8 August 2024
EMA/PRAC/343192/2024
Human Medicines Division

Pharmacovigilance Risk Assessment Committee (PRAC)

Minutes for the meeting on 10-13 June 2024

Vice-Chair: Martin Huber, deputising for the Chair Sabine Straus

Health and safety information

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

Disclaimers

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

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

Note on access to documents

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

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1. Introduction

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

The Vice-Chair opened the meeting by welcoming all participants. The meeting was held in-person.

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.

Due to unavailability, the Chair Sabine Straus was replaced by the Vice-Chair Martin Huber for the entire duration of the meeting.

The Vice-Chair thanked the departing members/alternates for their contributions to the Committee.

1.2. Agenda of the meeting on 10-13 June 2024

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 13-16 May 2024

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 13-16 May 2024 were published on the EMA website on 09 July 2024 (EMA/PRAC/303038/2024).

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

2.1. Newly triggered procedures

2.1.1. Metamizole (NAP); metamizole, caffeine (NAP); metamizole, caffeine, codeine (NAP); metamizole, caffeine, codeine, paracetamol (NAP); metamizole, caffeine, codeine, paracetamol, phenobarbital (NAP); metamizole, caffeine, drotaverine (NAP); metamizole, caffeine, thiamine (NAP); metamizole, hyoscine (NAP);

metamizole, pitofenone (NAP); metamizole, pitofenone, fenpipramide (NAP); metamizole, pitofenone, fenpiverinium (NAP); metamizole, triacetonamine (NAP) – EMEA/H/A-107i/1537

Applicant(s): various

PRAC Rapporteur: Julia Pallos; PRAC Co-rapporteur: Barbara Kovacic Bytyqi

Scope: Review of the benefit-risk balance following notification by Finland of a referral under Article 107i of Directive 2001/83/EC, based on pharmacovigilance data

Background

Metamizole is a pyrazolone derivate analgesic, authorised as a single agent and in several combination products. Metamizole-containing products are authorised in a number of EU member states with indications for the treatment of moderate to severe pain and fever under certain conditions.

The Finnish Medicine Agency (Fimea) sent a letter of notification dated 5 June 2024 along with a scientific background (rationale) triggering an urgent Union procedure under article 107i of Directive 2001/83/EC for the review of metamizole-containing products. The review was initiated following the fact that cases of agranulocytosis and related complications continue to be reported with metamizole, despite the implementation of successive and recent strengthened risk minimisation measures in Finland for the only metamizole-containing product (metamizole/pitofenone combination) authorised in this Member State. In addition, following the most recent reported cases, the MAH of this metamizole/pitofenone combination-containing product requested its marketing authorisation in Finland to be withdrawn for safety reasons.

Considering the above, Fimea triggered an urgent Union procedure resulting from pharmacovigilance data and requested PRAC to assess the impact of the above concerns on the benefit-risk balance of metamizole-containing products and to give its recommendation as to whether the marketing authorisations for these medicinal products should be maintained, varied, suspended or revoked across the EU.

Discussion

PRAC noted the notification letter and the scientific background from Fimea.

PRAC appointed Julia Pallos as Rapporteur and Barbara Kovacic Bytiqi as Co-Rapporteur for the procedure.

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

Summary of recommendation(s)/conclusions

- The Committee adopted a LoQ to the MAHs (EMA/PRAC/264726/2024) and a LoQ to stakeholders (EMA/PRAC/264723/2024). In addition, PRAC adopted a timetable for the procedure (EMA/PRAC/264725/2024).
- PRAC discussed the option to conduct a public hearing in the context of the current procedure according to the pre-defined criteria set out in the rules of procedure (EMA/11523/2023 Rev 2). It was agreed by the Committee that at this stage in the assessment, in light of the currently available data and the need to determine the

appropriate approach to stakeholder engagement, a public hearing would not be appropriate. PRAC can reconsider this at a later stage of the procedure, as needed.

- PRAC also agreed on the need to convene an ad-hoc expert group (AHEG) meeting. This will be further discussed in July 2024.

See the EMA press release (EMA/268985/2024) entitled 'Review of painkiller metamizole started'.

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]

For further details, see also the adopted PRAC recommendations on signals under the corresponding month.

[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

4.1. New signals detected from EU spontaneous reporting systems and/or other sources

See Annex I 14.1.

4.2. Signals follow-up and prioritisation

4.2.1. Axicabtagene ciloleucel - YESCARTA (CAP) - EMEA/H/C/004480/SDA/015.1; Brexucabtagene autoleucel - TECARTUS (CAP) - EMEA/H/C/005102/SDA/013.1; Ciltacabtagene autoleucel - CARVYKTI (CAP) - EMEA/H/C/005095/SDA/016.1; Idecabtagene vicleucel - ABECMA (CAP) - EMEA/H/C/004662/SDA/020.1; Lisocabtagene maraleucel - BREYANZI (CAP) - EMEA/H/C/004731/SDA/019.1; Tisagenlecleucel - KYMRIAH (CAP) - EMEA/H/C/004090/SDA/024.1

Applicant(s): Bristol-Myers Squibb Pharma EEIG (Abecma, Breyanzi), Kite Pharma EU B.V. (Tecartus, Yescarta), Janssen-Cilag International NV (Carvykti), Novartis Europharm Limited (Kymriah), ATMP[3]

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of secondary malignancy of T-cell origin

EPITT 20040 – Follow-up to April 2024

Background

For background information, see PRAC minutes April 2024.

The MAHs replied to the second request for information on the signal of secondary malignancy of T-cell origin and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence in EudraVigilance, including the cumulative review and responses to the list of questions submitted by the MAHs, PRAC agreed that there is sufficient evidence to update the product information of the mentioned CART- cell product to amend the existing warning on secondary malignancies for all of them, to add secondary malignancy of T-cell origin as an undesirable effect with a frequency 'rare' for Abecma (idecabtagene vicleucel), Yescarta (axicabtagene ciloleucel) and Kymriah (tisagenlecleucel), 'uncommon' for Breyanzi (lisocabtagene maraleucel) and Carvykti (ciltacabtagene autoleucel), and to mention that secondary malignancies have been reported following administration of other CAR-T cell products in case of Tecartus (brexucabtagene autoleucel). In addition, for all mentioned CART-cell products, Annex II-D should be amended to add the risk of secondary malignancy of T-cell origin in the educational program for healthcare professionals, as well as updates on the risk management plan (RMP) and circulation of a direct healthcare professional communication (DHPC).

Summary of recommendation(s)

- The MAHs for Yescarta (axicabtagene ciloleucel), Abecma (idecabtagene vicleucel), Breyanzi (lisocabtagene maraleucel), Carvykti (ciltabtagene autoleucel), Kymriah (tisagenlecleucel) and Tecartus (brexucabtagene autoleucel), should submit to EMA, within 60 days, a variation[4] to amend the product information.

[3] Advanced therapy medicinal product
[4] Update of SmPC sections 4.4 and 4.8. The package leaflet and Annex II are updated accordingly.

- In addition, all MAHs should submit to EMA, at the earliest time point possible within 4 months, an update of the RMP to reflect changes in the educational material, to update the safety specification in order to add secondary malignancy of T-cell origin as an important identified risk and to adapt accordingly the existing important potential risk of secondary malignancy by including 'except secondary malignancy of T-cell origin', to reflect in the RMP information for cases where patient material has been possible to obtain, on the pathology work-up, tumour sample collection, testing algorithm including transgene analysis. Furthermore, the MAHs for Yescarta (axicabtagene ciloleucel), Tecartus (brexucabtagene autoleucel), Carvykti (ciltabtagene autoleucel) and Kymriah (tisagenlecleucel) should update their RMPs to add a category 3 pharmacovigilance activity for the risk of secondary malignancy of T-cell origin, in order to cover an appropriate framework and process guidance to support and facilitate collection and testing of existing samples from patients who have developed secondary malignancy of T-cell origin in the post-marketing setting. Finally, all MAHs should provide new evidence for cases of secondary malignancy of T-cell in the nearest PSUR along with an updated causality assessment.

4.2.2. Medroxyprogesterone acetate (NAP)

Applicant: various

PRAC Rapporteur: Bianca Mulder

Scope: Signal of meningioma

EPITT 20030 – Follow-up to February 2024

Background

For background information, see PRAC minutes February 2024.

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

Discussion

Having considered the available evidence in EudraVigilance, including the epidemiological study and responses to the list of questions submitted by the MAH, PRAC agreed that there is sufficient evidence to update the product information of medroxyprogesterone acetate (MPA)-containing medicinal products to add meningioma or history of meningioma as a contraindication, to add meningioma as a warning and undesirable effect with a frequency 'not known' for all indications, as well as to reflect the results of the epidemiological.

Summary of recommendation(s)

- The innovator MAH for MPA-containing medicinal products as well as the MAHs for the MPA-combination product should submit to EMA, by 3 July 2024, their comments on the proposed amendments[5]. The innovator MAH should also provide comments on the proposed DHPC to be distributed, as well as to discuss the implications of the applicability of the results from *Roland et al.*[6] in the context of the bioavailability data for the different pharmaceutical forms according to the strength or posology authorised.

[5] Update of SmPC sections 4,3, 4.4, 4.8 and 5.1. The package leaflet is updated accordingly.
[6]Roland N, Neumann A, Hoisnard L, et al. Progestin use and risk of intracranial meningioma: a case-control study using data from the national health data system (SNDS) [abstract]. Rapport EPI-PHARE. 2023:1-97.

- PRAC also agreed to obtain further insight in the increased risk of meningioma with low dose oral MPA or MPA combined with other hormones and has agreed on a list of questions to the study authors of *Pourhadi et al*.[7]
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.2.3. Valaciclovir (NAP)

Applicant: various

PRAC Rapporteur: Jana Lukačišinová

Scope: Signal of acute hepatitis

EPITT 20047 – Follow-up to February 2024

Lead Member State(s): CZ

Background

For background information, see PRAC minutes February 2024.

The MAHs replied to the request for information on the signal of acute hepatitis and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence in EudraVigilance, the literature and the responses of the MAHs, PRAC agreed that the current evidence is insufficient to establish a causal relationship between valaciclovir and acute hepatitis to further warrant an update to the product information and/or risk management plan at present.

