisai GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of the final report from study IRENE 504 (E7389-M044-504), listed as a category 3 study in the RMP. This was a post authorisation non-interventional safety study to characterize and determine the incidence of eribulin-induced peripheral neuropathy (PN), and frequency and time to resolution of eribulin-induced PN in adult patients with locally advanced or metastatic breast cancer who have progressed after at least one chemotherapeutic regimen for advanced disease treated with eribulin. Prior therapy should have included an anthracycline and a taxane in either the adjuvant or metastatic setting unless patients were not suitable for these treatments. The RMP version 8 has also been submitted

17.4.4. 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

17.4.5. 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 Minimization 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

17.4.6. Infliximab - REMICADE (CAP) - EMEA/H/C/000240/II/0241

Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Mari Thorn

Scope: Submission of the final report for the PSOLAR (C0168Z03) registry "A Multicenter, Open Registry of Patients with Psoriasis Who Are Candidates for Systemic Therapy Including Biologics: PSOLAR", listed as a category 3 study in the RMP (MEA114). This is an international, multicenter, prospective observational registry for monitoring the long-term safety experience and clinical status of patients≥18 years of age who are eligible to receive or are actively receiving any systemic therapies for psoriasis, including those currently receiving or planning to receive infliximab. The RMP version 21.1 has also been submitted

17.4.7. Pegfilgrastim - NEULASTA (CAP) - EMEA/H/C/000420/II/0121

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Submission of the final report from PASS study 20170701 listed as a category 3 study in the RMP. This is a cross-sectional survey study to Assess the Effectiveness of the Neulasta Patient Alert Card and to Measure Medication Errors Related to the Use of the Neulasta On-Body Injector. The RMP version 9.0 has also been submitted

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 Utilization 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

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

17.5.1. Ataluren - TRANSLARNA (CAP) - EMEA/H/C/002720/MEA 002.9

Applicant: PTC Therapeutics International Limited

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Post-approval registry Protocol PTC124-GD-0250-DMD: Long-Term Observational Study of Translarna Safety and Effectiveness in Usual Care

17.5.2. Cabazitaxel - CABAZITAXEL ACCORD (CAP) - EMEA/H/C/005178/MEA 001.4

Applicant: Accord Healthcare S.L.U.

PRAC Rapporteur: Tiphaine Vaillant

Scope: The fifth six-monthly safety report for the category 3 study to review the cases reported for 'medication error'

17.5.3. Elasomeran - SPIKEVAX (CAP) - EMEA/H/C/005791/MEA 004.9

Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Fourth interim report for study mRNA-1273-P904 (study 1) (listed as a category 3 study in the RMP): a post-authorisation active surveillance safety study using secondary data to monitor real-world safety of Spikevax (COVID-19 mRNA-1273 vaccine) in Europe – an enhanced pharmacovigilance study to provide additional evaluation of adverse events of special interest (AESI) and emerging validated safety signals in European populations and electronic database assessment of use in pregnant women

17.5.4. Elasomeran - SPIKEVAX (CAP) - EMEA/H/C/005791/MEA 034.6

Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Third interim report for the study of monitoring safety of COVID-19 Vaccine Moderna in pregnancy: an observational study using routinely collected health data in five European countries - Post-marketing safety study for COVID-19 mRNA-1273 vaccine

17.5.5. Fenfluramine - FINTEPLA (CAP) - EMEA/H/C/003933/MEA 002.2

Applicant: UCB Pharma SA

PRAC Rapporteur: Martin Huber

Scope: MAH’s response to MEA 002.1 [Progress report for study ZX008-1503: an open-label extension trial to assess the long-term safety of ZX008 (fenfluramine hydrochloride) oral solution as an adjunctive therapy in children and young adults with Dravet syndrome] as per request for supplementary information (RSI) adopted in February 2023

17.5.6. Nonacog beta pegol - REFIXIA (CAP) - EMEA/H/C/004178/LEG 006.4

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Gabriele Maurer

Scope: MAH's response to LEG 006.3 [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] as per request for supplementary information (RSI), adopted in March 2023

17.5.7. Tolvaptan - JINARC (CAP) - EMEA/H/C/002788/ANX 002.4

Applicant: Otsuka Pharmaceutical Netherlands B.V.

PRAC Rapporteur: Amelia Cupelli

Scope: MAH's response to ANX 002.3 [interim report for study 156-12-299: a non-interventional PASS to investigate the risks of hepatotoxicity, basal cell carcinoma and glaucoma associated with the use of Jinarc (tolvaptan). In addition, the study investigates pregnancy outcomes in patients treated with Jinarc (tolvaptan), patterns of medicinal product utilisation especially with regards to off-label use and use in patients over 50 years old as well as adverse drug reactions (ADRs) associated with long term use of Jinarc (tolvaptan) [final clinical study report (CSR) expected by: Q1/2026]] as per the request for supplementary information (RSI) adopted in February 2023

17.5.8. Tozinameran - COMIRNATY (CAP) - EMEA/H/C/005735/MEA 017.6

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Third interim report for study C4591021 (former ACCESS/VAC4EU): an assessment

of potential increased risk of adverse events of special interest (AESI), including myocarditis/pericarditis after being vaccinated with COVID-19 messenger ribonucleic acid (mRNA) vaccine estimating the time trend, in relation to DHPC letter dissemination, of the proportion of individuals who received real-world clinical assessments for myocarditis/pericarditis following Comirnaty (tozinameran) vaccination

17.5.9. Ulipristal acetate - ESMYA (CAP) - EMEA/H/C/002041/MEA 018.7

Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Seventh yearly progress report for study PGL14-001: a prospective, multinational, multicentre, non-interventional study to evaluate the long-term safety of Esmya (ulipristal acetate) in particular the endometrial safety and the current prescription and management patterns of Esmya (ulipristal acetate) in a long-term treatment setting

17.5.10. Venetoclax - VENCLYXTO (CAP) - EMEA/H/C/004106/MEA 002.10

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Eva Jirsová

Scope: Prospective observational study to assess the long term safety profile of venetoclax in a Swedish cohort of Chronic Lymphocytic Leukaemia (CLL) patients

17.5.11. Voretigene neparvovec - LUXTURNA (CAP) - EMEA/H/C/004451/ANX 011

Applicant: Novartis Europharm Limited, ATMP[50]

PRAC Rapporteur: Gabriele Maurer

Scope: Interim report for study CLTW888A12401: a Post-Authorisation, Multicenter, Multinational, Longitudinal, Observational Safety Registry Study for Patients Treated with Voretigene Neparvovec

17.6. Others

None

17.7. New Scientific Advice

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

17.8. Ongoing Scientific Advice

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

[50] Advanced therapy medicinal product

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

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

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

Based on the review of the available pharmacovigilance data for the medicine(s) listed below and the CHMP Rapporteur's assessment report, PRAC considered that either the renewal of the marketing authorisation procedure could be concluded - and supported the renewal of their marketing authorisations for an unlimited or additional period, as applicable - or no amendments to the specific obligations of the marketing authorisation under exceptional 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. Amifampridine - FIRDAPSE (CAP) - EMEA/H/C/001032/S/0075 (without RMP)

Applicant: SERB SA

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Annual reassessment of the marketing authorisation

18.1.2. Chenodeoxycholic acid - CHENODEOXYCHOLIC ACID LEADIANT (CAP) - EMEA/H/C/004061/S/0022 (without RMP)

Applicant: Leadiant GmbH

PRAC Rapporteur: Adam Przybylkowski

Scope: Annual reassessment of the marketing authorisation

18.1.3. Idursulfase - ELAPRASE (CAP) - EMEA/H/C/000700/S/0111 (without RMP)

Applicant: Takeda Pharmaceuticals International AG Ireland Branch

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Annual reassessment of the marketing authorisation

18.1.4. Tecovirimat - TECOVIRIMAT SIGA (CAP) - EMEA/H/C/005248/S/0004 (without RMP)

Applicant: SIGA Technologies Netherlands B.V.

PRAC Rapporteur: Martin Huber

Scope: Annual reassessment of the marketing authorisation

18.1.5. Zanamivir - DECTOVA (CAP) - EMEA/H/C/004102/S/0016 (without RMP)

Applicant: GlaxoSmithKline Trading Services Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Annual reassessment of the marketing authorisation

18.2. Conditional renewals of the marketing authorisation

18.2.1. Amivantamab - RYBREVANT (CAP) - EMEA/H/C/005454/R/0007 (without RMP)

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Gabriele Maurer

Scope: Conditional renewal of the marketing authorisation

18.2.2. Ixazomib - NINLARO (CAP) - EMEA/H/C/003844/R/0043 (without RMP)

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Conditional renewal of the marketing authorisation

18.2.3. Pralsetinib - GAVRETO (CAP) - EMEA/H/C/005413/R/0014 (without RMP)

Applicant: Roche Registration GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Conditional renewal of the marketing authorisation