Summary of recommendation(s)

- In the next PSURs, the MAHs for valaciclovir-containing medicinal products should continue to monitor the risk of acute hepatitis, and to include 'drug related severe hepatic disorders' as an important potential risk.

4.3. 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.

[7]Pourhadi N, Meaidi A, Friis S, et al. Menopausal hormone therapy and central nervous system tumors: Danish nested case-control study. PLoS Med. 2023 Dec 19;20(12):e1004321. doi: 10.1371/journal.pmed.1004321. PMID: 38113227; PMCID: PMC10729984.

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. Bimatoprost - (CAP MAA) - EMEA/H/C/005916

Scope (pre D-180 phase): Indicated for the reduction of intraocular pressure (IOP) in adults with open angle glaucoma (OAG) or ocular hypertension (OHT) who are unsuitable for topical IOP-lowering medications

5.1.2. Liquid ethanolic extract 30 per cent (W/W) of Allium cepa fresh bulb and Citrus limon fresh fruit / Dry aqueous extract of Paullinia cupana seed / Dry hydroethanolic extract of theobroma cacao seed - (CAP MAA) - EMEA/H/C/004155

Scope (pre D-180 phase): Treatment of alopecia areata in children and adolescents

5.1.3. Meningococcal group A, B, C, W and Y vaccine - (CAP MAA) - EMEA/H/C/006165

Scope (pre D-180 phase): Indicated for active immunisation to prevent invasive disease caused by Neisseria meningitidis groups A, B, C, W, and Y

5.1.4. Mirvetuximab soravtansine - (CAP MAA) - EMEA/H/C/005036, Orphan

Applicant: Immunogen Biopharma (Ireland) Limited

Scope (pre D-180 phase): Treatment of ovarian, fallopian tube, or primary peritoneal cancer

5.1.5. Temozolomide - (CAP MAA) - EMEA/H/C/006169, Orphan

Applicant: Orphelia Pharma

Scope (pre D-180 phase): Treatment of neuroblastoma

5.1.6. Vilobelimab - (CAP MAA) - EMEA/H/C/006123

Scope (pre D-180 phase): Treatment of adult patients with SARS-CoV-2 induced septic acute respiratory distress syndrome (ARDS) receiving invasive mechanical ventilation (IMV) or extracorporeal membrane oxygenation (ECMO).

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

See Annex I 15.2.

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

See Annex I 15.3.

6. Periodic safety update reports (PSURs)

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

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

See also Annex I 16.1.

6.1.1. Ibrutinib - IMBRUVICA (CAP) - PSUSA/00010301/202311

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Barbara Kovacic Bytyqi

Scope: Evaluation of a PSUSA procedure

Background

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Imbruvica, a centrally authorised medicine containing ibrutinib 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 Imbruvica (ibrutinib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include of cutaneous vasculitis as an undesirable effect with a frequency uncommon. Therefore, the current terms of the marketing authorisation(s) should be varied[8].
- In the next PSUR, the MAH should provide detailed analyses of cases of fractures and pancreatitis from all sources, including clinical trials, post-marketing setting, literature. The MAH should also provide a cumulative review of cases of pulmonary arterial hypertension, including data from post-marketing setting, clinical trials and literature, along with a discussion on the possible mechanism of toxicity, using the SMQ Pulmonary hypertension as a basis for this review and discuss the need to update the product information as warranted. In addition, the MAH should provide a review of cases of progressive multifocal leukoencephalopathy (PML) in which PML was reported with implausible latency from discontinuation of prior immunosuppressive therapy to the first symptoms of PML and discuss the need to update the product information and/or RMP. The MAH should also provide a cumulative review of cases of macular oedema and cystoid macular oedema from all available sources and discuss on a possible biological mechanism. The MAH should continue to monitor cases of uveitis, other MedDRA PTs, macular degeneration, and retinal detachment), pneumothorax and adrenal insufficiency in the next PSUR.

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

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

6.1.2. Insulin glargine, lixisenatide - SULIQUA (CAP) - PSUSA/00010577/202311

Applicant: Sanofi Winthrop Industrie

PRAC Rapporteur: Bianca Mulder

Scope: Evaluation of a PSUSA procedure

Background

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Suliqua, a centrally authorised medicine containing insulin glargine/lixisenatide 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 Suliqua (insulin glargine/lixisenatide) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include dysgeusia as an undesirable effect with a frequency 'uncommon'. Therefore, the current terms of the marketing authorisation(s) should be varied[9].
- In the next PSUR, the MAH should continue to monitor cases of intestinal obstruction. In addition, the MAH should evaluate if cases where there was a confusion between different strengths of the product have been reported and discuss the appropriateness of current additional risk minimisation measures.

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

6.1.3. Ixazomib - NINLARO (CAP) - PSUSA/00010535/202311

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

Background

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Ninlaro, a centrally authorised medicine containing ixazomib 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 Ninlaro (ixazomib) in the approved indication(s) remains unchanged.

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

- Nevertheless, the product information should be updated to include arthralgia and pyrexia as undesirable effect with frequency 'very common'. 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 vasculitis and discuss the need for an update of the product information as warranted.

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

6.1.4. Obinutuzumab - GAZYVARO (CAP) - PSUSA/00010279/202310

Applicant: Roche Registration GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

Background

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Gazyvaro, a centrally authorised medicine containing obinutuzumab and issued a recommendation on 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 Gazyvaro (Obinutuzumab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include hypogammaglobulinemia as undesirable effect with a frequency 'uncommon'. Therefore, the current terms of the marketing authorisation(s) should be varied[11].
- In the next PSUR, the MAH should provide a review of cases of cytokine release syndrome (CRS), based on data from all relevant sources (clinical studies, post marketing and literature), in particular cases with any atypical presentations of this syndrome and discuss the need for an update of the product information as warranted.

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

6.1.5. Pasireotide - SIGNIFOR (CAP) - PSUSA/00009253/202310

Applicant: Recordati Rare Diseases

PRAC Rapporteur: Mari Thorn

Scope: Evaluation of a PSUSA procedure

Background

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

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Signifor, a centrally authorised medicine containing pasireotide 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 Signifor (pasireotide) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include steatorrhea and faeces discoloured as undesirable effects with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[12].

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. Pegcetacoplan - ASPAVELI (CAP) - PSUSA/00010974/202311

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

Background

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Aspaveli, a centrally authorised medicine containing pegcetacoplan 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 Aspaveli (pegcetacoplan) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include urticaria with a frequency 'uncommon'. Therefore, the current terms of the marketing authorisation(s) should be varied[13].
- In the next PSUR, the MAH should continue to monitor cases of anaphylactic reactions and provide a cumulative review of cases of opportunistic infections, including viral and fungal infections and discuss the need to update the product information and/or the RMP.

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

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

6.1.7. Respiratory syncytial virus vaccine (bivalent, recombinant) - ABRYSVO (CAP) - PSUSA/00000102/202311

Applicant: Pfizer Europe Ma EEIG

PRAC Rapporteur: Liana Martirosyan

Scope: Evaluation of a PSUSA procedure

Background

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Abrysvo, a centrally authorised medicine containing respiratory syncytial virus vaccine (bivalent, 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 Abrysvo (respiratory syncytial virus vaccine (bivalent, recombinant)) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to remove the footnote regarding Guillain-Barré syndrome and clinical trial cases under the table reflecting the list of adverse reactions, as it does not adequately reflect the cumulative evidence (including post-marketing cases) anymore. Therefore, the current terms of the marketing authorisation(s) should be varied[14].
- In the next PSUR, the MAH(s) should provide data on maternal exposure, and continue to monitor any new cases of Guillain-Barré syndrome and of atrial fibrillation.

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

6.1.8. Tirzepatide - MOUNJARO (CAP) - PSUSA/00011019/202311

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Bianca Mulder

Scope: Evaluation of a PSUSA procedure

Background

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Mounjaro, a centrally authorised medicine containing tirzepatide 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 Mounjaro (tirzepatide) in the approved indication(s) remains unchanged.

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

- Nevertheless, the product information should be updated to include dysgeusia as an undesirable effect with a frequency 'uncommon'. Therefore, the current terms of the marketing authorisation(s) should be varied[15].
- In the next PSUR, the MAH should provide cumulative reviews of cases of malnutrition, starvation ketoacidosis and cachexia, including a detailed causality assessment. In addition, the MAH should provide a cumulative review of cases of cases of gastroparesis, including a detailed discussion on non-serious cases. In the next PSUR, the MAH should also continue to monitor cases of alopecia/hair loss and of intestinal obstruction and ileus.

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

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

See also Annex I 16.2.

6.2.1. Methotrexate - JYLAMVO (CAP); NORDIMET (CAP); NAP - PSUSA/00002014/202310

Applicant(s): Nordic Group B.V. (Nordimet), Therakind (Europe) Limited (Jylamvo), various

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

Methotrexate is a folic acid analogue indicated for the treatment of different types of cancer such as acute lymphoblastic leukaemia, non-Hodgkin's lymphoma, breast carcinoma, small-cell lung carcinoma, epidermal tumours on the head and neck, ovarian carcinoma, and osteosarcoma, and of autoimmune diseases such as rheumatoid arthritis (RA), psoriasis vulgaris, psoriatic arthritis, and Crohn's disease, subject to certain conditions.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of Jylamvo and Nordimet, centrally authorised medicines containing methotrexate, and nationally authorised medicines containing methotrexate 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 methotrexate-containing product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add or revise photosensitivity reactions as an undesirable effect with a frequency 'uncommon' and to add a warning on the risk of photosensitivity. Also, the product information should be updated to amend the existing information regarding interaction between methotrexate

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

and metamizole. Therefore, the current terms of the marketing authorisations should be varied[16].

- In the next PSUR, all MAHs should comment on the use of methotrexate in patients with a creatinine clearance of 30-45 mL/min and discuss the need to update the product information. In addition, all MAHs should provide a cumulative review of cases of bone toxicity, focussing on low doses of methotrexate, and to discuss the need for any new risk minimisation measures in light of new information. All MAHs should provide reviews of cases of hyperhomocysteinaemia and the MAH medac should also provide reviews of cases of lymphadenopathy and thorough assessment of cases concerning gastrointestinal inflammation for those terms (PTs) which are not yet included in 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. PSUR single assessment (PSUSA) procedures including nationally authorised products (NAPs) only

See also Annex I 16.3.