18.2.4. Spesolimab - SPEVIGO (CAP) - EMEA/H/C/005874/R/0005 (without RMP)

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Nathalie Gault

Scope: Conditional renewal of the marketing authorisation

18.3. Renewals of the marketing authorisation

18.3.1. Apalutamide - ERLEADA (CAP) - EMEA/H/C/004452/R/0030 (with RMP)

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Tiphaine Vaillant

Scope: 5-year renewal of the marketing authorisation

18.3.2. Dimethyl fumarate - TECFIDERA (CAP) - EMEA/H/C/002601/R/0083 (without RMP)

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Martin Huber

Scope: 5-year renewal of the marketing authorisation

18.3.3. Galcanezumab - EMGALITY (CAP) - EMEA/H/C/004648/R/0023 (with RMP)

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Kirsti Villikka

Scope: 5-year renewal of the marketing authorisation

18.3.4. Glycopyrronium, formoterol fumarate dihydrate - BEVESPI AEROSPHERE (CAP) - EMEA/H/C/004245/R/0017 (without RMP)

Applicant: AstraZeneca AB

PRAC Rapporteur: Jan Neuhauser

Scope: 5-year renewal of the marketing authorisation

18.3.5. Lidocaine, prilocaine - FORTACIN (CAP) - EMEA/H/C/002693/R/0038 (without RMP)

Applicant: Recordati Ireland Ltd

PRAC Rapporteur: Maria del Pilar Rayon

Scope: 5-year renewal of the marketing authorisation

18.3.6. Paclitaxel - APEALEA (CAP) - EMEA/H/C/004154/R/0017 (with RMP)

Applicant: Inceptua AB

PRAC Rapporteur: Inês Ribeiro-Vaz

Scope: 5-year renewal of the marketing authorisation

18.3.7. Pegfilgrastim - FULPHILA (CAP) - EMEA/H/C/004915/R/0042 (without RMP)

Applicant: Viatris Limited

PRAC Rapporteur: Menno van der Elst

Scope: 5-year renewal of the marketing authorisation

18.3.8. Radium (Ra^{223}) - XOFIGO (CAP) - EMEA/H/C/002653/R/0049 (with RMP)

Applicant: Bayer AG

PRAC Rapporteur: Rugile Pilviniene

Scope: 5-year renewal of the marketing authorisation

18.3.9. Ropeginterferon alfa-2b - BESREMI (CAP) - EMEA/H/C/004128/R/0031 (without RMP)

Applicant: AOP Orphan Pharmaceuticals GmbH

PRAC Rapporteur: Inês Ribeiro-Vaz

Scope: 5-year renewal of the marketing authorisation

18.3.10. Silodosin - SILODOSIN RECORDATI (CAP) - EMEA/H/C/004964/R/0012 (without RMP)

Applicant: Recordati Ireland Ltd

PRAC Rapporteur: Valentina Di Giovanni

Scope: 5-year renewal of the marketing authorisation

18.3.11. Tobramycin - VANTOBRA (CAP) - EMEA/H/C/005086/R/0009 (without RMP)

Applicant: PARI Pharma GmbH

PRAC Rapporteur: Ulla Wändel Liminga

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 03-06 July 2023 meeting.

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

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Marie Louise Schougaard Christiansen	Alternate	Denmark	No interests declared	
Maia Uusküla	Member	Estonia	No interests declared	
Kirsti Villikka	Member	Finland	No interests declared	
Kimmo Jaakkola	Alternate	Finland	No interests declared	
Tiphaine Vaillant	Member	France	No interests declared	
Nathalie Gault	Alternate	France	No interests declared	
Martin Huber	Member (Vice-Chair)	Germany	No interests declared	
Gabriele Maurer	Alternate	Germany	No participation in final deliberations and voting on:	15.3.22. Nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/II/0130
Sofia Trantza	Member	Greece	No interests declared	
Georgia Gkegka	Alternate	Greece	No interests declared	
Julia Pallos	Member	Hungary	No participation in final deliberations and voting on:	15.3.22. Nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/II/0130 16.1.22. Luspatercept - REBLOZYL (CAP) - PSUSA/00010860/202212 17.1.1. Lenalidomide - REVLIMID (CAP) - EMEA/H/C/PSA/S/0093.2
Guðrún Stefánsdóttir	Member	Iceland	No participation	6.1.3. Blinatumomab - BLINCYTO (CAP)