6.3.1. Atorvastatin (NAP) - PSUSA/00010347/202310

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

Atorvastatin is an inhibitor of 3-hydroxy 3-methylglutaryl coenzyme A (HMG-CoA) reductase and it is indicated for the treatment of hypercholesterolaemia in adults, adolescents and children aged 10 years or older with primary hypercholesterolaemia, including familial hypercholesterolaemia or combined hyperlipidaemia. It is also indicated for the treatment of homozygous familial hypercholesterolaemia and for the prevention of cardiovascular events in adult patients.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing atorvastatin 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 atorvastatin-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a drug-drug interaction between atorvastatin and daptomycin, including a respective warning/precaution and add lichenoid drug reaction and vasculitis as undesirable effects

[16] Update of SmPC sections 4.4, 4.5 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion

with a frequency 'rare'. Therefore, the current terms of the marketing authorisation(s) should be varied[17].

- In the next PSUR, the MAH(s) should provide cumulative reviews of cases of suicide/self-injury related preferred terms (PTs), bullous pemphigoid, microscopic colitis and of drug-drug interaction between atorvastatin and clopidogrel from all sources, including clinical trials, post-marketing setting and literature, as well as of photosensitivity with post-marketing and literature data including a discussion on the update of the product information as warranted. The MAH Viatris should provide a cumulative review of cases of sexual dysfunction and a review of new cases or follow-ups for bullous pemphigoid. In addition, all MAHs should monitor the matter concerning genetic polymorphisms associated with an increased risk for statin-associated muscle symptom, as well as the drug-drug interaction between atorvastatin and sofosbuvir/velpatasvir, between atorvastatin and ticagrelor and cases of drug reaction with eosinophilia and systemic symptoms (DRESS).

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. Ceftazidime (NAP) - PSUSA/00000608/202310

Applicant(s): various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

Background

Ceftazidime is a third-generation cephalosporin antibiotic for parenteral administration as a powder for either intravenous or intramuscular infusion/injection. It is indicated for the treatment of severe infections; respiratory tract infections including lung infection in cystic fibrosis; ear, nose and throat infections; urinary tract infections; skin and soft-tissue infections; gastrointestinal, biliary and abdominal infections; bone and joint infections; infections associated with dialysis and as prophylaxis for prostate surgery.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing ceftazidime 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 ceftazidime-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis (AGEP) as a warning and to add acute generalized exanthematous pustulosis (AGEP) as an undesirable effect with a frequency

[17] Update of SmPC sections 4.4, 4.5 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position

'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[18].

- In the next PSUR, the MAH(s) should perform an analysis of cases related to neurotoxicity in patients with no known renal impairment or kidney disease, in order to better characterise the risk of neurotoxic adverse reactions, including seizures.

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

6.3.3. Clevidipine (NAP) - PSUSA/00010288/202311

Applicant(s): various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

Background

Clevidipine is a dihydropyridine L-type calcium channel blocker and it is indicated for the rapid reduction of blood pressure in the perioperative setting.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing clevidipine 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 clevidipine-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add blood triglycerides increase as an undesirable effect with a frequency 'uncommon'. Therefore, the current terms of the marketing authorisation(s) should be varied[19].
- In the next PSUR, the MAH should closely monitor cases of bradycardia and pancreatitis.

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

6.3.4. Hydrochlorothiazide, nebivolol (NAP) - PSUSA/00001658/202311

Applicant(s): various

PRAC Lead: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

Background

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

Nebivolol is a selective beta-receptor antagonist, and hydrochlorothiazide is a thiazide diuretic. The combination hydrochlorothiazide/nebivolol has an additive antihypertensive effect, reducing blood pressure to a greater degree than either component alone.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing hydrochlorothiazide/nebivolol 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 hydrochlorothiazide/nebivolol-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add the risk of severe hypoglycaemia following the concomitant use of beta-blockers and sulfonylureas as a warning. Therefore, the current terms of the marketing authorisation(s) should be varied[20].
- In the next PSUR, the MAH(s) should provide a cumulative review of cases of hypoglycaemia, discussing the causal relationship and the biological mechanism, providing and discussing also the updated literature research on this topic and considering if the adverse event could be evaluated as a class effect for β-blockers. The MAH should discuss the need for an updated product information as warranted. In addition, the MAH(s) should monitor cases of hypophosphatemia, hyperuricaemia and gout, as well as of liver injury and skin cancer with specific reference to findings about melanoma from any sources.

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

6.3.5. Minoxidil[21] (NAP) - PSUSA/00002067/202310

Applicant(s): various

PRAC Lead: Eamon O'Murchu

Scope: Evaluation of a PSUSA procedure

Background

Minoxidil is an antihypertensive vasodilating agent and it is indicated as topical formulation, for the treatment of androgenetic alopecia in males and females aged ≥18 years, subject to certain conditions.

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

Summary of recommendation(s) and conclusions

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

- Based on the review of the data on safety and efficacy, the benefit-risk balance of minoxidil-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information for minoxidil-containing product as topical formulations should be updated to include a warning on the risk of hypertrichosis in infants and children following inadvertent topical exposure to minoxidil. Therefore, the current terms of the marketing authorisation(s) should be varied[22].
- In the next PSUR, all MAHs should continue to monitor cases of hypertrichosis in children following accidental exposure via patients with minoxidil and provide any new cases. In addition, all MAHs should continue to monitor the following safety issues in future PSURs: cardiovascular disorders, hypersensitivity to minoxidil or any of the ingredients, accidental ingestion of minoxidil may cause severe systemic effects, use during pregnancy and breastfeeding.

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

6.3.6. Nimodipine (NAP) - PSUSA/00002166/202311

Applicant(s): various

PRAC Lead: Karen Pernille Harg

Scope: Evaluation of a PSUSA procedure

Background

Nimodipine is a calcium antagonist of the 1,4-dihydropyridine class that presumably exerts a neuroprotective influence by reduction of the transmembrane influx through the L-type calcium channels and it is indicated for the treatment of aneurysmal subarachnoid haemorrhage, impaired brain function of old age, for the prevention and therapy of ischemic neurological deficits correlated to cerebral vasospasm, for reduction of neurological deficits following aneurysmal subarachnoid haemorrhage (SAH), and for prevention of neurological deficits caused by cerebral vasospasm following aneurysmal SAH.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing nimodipine 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 nimodipine-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add hypoxia as an undesirable effect with a frequency 'not known'. Where the product information does not already contain a similar warning, the outer and immediate packaging should also be updated to ensure that the warning 'Do not ingest' is included and displayed in a

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

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

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. Delafloxacin - QUOFENIX (CAP) - EMEA/H/C/004860/LEG 004

Applicant: A. Menarini Industrie Farmaceutiche Riunite s.r.l.

PRAC Rapporteur: Eva Jirsová

Background

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

As a consequence of the Article 31 referral procedure concluded in November 2018 and following the evaluation of the most recently submitted PSUR(s) for the above-mentioned medicine(s), PRAC requested the MAH to submit further data on prolonged, potentially irreversible, serious suspected adverse drug reactions to fluoroquinolones. The responses were assessed by the Rapporteur for further PRAC advice. See also section 11.1 in the current Agenda.

Summary of advice/conclusion(s)

- Based on the available data from the MAH's safety database, EudraVigilance and literature and the Rapporteur's assessment, considering also a neurotoxicity/ neuropsychiatric potential mechanism, PRAC agreed that the product information of Quofenix (delafloxacin) should be updated to reflect the new aspects of prolonged, disabling and potentially irreversible adverse reactions. The MAH should provide its comments on the proposed update of the product information.
- The MAH should submit to EMA, within 30 days, a response to the request for supplementary information (RSI).

6.4.2. Levofloxacin - QUINSAIR (CAP) - EMEA/H/C/002789/LEG 006

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Eva Jirsová

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.

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

As a consequence of the Article 31 referral procedure concluded in November 2018 and following the evaluation of the most recently submitted PSUR(s) for the above-mentioned medicine(s), PRAC requested the MAH to submit further data on prolonged, potentially irreversible, serious suspected adverse drug reactions to fluoroquinolones. The responses were assessed by the Rapporteur for further PRAC advice. See also section 11.1 in the current Agenda.

Summary of advice/conclusion(s)

- Based on the available data from the MAH's safety database, EudraVigilance and literature and the Rapporteur's assessment, considering also a neurotoxicity/ neuropsychiatric potential mechanism, PRAC agreed that the product information of Quinsair (levofloxacin) should be updated to reflect the new aspects of prolonged, disabling and potentially irreversible adverse reactions. The MAH should provide its comments on the proposed update of the product information.
- The MAH should submit to EMA, within 30 days, a response to the request for supplementary information (RSI).

6.5. Variation procedure(s) resulting from PSUSA evaluation

See also Annex I 16.5.

6.5.1. Atazanavir - REYATAZ (CAP) - EMEA/H/C/000494/II/0140

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Nathalie Gault

Background

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

Following the evaluation of the most recently submitted PSUR(s) for the above-mentioned medicine(s), PRAC requested the MAH to submit a variation to clarify and update the warning regarding dyslipidaemia in relation to other comparators. PRAC is responsible for adopting an outcome based on the assessment report from the PRAC Rapporteur, to be further considered at the level of CHMP, responsible for adopting an opinion on this variation.

Summary of recommendation(s)

- Based on the available data and the Rapporteur's assessment, PRAC agreed that the product information[24] should be updated to reflect that, in clinical studies, atazanavir with ritonavir has been shown to induce dyslipidaemia to a lesser extent than lopinavir with ritonavir in either treatment-naïve patients or treatment-experienced patients.

6.5.2. Meningococcal Group A, C, W and Y conjugate vaccine - MENQUADFI (CAP) - EMEA/H/C/005084/II/0031

Applicant: Sanofi Pasteur

[24] Update of section 4.4

PRAC Rapporteur: Jean-Michel Dogné

Background

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

Following the evaluation of the most recently submitted PSUR(s) for the above-mentioned medicine(s), PRAC requested the MAH to submit a variation to add 'hypersensitivity including anaphylaxis' to the list of adverse drug reactions (ADRs), based on a cumulative review of cases of hypersensitivity/allergic reaction (including anaphylaxis). PRAC is responsible for adopting an outcome based on the assessment report from the PRAC Rapporteur, to be further considered at the level of CHMP, responsible for adopting an opinion on this variation.

Summary of recommendation(s)

- Based on the available data and the Rapporteur's assessment, PRAC agreed that the product information[25] should be updated to add hypersensitivity and anaphylaxis as undesirable effect with a frequency 'not known' and 'very rare' respectively.

6.6. Expedited summary safety reviews[26]

None

7. Post-authorisation safety studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)[27]

See also Annex I 17.1.

7.1.1. Exagamglogene autotemcel - CASGEVY (CAP) - EMEA/H/C/PSA/S/0113

Applicant: Vertex Pharmaceuticals (Ireland) Limited, ATMP

PRAC Rapporteur: Bianca Mulder

Scope: Substantial amendment to a protocol for a long-term registry-based study of patients with transfusion-dependent β-thalassemia (TDT) or sickle cell disease (SCD) treated with exagamglogene autotemcel (exa-cel)

Background

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

In order to fulfil the specific obligation to conduct a PASS (Annex II-E) imposed as conditions to the marketing authorisation, the MAH Vertex Pharmaceuticals (Ireland) Limited submitted to EMA an amended PASS protocol version 1.1 for a study entitled: 'Long-term registry-

[25] Update of section 4.8. The package leaflet is updated accordingly
[26] 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
[27] In accordance with Article 107n of Directive 2001/83/EC

based study of patients with transfusion-dependent β-thalassemia (TDT) or sickle cell disease (SCD) treated with exagamglogene autotemcel (exa-cel)' for review by PRAC. PRAC is responsible for evaluating the PASS protocol.

Endorsement/Refusal of the protocol

- Having considered the draft protocol version 1.1 in accordance with Article 107o of Directive 2001/83/EC, PRAC objected to the draft protocol for the above listed medicinal product(s). PRAC agreed that the PASS is non-interventional, but the study design does not fulfil the study objectives at this stage.
- The MAH should provide clarifications on the safety outcome variables, the data analysis, and to the management of adverse events, as well as to add 'hospitalisation for severe vaso-occlusive crisis (VOCs)' as one of the effectiveness outcomes.
- The MAH should submit a revised PASS protocol within 60 days to EMA. A 60 days-assessment timetable will be followed.

7.2. Protocols of PASS non-imposed in the marketing authorisation(s)[28]

See also Annex I 17.1.1.

7.2.1. Piflufolastat (18F) - PYLCLARI (CAP) - EMEA/H/C/005520/MEA 002

Applicant: Curium Pet France

PRAC Rapporteur: Kimmo Jaakkola

Scope: From initial MAA
PROTOCOL PASS NO. CURF18PSM0002 (NI/NI/RMP/Cat. 3)
A observational study to evaluation the effectiveness of the self-administered educational training programme to the nuclear medicine physicians who will have to interpret PET findings with Pylclari

Background

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

As part of the RMP for Pylclari (piflufolastat (18F)), the MAH was required to conduct an observational study in order to mitigate the risk for PET imaging interpretation errors. The MAH submitted a protocol for a study (as part of the RMP but outside the scope of Article 107n of Directive 2001/83/EC) which was assessed by the Rapporteur. PRAC was requested to provide advice to CHMP on the protocol submitted by the MAH.

Summary of advice

- PRAC considered that the study, by design, cannot evaluate the effectiveness of the educational material since it will not allow detection of actual PET interpretation errors, thus the MAH should update the RMP at the next regulatory opportunity to remove the requirement for this non-imposed PASS. In addition, PRAC agreed that 'PET imaging interpretation errors' should be removed from the safety concerns of the RMP and the

[28] 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

educational material, and this risk should be adequately monitored during the routine pharmacovigilance activities including the PSUR reporting.

7.3. Results of PASS imposed in the marketing authorisation(s)[29]

None

7.4. Results of PASS non-imposed in the marketing authorisation(s)[30]

See Annex I 17.4.

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

None

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.

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.

[29] In accordance with Article 107p-q of Directive 2001/83/EC
[30] 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

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. Fluoroquinolones for systemic and inhalation use: ciprofloxacin (NAP); levofloxacin (NAP); lomefloxacin (NAP); moxifloxacin (NAP); norfloxacin (NAP); ofloxacin (NAP); pefloxacin (NAP); prulifloxacin (NAP); rufloxacin (NAP) -

Applicant: various

PRAC Lead: Eva Jirsová

Scope: PRAC consultation on a PSUR follow-up procedure regarding risk minimisation measures following submission of cumulative reviews of spontaneously reported cases of prolonged, potentially irreversible, serious suspected adverse drug reactions, in accordance with the outcome of the referral procedure under Article 31 of Directive 2001/83/EC (EMEA/H/A-31/1452) concluded in 2019, at the request of Czech Republic

Background

Fluoroquinolones are a class of broad-spectrum antibiotics that are active against bacteria of both Gram-negative and Gram-positive classes.

Based on the outcome of the Article 31 referral procedure, fluoroquinolones´ indications have been significantly restricted with comprehensive warnings implemented in the product information to inform about the risks. For further background information, see Quinolone- and fluoroquinolone-containing medicinal products - referral. Following the referral, the MAHs should perform a detailed follow-up of all incoming spontaneously reported cases of prolonged, potentially irreversible, serious suspected adverse drug reactions (ADRs) to fluoroquinolones.

In the context of the evaluation of a PSUR follow-up procedure regarding risk minimisation measures following submission of cumulative reviews of spontaneously reported cases of prolonged, potentially irreversible, serious suspected ADRs, Czech Republic requested PRAC advice on its assessment.

Summary of advice

- Based on the review of the available information, PRAC noted that, although the available evidence is limited, the product information should be updated to include anxiety, suicidal ideation, panic attack, neuralgia and concentration impairment as potential aspects of fluoroquinolone induced long-lasting and disabling adverse drug reactions (ADRs); the deletion of the expression regarding frequency of occurrence is not endorsed as the information is considered important and the newly available evidence does not provide sufficient justification for its removal. Furthermore, PRAC agreed that a dissemination of an EU-wide communication is currently not recommended due to differences in already implemented communication strategies, but Member States can consider communication at national level, tailoring it to the needs of their national communication strategy. In addition, PRAC supported that further follow-up of long-lasting, disabling and potentially irreversible ADRs via routine pharmacovigilance is needed but with no specific request for a cumulative review to be provided in the next PSUR. Finally, PRAC considered that a consultation with the Infectious Disease Working Party (IDWP) is not warranted, as fluoroquinolones' indications have been thoroughly discussed and restricted during the Article 31 referral and the current EU recommendations are considered adequate.

11.2. Other requests

None

12. Organisational, regulatory and methodological matters

12.1. Mandate and organisation of PRAC

12.1.1. PRAC membership

The PRAC Vice-Chair thanked Tania Schink for her contribution as Independent Scientific Expert appointed by the European Commission (end of mandate: 02 July 2024).

12.1.2. Vote by proxy

None

12.1.3. Scientific Committee Meetings – alternating face-to-face and virtual meetings schedule for 2025

The EMA Secretariat presented the alternating face-to-face and virtual meetings schedule for 2025. 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

12.3.1. Real World Evidence European Specialised Expert Community (ESEC) – update

The EMA Secretariat presented to PRAC the Real-World Evidence ESEC along with details related to its activities and membership. The PRAC members were invited to express their interest to join the community. PRAC noted the information.

12.4. Cooperation within the EU regulatory network

None

12.5. Cooperation with International Regulators

None

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

None

12.7. PRAC work plan

None

12.8. Planning and reporting

None

12.9. Pharmacovigilance audits and inspections

12.9.1. Pharmacovigilance systems and their quality systems

None

12.9.2. Pharmacovigilance inspections

None

12.9.3. Pharmacovigilance audits

None

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

12.10.1. Periodic safety update reports

None

12.10.2. Granularity and Periodicity Advisory Group (GPAG)

None

12.10.3. PSURs repository

None

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

In line with the criteria for plenary presentation of updates to the EURD List adopted by PRAC in December 2021, PRAC endorsed the draft revised EURD list, version June 2024, 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 June 2024, the updated EURD list was adopted by CHMP and CMDh at their June 2024 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) – review of 'other considerations' section in the assessment report – proposed approach post pilot phase

PRAC lead: Sabine Straus, Martin Huber

At the organisational, regulatory and methodological matters (ORGAM) meeting on 27 June 2024, the PRAC's Vice chair Martin Huber presented the results of the pilot phase in which the 'other considerations' section (section 6) was removed from the PSUSA assessment report (AR) for all PSUSA types (CAP only, mix CAP/NAP and NAPs only) in order to streamline the PSUSA AR and based on the previous discussions at both PRAC and CMDh levels (see PRAC minutes March 2023, PRAC minutes May 2023 and PRAC minutes November 2023). Based on the analysis of the results from the pilot phase, PRAC was informed on the proposal to permanently remove the mentioned section from all PSUSA AR templates going forward, but it was agreed to await feedback from CMDh SOS WG on proposals focusing on extrapolation and DDI before reaching a final decision. As a result, the Committee agreed that a final decision will be taken during the July PRAC meeting after incorporation of the CMDh SOS WG feedback received.

12.11. Signal management

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

None

12.12. Adverse drug reactions reporting and additional monitoring

12.12.1. Management and reporting of adverse reactions to medicinal products

None

12.12.2. Additional monitoring

None

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

PRAC was informed on the updates made to the list of products under additional monitoring.

Post-meeting note: The updated additional monitoring list was published on the EMA website, see: Home>Human Regulatory>Post-authorisation>Pharmacovigilance>Medicines under additional monitoring>List of medicines under additional monitoring

12.13. EudraVigilance database

12.13.1. Activities related to the confirmation of full functionality

None

12.14. 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

12.15.3. Good pharmacovigilance practices (GVP) module VIII on 'Post-authorisation safety studies (PASS)' Revision 4 – update

The topic was postponed for the July 2024 PRAC meeting.

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. Good pharmacovigilance practice (GVP) module XVI on 'Risk minimisation measures: selection of tools and effectiveness indicators' – revision 3 on principles and methods to evaluate the effectiveness of risk minimisation measures (RMM)

PRAC lead: Sabine Straus

The updated GVP M XVI (Rev.3) on principles and methods to evaluate the effectiveness of methods for RMMs effectiveness evaluation following the public consultation launched in 2021 was adopted by PRAC. For background information, see PRAC minutes April 2024.