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			in final deliberations and voting on:	- PSUSA/00010460/202212 15.3.7. Denosumab - PROLIA (CAP) - EMEA/H/C/001120/II/0098 15.3.35. Sotorasib - LUMYKRAS (CAP) - EMEA/H/C/005522/II/0007 16.1.36. Sotorasib - LUMYKRAS (CAP) - PSUSA/00010970/202211 17.2.14. Talimogene laherparepvec - IMLYGIC (CAP) - EMEA/H/C/002771/MEA 005.2 17.4.4. Etelcalcetide - PARSABIV (CAP) - EMEA/H/C/003995/II/0021 17.4.7. Pegfilgrastim - NEULASTA (CAP) - EMEA/H/C/000420/II/0121
Rhea Fitzgerald	Member	Ireland	No interests declared	
Eamon O Murchu	Alternate	Ireland	No interests declared	
Amelia Cupelli	Member	Italy	No interests declared	
Valentina Di Giovanni	Alternate	Italy	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Zane Neikena	Member	Latvia	No interests declared	
Zane Stade	Alternate	Latvia	No interests declared	
Lina Seibokiene	Alternate	Lithuania	No restrictions applicable to this meeting	
Nadine Petitpain	Member	Luxembourg	No restrictions applicable to this meeting	
John Joseph Borg	Member (CHMP member)	Malta	No interests declared	
Benjamin Micallef	Alternate	Malta	No interests declared	
Menno van der Elst	Member	Netherlands	No interests declared	
Liana Gross-Martirosyan	Alternate	Netherlands	No interests declared	
David Olsen	Member	Norway	No participation in final deliberations and voting on:	6.1.1. Aflibercept - EYLEA (CAP) - PSUSA/00010020 /202211 6.3.2. Flurbiprofen (NAP) - PSUSA/00001450 /202211 16.1.19. Larotrectinib - VITRAKVI (CAP) - PSUSA/00010799 /202211 16.3.9. Dienogest (NAP) - PSUSA/00003167 /202212 18.3.8. Radium (Ra223) - XOFIGO (CAP) - EMEA/H/C/00265

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				3/R/0049 (with RMP)
Pernille Harg	Alternate	Norway	No interests declared	
Adam Przybylkowski	Member	Poland	No interests declared	
Ana Sofia Diniz Martins	Member	Portugal	No interests declared	
Roxana Dondera	Member	Romania	No interests declared	
Anna Mareková	Member	Slovakia	No interests declared	
Miroslava Gocova	Alternate	Slovakia	No interests declared	
Polona Golmajer	Member	Slovenia	No interests declared	
Maria del Pilar Rayon	Member	Spain	No interests declared	
Monica Martinez Redondo	Alternate	Spain	No interests declared	
Ulla Wändel Liminga	Member	Sweden	No interests declared	
Mari Thorn	Alternate	Sweden	No restrictions applicable to this meeting	
Annalisa Capuano	Member	Independent scientific expert	No interests declared	
Milou Daniel Drici	Member	Independent scientific expert	No interests declared	
Maria Teresa Herdeiro	Member	Independent scientific expert	No interests declared	
Patricia McGettigan	Member	Independent scientific expert	No interests declared	
Tania Schink	Member	Independent scientific expert	No restrictions applicable to this meeting	
Hedvig Nordeng	Member	Independent scientific expert	No interests declared	
Roberto Frontini	Member	Healthcare Professionals' Representative	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	
Salvatore Messana	Alternate	Healthcare Professionals' Representative	No interests declared	
Christelle Bizimungu	Expert	Belgium	No restrictions applicable to this meeting	
Laurence de Fays	Expert	Belgium	No interests declared	
Martine Sabbe	Expert	Belgium	No interests declared	
Michaela Dlouhá	Expert	Czechia	No interests declared	
Lucie Skálová	Expert	Czechia	No interests declared	
Karin Erneholm	Expert	Denmark	No restrictions applicable to this meeting	
Kirsten Egebjerg Juul	Expert	Denmark	No interests declared	
Kristina Laursen	Expert	Denmark	No interests declared	
Line Michan	Expert	Denmark	No interests declared	
Annette Cleveland Nielsen	Expert	Denmark	No restrictions applicable to this meeting	
Moritz Sander	Expert	Denmark	No interests declared	
Barbara Blicher Thomsen	Expert	Denmark	No interests declared	
Vincent Gazin	Expert	France	No interests declared	
So Min Lee	Expert	Germany	No interests declared	
Dennis Lex	Expert	Germany	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Birte Niemann	Expert	Germany	No interests declared	
Eleanor Carey	Expert	Ireland	No interests declared	
Aine McKenna	Expert	Ireland	No interests declared	
Diāna Litenboka	Expert	Latvia	No interests declared	
Diāna Inga Paegle	Expert	Latvia	No interests declared	
Petrus Luijsterburg	Expert	Netherlands	No interests declared	
Evelyn Mulder-Olthof	Expert	Netherlands	No interests declared	
Anja Van Haren	Expert	Netherlands	No interests declared	
Carla Torre	Expert	Portugal	No interests declared	
Eva Cantarero	Expert	Spain	No interests declared	
Consuelo Mejías	Expert	Spain	No interests declared	
Charlotte Backman	Expert	Sweden	No interests declared	
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, see:

List of abbreviations used in EMA human medicines scientific committees and CMDh documents, and in relation to EMA's regulatory activities

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