Post meeting note: GVP M XVI (Rev.3) was published on the EMA website on 5 August 2024 along with the Module XVI Addendum II and the GVP Annex I on definitions (Rev.5). For further information on the changes, see 'Guidelines on good pharmacovigilance practices (GVP) - Introductory cover note, last updated with final revision 3 of Module XVI on risk minimisation measures and its Addendum II on their effectiveness evaluation, and revision 5 of Annex I on definitions' (EMA/340669/2024).

12.21. Others

12.21.1. Real World Evidence and Data analysis and real-world interrogation network (DARWIN EU®) – quarterly update

At the organisational, regulatory and methodological matters (ORGAM) meeting on 27 June 2024, the EMA Secretariat presented to PRAC the quarterly update on real world evidence (RWE) topic with a summary of completed, ongoing and planned studies under DARWIN EU®, framework contract (FWC) or in-house, including an update on the studies under the pharmacogenomics pilot. In addition, following the previous discussions on the proposal to start a RWD pilot in the context of the PSUSA procedures (see PRAC minutes April 2024), the EMA Secretariat presented to PRAC some study proposals deriving from PSUSAs of the April and May meetings; PRAC agreed to start the pilot phase. Finally, PRAC was updated on recent/upcoming events in relation to RWD/RWE as well as on the ICH reflection papers and guidelines.

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. Roxadustat - EVRENZO (CAP)

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Anna Mareková

Scope: Signal of thrombocytopenia

EPITT 20079 – New signal

Lead Member State(s): SK

14.2. New signals detected from other sources

None

15. Annex I – Risk management plans

15.1. Medicines in the pre-authorisation phase

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

15.1.1. Aflibercept - (CAP MAA) - EMEA/H/C/006150

Scope (pre D-180 phase): Treatment of age-related macular degeneration (AMD), visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO), due to diabetic macular oedema (DME) and due to myopic choroidal neovascularisation (myopic CNV)

15.1.2. Aflibercept - (CAP MAA) - EMEA/H/C/006056

Scope (pre D-180 phase): Treatment of age-related macular degeneration (AMD) and visual impairment

15.1.3. Ustekinumab - (CAP MAA) - EMEA/H/C/006585

Scope (pre D-180 phase): Treatment of active plaque psoriasis, paediatric plaque psoriasis, psoriatic arthritis (PsA) and Crohn’s disease

15.1.4. Ustekinumab - (CAP MAA) - EMEA/H/C/006221

Scope (pre D-180 phase): Treatment of active plaque psoriasis, Crohn’s disease, active ulcerative colitis and active psoriatic arthritis

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. Cinacalcet - CINACALCET ACCORDPHARMA (CAP); NAP - EMEA/H/C/005236/WS2686/0011

Applicant(s): Accord Healthcare S.L.U., various

PRAC Rapporteur: Mari Thorn

Scope: To update the RMP to make updated in following safety concerns (important identified risks) after approval of the same changes in the reference product, Mimpara (in procedure EMEA/H/C/000570/IB/0069):
-Update of "Hypocalcemia" to "Hypocalcemia in the pediatric population"
-Removal of "QT prolongation and ventricular arrhythmias secondary to hypocalcaemia"
-Removal of "Convulsions/seizures"

Furthermore, the Marketing Authorisation Holder is taking the opportunity to consolidate into a single RMP the RMPs approved for Cinacalcet 30mg/60mg/90mg Film-coated tablets through CP (EMEA/H/C/005236) and DCP (FI/H/869/01-03/DC) procedures

15.2.2. Dasatinib - SPRYCEL (CAP) - EMEA/H/C/000709/II/0090

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Submission of an updated RMP version 18.0 in order to reflect the proposed revised commitments to assess the growth and development disorders and bone mineral metabolism disorders in paediatric subjects

15.2.3. Human thrombin, human fibrinogen - TACHOSIL (CAP) - EMEA/H/C/000505/II/0124

Applicant: Corza Medical GmbH

PRAC Rapporteur: Gabriele Maurer

Scope: Submission of an updated RMP version 9.1 in order to reflect the extension of indication to include the paediatric population and to update the details of the planned non-interventional PASS: PASS-TachoSil Evaluation (PasTel)

15.2.4. Mavacamten - CAMZYOS (CAP) - EMEA/H/C/005457/II/0008

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Kimmo Jaakkola

Scope: Submission of an updated RMP version 3.0 in order to revise the number of patients planned to be enrolled in DISCOVER-HCM US-registry study CV027012 (MEA 005). In addition, the MAH took this opportunity to update protocol title for MAVEL-HCM study

(CV027013) and include reference to study protocol in Annex 3 of the RMP, following the assessment of PAM procedure MEA 001

15.2.5. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/II/0063

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Martirosyan

Scope: Submission of an updated RMP version 32.0 in order to propose the removal of category 3 study A3921329 (A Long-Term, Observational Study within the CorEvitas [formerly Corrona] Inflammatory Bowel Disease (IBD) Registry to Characterize the Safety of Tofacitinib in Patients with Ulcerative Colitis in the Post-Approval Setting). In addition, the MAH took the opportunity to update the RMP with some other minor updates

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. Axicabtagene ciloleucel - YESCARTA (CAP) - EMEA/H/C/004480/II/0075/G, Orphan,

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

PRAC Rapporteur: Karin Erneholm

Scope: Grouped application comprising two type II variations as follows:
C.I.13 - Submission of the final report from study KTE-C19-101 (ZUMA-1) listed as a category 3 study in the RMP. This is a Phase 1/2 Multicenter Study Evaluating The Safety And Efficacy Of Kte-C19 In Subjects With Refractory Aggressive Non-Hodgkin Lymphoma.
C.I.13 - Submission of the final report from study KTE-C19-106 (ZUMA-6) listed as a category 3 study in the RMP. This is a Phase 1-2 Multi-Center Study Evaluating The Safety And Efficacy Of Kte-C19 In Combination With Atezolizumab In Subjects With Refractory Diffuse Large B-Cell Lymphoma (Dlbcl).
The RMP version 9.2 has also been submitted

15.3.2. Benralizumab - FASENRA (CAP) - EMEA/H/C/004433/II/0052

Applicant: AstraZeneca AB

PRAC Rapporteur: David Olsen

Scope: Extension of indication to include treatment of eosinophilic granulomatosis with polyangiitis (EGPA) for Fasenra, based on results from study D3253C00001 (Mandara); this was a randomised, double-blind, multicentre, parallel group, active-controlled, non-inferiority study that evaluated the efficacy and safety of benralizumab compared with mepolizumab in treatment of patients with EGPA on corticosteroid therapy with or without stable immunosuppressive therapy. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet is updated in accordance. Version 6.1 of the RMP has also been submitted. In addition, the MAH took this opportunity to introduce editorial changes. As part of the application, the MAH is requesting a 1-year extension of

[33] Advanced therapy medicinal product

the market protection

15.3.3. Bulevirtide - HEPCLUDEX (CAP) - EMEA/H/C/004854/II/0031, Orphan

Applicant: Gilead Sciences Ireland Unlimited Company

PRAC Rapporteur: Adam Przybylkowski

Scope: Extension of indication to include treatment of chronic hepatitis delta virus (HDV) infection in paediatric patients 3 years of age and older weighing at least 10 kg with compensated liver disease for Hepcludex, based on a modelling and simulation study and an extrapolation study to evaluate the use of Bulevirtide for the treatment of chronic hepatitis D infection in children from 3 to less than 18 years of age. As a consequence, sections 4.1, 4.2, 5.1 and 5.2 of the SmPC are updated. The package leaflet has been updated accordingly. Version 4.1 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

15.3.4. Canagliflozin - INVOKANA (CAP) - EMEA/H/C/002649/WS2619/0066/G; Canagliflozin, metformin - VOKANAMET (CAP) - EMEA/H/C/002656/WS2619/0073/G

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Martin Huber

Scope: A grouped application consisting of two Type II variations, as follows:
C.I.4: Update of section 4.4 of the SmPC in order to amend an existing warning on diabetic ketoacidosis based on literature. The package leaflet is updated accordingly.
C.I.4: Update of sections 4.6 and 5.3 of the SmPC in order to update information on pregnancy based on literature. The RMP version 11.1 has also been submitted

15.3.5. Ceftazidime, avibactam - ZAVICEFTA (CAP) - EMEA/H/C/004027/II/0035

Applicant: Pfizer Ireland Pharmaceuticals

PRAC Rapporteur: Rugile Pilviniene

Scope: Extension of indication to include treatment of paediatric patients from birth to less than 3-months of age in the following infections: complicated intra-abdominal infection (cIAI), complicated urinary tract infection (cUTI), including pyelonephritis, hospital-acquired pneumonia (HAP), including ventilator associated pneumonia (VAP) and in the treatment of infections due to aerobic Gram-negative organisms in patients with limited treatment options, for ZAVICEFTA, based on final results from study C3591024 and the population PK modelling/simulation analyses. Study C3591024 is a Phase 2a, 2-part, open-label, non-randomised, multicenter, single and multiple dose trial to evaluate pharmacokinetics, safety and tolerability of ceftazidime and avibactam in neonates and infants from birth to less than 3 months of age with suspected or confirmed infections due to gram-negative pathogens requiring intravenous antibiotic treatment. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2, 6.3 and 6.6 of the SmPC are updated. The package leaflet is updated in accordance. Version 3.3 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the product information

15.3.6. Cetuximab - ERBITUX (CAP) - EMEA/H/C/000558/II/0099

Applicant: Merck Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of sections 4.2, 4.4 and 4.9 of the SmPC in order to introduce every two-weeks (Q2W) dosing regimen as an alternative to the already approved every week (Q1W) dosing regimen for the indications of metastatic colorectal cancer (CRC) and the recurrent/metastatic squamous cell cancer of the head and neck (SCCHN) in combination with platinum-based chemotherapy, based on pharmacokinetic (PK)-TGI-OS modelling and simulations. The package leaflet is updated accordingly. The RMP version 19.1 has also been submitted. In addition, the MAH took the opportunity to introduce minor changes to the product information

15.3.7. Crizotinib - XALKORI (CAP) - EMEA/H/C/002489/X/0080/G

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Tiphaine Vaillant

Scope: Extension application to introduce a new pharmaceutical form (granules in capsules for opening) associated with new strengths (20, 50 and 150 mg), grouped with a type II variation (C.I.6.a) to include the treatment of paediatric patients with relapsed or refractory, systemic ALK-positive ALCL or unresectable, recurrent, or refractory ALK-positive IMT to change the lower end of the age range from ≥6 years to ≥1 year for Xalkori following the assessment of II/0072 based on final results from study ADVL0912. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The package leaflet is updated in accordance. Version 9.1 of the RMP has also been submitted

15.3.8. Dapagliflozin, metformin - EBYMECT (CAP) - EMEA/H/C/004162/WS2664/0066; Saxagliptin, dapagliflozin - QTERN (CAP) - EMEA/H/C/004057/WS2664/0043; Dapagliflozin, metformin - XIGDUO (CAP) - EMEA/H/C/002672/WS2664/0076

Applicant: AstraZeneca AB

PRAC Rapporteur: Bianca Mulder

Scope: Update of sections 4.2, 4.4, 4.5, 4.8, 5.1 and 6.1 of the SmPC in order to align dapagliflozin related information in Fixed Dose Combination with Forxiga. The package leaflet is updated accordingly. The RMPs version 15.1 (Xigduo and Wbymect) and 9.1 (Qtern) has also been submitted. In addition, the MAH took the opportunity to introduce editorial changes to the product information

15.3.9. Dapivirine - DAPIVIRINE VAGINAL RING 25 MG (Art 58[34]) - EMEA/H/W/002168/II/0025/G

Applicant: International Partnership for Microbicides Belgium AISBL

PRAC Rapporteur: Jan Neuhauser

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

Scope: A grouped application consisting of:
Type II (C.I.4): Update of section 4.6 of the SmPC in order to update information on breastfeeding based on final results from study MTN-043 (B-PROTECTED) listed as a category 3 study in the RMP (MEA/009). MTN-043 is a Phase 3b, randomised, open-label, safety, and drug detection study of dapivirine vaginal ring and oral truvada in breastfeeding mother-infant pairs. The package leaflet is updated accordingly. The RMP version 1.4 has also been submitted. In addition, the MAH took the opportunity to update Annex II of the product information
Type IB (C.I.11.z): Submission of an updated RMP version 1.4 in order to request a change on the due date for the MTN-034 (REACH) study

15.3.10. Daratumumab - DARZALEX (CAP) - EMEA/H/C/004077/II/0072, Orphan

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Carla Torre

Scope: Extension of indication to include, in combination with bortezomib, lenalidomide and dexamethasone, the treatment of adult patients with newly diagnosed multiple myeloma, who are eligible for autologous stem cell transplant for Darzalex, based on the primary analysis results from the pivotal study 54767414MMY3014 (PERSEUS) and the results from study 54767414MMY2004 (GRIFFIN) and the D-VRd cohort of study 54767414MMY2040 (PLEIADES).
MMY3014 (PERSEUS) is a randomised, open-label, active-controlled, multicentre phase 3 study in adult subjects with newly diagnosed multiple myeloma, who are eligible for high dose therapy (as required for autologous stem cell transplant). The primary objective is to compare the efficacy of (subcutaneous) daratumumab in combination with bortezomib, lenalidomide and dexamethasone (D-VRd) versus bortezomib, lenalidomide and dexamethasone (VRd) in terms of progression free survival (PFS).
MMY2004 (GRIFFIN) is a randomised, open-label, active controlled, multicentre phase 2 study in adult subjects with newly diagnosed multiple myeloma, who are eligible for high dose therapy and autologous stem cell transplant. The primary objective is to compare the efficacy of daratumumab in combination with bortezomib, lenalidomide and dexamethasone (D-VRd) versus bortezomib, lenalidomide and dexamethasone (VRd), in terms of stringent complete response (sCR) rate.
MMY2040 (PLEIADES) is a randomised, open-label, multicentre phase 2 study to evaluate subcutaneous daratumumab in combination with standard multiple myeloma treatment regimens. The D-VRd cohort included adult subjects with newly diagnosed multiple myeloma, who were evaluated for clinical benefit in terms of very good partial response or better (VGPR) rate.
As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet is updated in accordance. Version 10.1 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

15.3.11. Ebola vaccine (rDNA, replication-incompetent) - MVABEA (CAP) - EMEA/H/C/005343/II/0021

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Jean-Michel Dogné

Scope: Update of sections 4.6 and 5.1 of the SmPC in order to update information on pregnancy based on final results from study VAC52150EBL3010 listed as a category 3 study in the RMP as well as study VAC52150EBL3008 and two post-authorisation vaccination campaigns. Study VAC52150EBL3010 is a phase 3 open-label randomised clinical trial to evaluate the safety, reactogenicity and immunogenicity of a 2-dose Ebola vaccine regimen of Ad26.ZEBOV followed by MVA-BN-Filo in healthy pregnant women. The package leaflet is updated accordingly. The RMP version 3.3 has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the product information

15.3.12. Ebola vaccine (rDNA, replication-incompetent) - ZABDENO (CAP) - EMEA/H/C/005337/II/0019

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Jean-Michel Dogné

Scope: Update of sections 4.6 and 5.1 of the SmPC in order to update information on pregnancy based on final results from study VAC52150EBL3010 listed as a category 3 study in the RMP as well as study VAC52150EBL3008 and two post-authorisation vaccination campaigns. Study VAC52150EBL3010 is a phase 3 open-label randomised clinical trial to evaluate the safety, reactogenicity and immunogenicity of a 2-dose Ebola vaccine regimen of Ad26.ZEBOV followed by MVA-BN-Filo in healthy pregnant women. The package leaflet is updated accordingly. The RMP version 3.3 has also been submitted. In addition, the MAH took the opportunity to introduce minor changes to the product information

15.3.13. Elasomeran - SPIKEVAX (CAP) - EMEA/H/C/005791/II/0136

Applicant: Moderna Biotech Spain S.L.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Addition of a new strain (Spikevax JN.1, SARS-CoV-2 JN.1 mRNA) resulting in eight new monovalent presentations.
The Annex A, the SmPC, the Package Leaflet and Labelling are updated accordingly.
Editorial changes: In addition to the change described above, minor editorial updates to table footers throughout CTD sections including the addition of abbreviations have been included.
In addition, version 9.0 of the RMP has also been submitted.

15.3.14. Enalapril maleate - AQUMELDI (CAP) - EMEA/H/C/005731/X/0001/G

Applicant: Proveca Pharma Limited

PRAC Rapporteur: Mari Thorn

Scope: Extension application to add a new strength of 1 mg orodispersible tablet grouped with a type IB variation (C.I.z) to correct the SmPC to remove the recommended dose of epinephrine from Section 4.4. RMP version 1.1 was submitted

15.3.15. Etrasimod - VELSIPITY (CAP) - EMEA/H/C/006007/II/0001

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Mari Thorn

Scope: Update of section 4.4 to modify the macular oedema (MO) warning based on the evaluation of the cases of MO/cystoid MO reported in the etrasimod clinical studies and other S1P labels in the EU. The package leaflet and Annex II are updated in accordance. RMP version 1.1 has also been submitted. In addition, the MAH took this opportunity to introduce editorial changes to the product information

15.3.16. Faricimab - VABYSMO (CAP) - EMEA/H/C/005642/II/0005

Applicant: Roche Registration GmbH

PRAC Rapporteur: Carla Torre

Scope: Extension of indication to include treatment of adult patients with visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO) for Vabysmo, based on results from the two phase 3 studies: GR41984 (BALATON) in patients with branch retinal vein occlusion (BRVO) and GR41986 (COMINO) in patients with central retinal vein occlusion (CRVO) or hemiretinal vein occlusion (HRVO). These are global, multicentre, randomised, double-masked, active comparator-controlled, parallel-group, 2-part studies evaluating the efficacy, safety, and PK of faricimab. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated. The package leaflet is updated in accordance. Version 3.0 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce minor changes to the product information

15.3.17. Fenfluramine - FINTEPLA (CAP) - EMEA/H/C/003933/II/0022/G, Orphan

Applicant: UCB Pharma SA

PRAC Rapporteur: Martin Huber

Scope: A grouped application comprised of three Type II variations, as follows:
C.I.4: Update of sections 4.4 and 4.8 of the SmPC in order to modify the list of adverse drug reactions based on a revised safety ADR methodology for Dravet and Lennox-Gastaut syndromes, which includes pooled analyses encompassing studies ZX008-1503 and ZX008-1601 cohort B. The package leaflet is updated accordingly.
C.I.4: Update of section 5.1 of the SmPC in order to update clinical efficacy information for Dravet syndrome based on final results from study ZX008-1503 listed as a category 3 study in the RMP. This is 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.
C.I.4: Update of section 5.1 of the SmPC in order to update clinical efficacy information for Lennox-Gastaut syndrome based on final results from study ZX008-1601 Part 1 cohort B and interim results for study ZX008-1601 Part 2 cohort B. Study 1601 Part 1 was an international, randomised, double-blind, parallel-group, placebo-controlled study in subjects with LGS 2 to 35 years of age, while study 1601 Part 2 is a long-term, open-label, flexible-dose extension for subjects who completed study 1601 Part 1.
The RMP version 3.0 has also been submitted. In addition, the MAH took the opportunity to introduce minor changes to the product information, including to section 4.2 of the SmPC

15.3.18. Fenofibrate, pravastatin sodium - PRAVAFENIX (CAP) - EMEA/H/C/001243/II/0037

Applicant: Laboratoires SMB s.a.

PRAC Rapporteur: Nathalie Gault

Scope: Extension of indication to include treatment of mixed hyperlipidaemia in adult patients while on a treatment with pravastatin 40 mg monotherapy or on another moderate-intensity statin regimen for PRAVAFENIX, based on final results from the non-interventional PASS: POSE (Pravafenix Observational Study in Europe); this is a European, observational, three-year cohort comparative study on the safety of the fixed dose combination pravastatin 40 mg/fenofibrate 160 mg (Pravafenix) versus statin alone in real clinical practice. As a consequence, sections 4.1 and 4.2 of the SmPC are updated. The package leaflet is updated in accordance. Version 4.1 of the RMP has also been submitted

15.3.19. Inclisiran - LEQVIO (CAP) - EMEA/H/C/005333/II/0021

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Kimmo Jaakkola

Scope: Submission of the final report from study ORION-8 - a long-term extension trial of the phase III lipid-lowering trials to assess the effect of long-term dosing of inclisiran given as subcutaneous injections in subjects with high cardiovascular risk and elevated LDL-C, listed as a category 3 study in the RMP. The RMP version 3.0 has also been submitted

15.3.20. Ivacaftor - KALYDECO (CAP) - EMEA/H/C/002494/II/0126

Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Monica Martinez Redondo

Scope: Submission of the final report from study VX15-770-126 (study 126) listed as a category 3 study in the RMP; this is a phase 3, 2-arm, multicenter open-label study to evaluate the safety and pharmacodynamics of long-term ivacaftor treatment in subjects with cystic fibrosis who are less than 24 months of age at treatment initiation and have an approved ivacaftor-responsive mutation. The RMP version 16.0 has also been submitted

15.3.21. Macitentan - OPSUMIT (CAP) - EMEA/H/C/002697/X/0051/G

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Extension application to introduce a new pharmaceutical form associated with new strengths (1 and 2.5 mg dispersible tablet) grouped with an extension of indication (C.I.6.a) to include, as monotherapy or in combination, the long-term treatment of pulmonary arterial hypertension (PAH) in paediatric patients aged 1 month to less than 18 years of age of WHO Functional Class (FC) I to III for OPSUMIT, based on interim results from AC-055-312 study (TOMORROW). This is a multicentre, open-label, randomised study with single-arm extension period to assess the pharmacokinetics, safety, and efficacy of macitentan versus standard of care in children with pulmonary arterial hypertension. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 4.9, 5.1 and 5.2 of the SmPC for film-coated tablets are updated. The package leaflet and Labelling are updated in accordance. Version 14.1 of the RMP has also been submitted

15.3.22. Ozanimod - ZEPOSIA (CAP) - EMEA/H/C/004835/II/0024/G

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Grouped application comprising two variations as follows:
Type II (C.I.4) – Update of sections 4.4 and 4.8 the SmPC in order to add a new warning on liver injury, to add liver injury to the list of adverse drug reactions (ADRs) with frequency rare based on the cumulative review of the MAH safety database, clinical trials and literature search. The RMP version 8.0 also been submitted.
Type IA (A.6) – To change the ATC code from L04AA38 to L04AE02

15.3.23. Pegzilarginase - LOARGYS (CAP) - EMEA/H/C/005484/II/0002/G, Orphan

Applicant: Immedica Pharma AB

PRAC Rapporteur: Martin Huber

Scope: Grouped application comprising two type II variations as follows:
C.I.4 – Update of sections 4.8 and 5.1 of the SmPC in order to update efficacy and safety information based on final results from study CAEB1102-300A (SOB 003), listed as a specific obligation in Annex II. Study 300A was a Phase 3, randomised, double blind, placebo-controlled study of the efficacy and safety of pegzilarginase in adults, adolescents and children with arginase 1 deficiency (ARG1 D).
C.I.4 – Update of section 4.8 of the SmPC in order to update efficacy and safety information based on final results from study CAEB1102-102A (SOB 004), listed as a specific obligation in Annex II.
Study 102A was an open label extension study to evaluate the long-term safety, tolerability, and efficacy of pegzilarginase in adults, adolescents and children with arginase 1 deficiency (ARG1 D).
The package leaflet and Annex II are updated accordingly. The RMP version 1.1 has also been submitted. In addition, the MAH took the opportunity to bring the product information in line with the latest QRD template version 10.4 and to introduce minor editorial changes

15.3.24. Pembrolizumab - KEYTRUDA (CAP) - EMEA/H/C/003820/II/0153

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Bianca Mulder

Scope: Extension of indication for KEYTRUDA in combination with carboplatin and paclitaxel to include first-line treatment of primary advanced or recurrent endometrial carcinoma in adults, based on final results from study KEYNOTE-868. This is a randomised Phase 3, placebo-controlled, double-blind study of pembrolizumab vs placebo in combination with chemotherapy (paclitaxel plus carboplatin) for newly diagnosed Stage III/Stage IVA, Stage IVB, or recurrent endometrial cancer.
As a consequence, sections 4.1 and 5.1 of the SmPC are updated. Version 46.1 of the RMP has also been submitted

15.3.25. Pirtobrutinib - JAYPIRCA (CAP) - EMEA/H/C/005863/II/0002

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Bianca Mulder

Scope: Extension of indication to include treatment of adult patients with chronic lymphocytic leukemia (CLL) who have been previously treated with a Bruton's tyrosine kinase (BTK) inhibitor for JAYPIRCA, based on interim results from study LOXO-BTK-20020 (BRUIN CLL-321); this is a phase 3 open-label, randomised study of LOXO-305 versus investigator's choice of idelalisib plus rituximab or bendamustine plus rituximab in BTK inhibitor pretreated CLL/SLL.
As a consequence, sections 4.1, 4.2, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet is updated in accordance. Version 1.1 of the RMP has also been submitted. As part of the application the MAH is requesting a 1-year extension of the market protection

15.3.26. Ranibizmab - BYOOVIZ (CAP) - EMEA/H/C/005545/II/0016/G

Applicant: Samsung Bioepis NL B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: 1. Type II (B.II.e.1.b.2) The updated RMP version 3.1 has also been submitted to introduce changes and to update the MedDRA Search Terms version and applicant's overall search terms strategy for the purpose of safety surveillance.

2. Type IB (B.II.b.3.z)

15.3.27. Sapropterin - KUVAN (CAP) - EMEA/H/C/000943/II/0078

Applicant: BioMarin International Limited

PRAC Rapporteur: Eamon O'Murchu

Scope: Submission of the final report from study KOGNITO, listed as a category 3 study in the RMP. This is a phase IV open-label, single-cohort study of the long-term neurocognitive outcomes in 4- to 5-year-old children with phenylketonuria treated with sapropterin dihydrochloride (Kuvan) for 7 years. The RMP version 16.0 has also been submitted

15.3.28. Selpercatinib - RETSEVMO (CAP) - EMEA/H/C/005375/II/0028

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Bianca Mulder

Scope: Update of sections 4.8 and 5.1 of the SmPC in order to update efficacy and safety information based on interim results from study LIBRETTO-431 (JZJC) listed as a specific obligation in the Annex II (SOB/002); this is a randomised Phase 3 study comparing selpercatinib to platinum-based and pemetrexed therapy with or without pembrolizumab in patients with locally advanced or metastatic, RET-fusion-positive NSCLC. The package leaflet is updated accordingly. The RMP version 6.1 has also been submitted. In addition, the MAH took the opportunity to update Annex II

15.3.29. Setmelanotide - IMCIVREE (CAP) - EMEA/H/C/005089/II/0018, Orphan

Applicant: Rhythm Pharmaceuticals Netherlands B.V.,

PRAC Rapporteur: Anna Mareková

Scope: Extension of indication to include the population of children aged 2 years and above for the treatment of pro-opiomelanocortin (POMC), proprotein convertase subtilisin/kexin Type 1 (PCSK1) deficiency or biallelic leptin receptor (LEPR) deficiency and Bardet-Biedl Syndrome (BBS) for IMCIVREE, based on the final results from study RM-493-033 "A Phase 3 multicentre, one-year, open-label study of setmelanotide in paediatric patients aged 2 to <6 years of age with rare genetic causes of obesity"; this is an open label study to evaluate the weight-related parameters along with the safety and tolerability of setmelanotide in patients aged 2 to <6 years. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet is updated in accordance. Version 2.1 of the RMP has also been submitted. In addition, the MAH took this opportunity to introduce editorial changes to the product information

15.3.30. Sodium phenylbutyrate - PHEBURANE (CAP) - EMEA/H/C/002500/X/0037

Applicant: Eurocept International B.V.

PRAC Rapporteur: Eamon O'Murchu

Scope: Extension application to introduce a new pharmaceutical form associated with new strength (500 mg film-coated tablets). The RMP (version 1.1) is updated in accordance

15.3.31. Tildrakizumab - ILUMETRI (CAP) - EMEA/H/C/004514/II/0055

Applicant: Almirall S.A

PRAC Rapporteur: Adam Przybylkowski

Scope: Type II (B.IV.1.c); RMP version 1.5 was submitted

15.3.32. Tocilizumab - ROACTEMRA (CAP) - EMEA/H/C/000955/II/0121

Applicant: Roche Registration GmbH

PRAC Rapporteur: Gabriele Maurer

Scope: Submission of the final report from study ZUMA-8 (PAM). This is a phase 1 multicenter study evaluating the safety and tolerability of KTE-X19 in adult subjects with Relapsed/Refractory Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma. The RMP version 29.0 has also been submitted

15.3.33. Turoctocog alfa pegol - ESPEROCT (CAP) - EMEA/H/C/004883/II/0023

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Gabriele Maurer

Scope: Extension of indication to include children below 12 years of age for treatment and prophylaxis of bleeding with haemophilia A for Esperoct, including previously untreated patients (PUPs) based on the final results from studies 3776, 4410, 3908, 3859, 3885, 3860, 4033 and 4595. As a consequence, section 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet is updated in accordance. Version 3.0 of the RMP has also been submitted. Furthermore, the product information is brought in line with the latest QRD template version 10.4

15.3.34. Ustekinumab - UZPRUVO (CAP) - EMEA/H/C/006101/X/0001

Applicant: STADA Arzneimittel AG

PRAC Rapporteur: Rhea Fitzgerald

Scope: Extension application to introduce a new pharmaceutical form associated with a new strength (130 mg concentrate for solution for infusion) and a new route of administration (intravenous use). The RMP version 1.1 is updated in accordance

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. Amivantamab - RYBREVANT (CAP) - PSUSA/00010977/202311

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Gabriele Maurer

Scope: Evaluation of a PSUSA procedure

16.1.2. Buprenorphine[35] - SIXMO (CAP) - PSUSA/00010778/202311

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

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.3. Capmatinib - TABRECTA (CAP) - PSUSA/00011022/202311

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Carla Torre

Scope: Evaluation of a PSUSA procedure

[35] Implant

16.1.4. Cefiderocol - FETCROJA (CAP) - PSUSA/00010849/202311

Applicant: Shionogi B.V.

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.5. Cobicistat, elvitegravir, emtricitabine, tenofovir alafenamide - GENVOYA (CAP) - PSUSA/00010449/202311

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.1.6. Coronavirus (COVID-19) vaccine (B.1.351 variant, prefusion Spike delta TM protein, recombinant) - VIDPREVTYN BETA (CAP)[36] - PSUSA/00011035/202311

Applicant: Sanofi Pasteur

PRAC Rapporteur: Jana Lukacisinova

Scope: Evaluation of a PSUSA procedure

Based on the PRAC Rapporteur review of data on safety and efficacy, PRAC is of the view that the reported data does not warrant an update to the product information. However, no PRAC recommendation was adopted due to the withdrawal of the marketing authorisation of SARS-CoV-2, B.1.351 variant, prefusion Spike delta TM protein, recombinant. Therefore, no further PSUR should be submitted.

16.1.7. Darbepoetin alfa - ARANESP (CAP) - PSUSA/00000932/202310

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.8. Defibrotide - DEFITELIO (CAP) - PSUSA/00010086/202310

Applicant: Gentium S.r.l.

PRAC Rapporteur: Mari Thorn

Scope: Evaluation of a PSUSA procedure

16.1.9. Dinutuximab beta - QARZIBA (CAP) - PSUSA/00010597/202311

Applicant: Recordati Netherlands B.V.

PRAC Rapporteur: Gabriele Maurer

Scope: Evaluation of a PSUSA procedure

[36] Marketing Authorisation was withdrawn – Comission Implementing Decision date 11 March 2024:

16.1.10. Diphtheria, tetanus, pertussis antigens (pertussis toxoid, filamentous haemagglutinin, pertactin) (acellular, component), hepatitis B (rDNA), poliomyelitis (inactivated), haemophilus type b conjugate vaccines (adsorbed) - INFANRIX HEXA (CAP) - PSUSA/00001122/202310

Applicant: GlaxoSmithkline Biologicals SA

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

16.1.11. Drospirenone, estetrol - DROVELIS (CAP); LYDISILKA (CAP) - PSUSA/00010938/202311

Applicant: Chemical Works of Gedeon Richter Plc. (Gedeon Richter Plc.) (Drovelis), Estetra SRL (Lydisilka)

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.12. Emicizumab - HEMLIBRA (CAP) - PSUSA/00010668/202311

Applicant: Roche Registration GmbH

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.1.13. Empagliflozin, linagliptin - GLYXAMBI (CAP) - PSUSA/00010539/202311

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

16.1.14. Etranacogene dezaparvovec - HEMGENIX (CAP) - PSUSA/00011037/202311

Applicant: CSL Behring GmbH, ATMP[37]

PRAC Rapporteur: Bianca Mulder

Scope: Evaluation of a PSUSA procedure

16.1.15. Fosamprenavir - TELZIR (CAP) - PSUSA/00001470/202310

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Nathalie Gault

Scope: Evaluation of a PSUSA procedure

[37] Advanced therapy medicinal product

16.1.16. Givosiran - GIVLAARI (CAP) - PSUSA/00010839/202311

Applicant: Alnylam Netherlands B.V.

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.17. Glasdegib - DAURISMO (CAP) - PSUSA/00010859/202311

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Bianca Mulder

Scope: Evaluation of a PSUSA procedure

16.1.18. Granisetron[38] - SANCUSO (CAP) - PSUSA/00010101/202310

Applicant: Kyowa Kirin Holdings B.V.

PRAC Rapporteur: Rugile Pilviniene

Scope: Evaluation of a PSUSA procedure

16.1.19. Hepatitis B surface antigen, CpG 1018 adjuvant - HEPLISAV B (CAP) - PSUSA/00010919/202311

Applicant: Dynavax GmbH

PRAC Rapporteur: Gabriele Maurer

Scope: Evaluation of a PSUSA procedure

16.1.20. Insulin human - ACTRAPID (Art 58[39]) - EMEA/H/W/005779/PSUV/0006

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Evaluation of a PSUR procedure

16.1.21. Insulin human - INSULATARD (Art 58[9]) - EMEA/H/W/005780/PSUV/0005

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Evaluation of a PSUR procedure

16.1.22. Ivosidenib - TIBSOVO (CAP) - PSUSA/00011048/202311

Applicant: Les Laboratoires Servier

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

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Evaluation of a PSUSA procedure

16.1.23. Larotrectinib - VITRAKVI (CAP) - PSUSA/00010799/202311

Applicant: Bayer AG

PRAC Rapporteur: Rugile Pilviniene

Scope: Evaluation of a PSUSA procedure

16.1.24. Linzagolix choline - YSELTY (CAP) - PSUSA/00010998/202311

Applicant: Theramex Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.25. Lonafarnib - ZOKINVY (CAP) - PSUSA/00011005/202311

Applicant: EigerBio Europe Limited

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.26. Lumasiran - OXLUMO (CAP) - PSUSA/00010884/202311

Applicant: Alnylam Netherlands B.V.

PRAC Rapporteur: Mari Thorn

Scope: Evaluation of a PSUSA procedure

16.1.27. Lurasidone - LATUDA (CAP) - PSUSA/00010114/202310

Applicant: Aziende Chimiche Riunite Angelini Francesco A.C.R.A.F. S.p.A.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.28. Macitentan - OPSUMIT (CAP) - PSUSA/00010115/202310

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

16.1.29. Maribavir - LIVTENCITY (CAP) - PSUSA/00011024/202311

Applicant: Takeda Pharmaceuticals International AG Ireland Branch

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.30. Nelarabine - ATRIANCE (CAP) - PSUSA/00002132/202310

Applicant: Sandoz Pharmaceuticals d.d.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Evaluation of a PSUSA procedure

16.1.31. Obeticholic acid - OCALIVA (CAP) - PSUSA/00010555/202311

Applicant: Advanz Pharma Limited

PRAC Rapporteur: Liana Martirosyan

Scope: Evaluation of a PSUSA procedure

16.1.32. Pandemic influenza vaccine (H5N1) (live attenuated, nasal) - PANDEMIC INFLUENZA VACCINE H5N1 ASTRAZENECA (CAP) - PSUSA/00010501/202311

Applicant: AstraZeneca AB

PRAC Rapporteur: Sonja Hrabcik

Scope: Evaluation of a PSUSA procedure

16.1.33. Patiromer - VELTASSA (CAP) - PSUSA/00010618/202310

Applicant: Vifor Fresenius Medical Care Renal Pharma France

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

16.1.34. Pegunigalsidase alfa - ELFABRIO (CAP) - PSUSA/00011049/202311

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Liana Martirosyan

Scope: Evaluation of a PSUSA procedure

16.1.35. Piflufolastat (^{18}F) - PYLCLARI (CAP) - PSUSA/00000097/202311

Applicant: Curium Pet France

PRAC Rapporteur: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

16.1.36. Prucalopride - RESOLOR (CAP) - PSUSA/00002568/202310

Applicant: Takeda Pharmaceuticals International AG Ireland Branch

PRAC Rapporteur: Mari Thorn

Scope: Evaluation of a PSUSA procedure

16.1.37. Relugolix, estradiol, norethisterone acetate - RYEQO (CAP) - PSUSA/00010942/202311

Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.38. Rituximab - BLITZIMA (CAP); MABTHERA (CAP); RIXATHON (CAP); RIXIMYO (CAP); RUXIENCE (CAP); TRUXIMA (CAP) - PSUSA/00002652/202311

Applicant: Roche Registration GmbH (MabThera), Sandoz GmbH (Rixathon, Riximyo), Pfizer Europe MA EEIG (Ruxience), Celltrion Healthcare Hungary Kft. (Blitzima, Truxima)

PRAC Rapporteur: Karin Erneholm

Scope: Evaluation of a PSUSA procedure

16.1.39. Rurioctocog alfa pegol - ADYNOVI (CAP) - PSUSA/00010663/202311

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Bianca Mulder

Scope: Evaluation of a PSUSA procedure

16.1.40. Satralizumab - ENSPRYNG (CAP) - PSUSA/00010944/202311

Applicant: Roche Registration GmbH

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.1.41. Selpercatinib - RETSEVMO (CAP) - PSUSA/00010917/202311

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Bianca Mulder

Scope: Evaluation of a PSUSA procedure

16.1.42. Setmelanotide - IMCIVREE (CAP) - PSUSA/00010941/202311

Applicant: Rhythm Pharmaceuticals Netherlands B.V.,

PRAC Rapporteur: Anna Mareková

Scope: Evaluation of a PSUSA procedure

16.1.43. Sirolimus[40] - HYFTOR (CAP) - PSUSA/00000025/202311

Applicant: Plusultra pharma GmbH

PRAC Rapporteur: Mari Thorn

[40] Indicated for treatment of angiofibroma associated with tuberous sclerosis complex only

Scope: Evaluation of a PSUSA procedure

16.1.44. Sotorasib - LUMYKRAS (CAP) - PSUSA/00010970/202311

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Evaluation of a PSUSA procedure

16.1.45. Stiripentol - DIACOMIT (CAP) - PSUSA/00002789/202311

Applicant: BIOCODEX

PRAC Rapporteur: Maia Uusküla

Scope: Evaluation of a PSUSA procedure

16.1.46. Tixagevimab, cilgavimab - EVUSHELD (CAP) - PSUSA/00010992/202311

Applicant: AstraZeneca AB

PRAC Rapporteur: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

16.1.47. Tofacitinib - XELJANZ (CAP) - PSUSA/00010588/202311

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Martirosyan

Scope: Evaluation of a PSUSA procedure

16.1.48. Turoctocog alfa - NOVOEIGHT (CAP) - PSUSA/00010138/202310

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Gabriele Maurer

Scope: Evaluation of a PSUSA procedure

16.1.49. Vestronidase alfa - MEPSEVII (CAP) - PSUSA/00010709/202311

Applicant: Ultragenyx Germany GmbH

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

16.1.50. Zanubrutinib - BRUKINSA (CAP) - PSUSA/00010960/202311

Applicant: BeiGene Ireland Ltd

PRAC Rapporteur: Bianca Mulder

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. Insulin human - ACTRAPID (CAP), INSUMAN (CAP); insulin human, insulin isophane[41] - ACTRAPHANE (CAP), INSULATARD (CAP), MIXTARD (CAP), PROTAPHANE (CAP); NAP - PSUSA/00001753/202310

Applicant(s): Novo Nordisk A/S (Actraphane, Actrapid, Insulatard, Mixtard, Protaphane), Sanofi-Aventis Deutschland GmbH (Insuman), various

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Evaluation of a PSUSA procedure

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

16.3.1. Ascorbic acid, chlorphenamine maleate, paracetamol (NAP) - PSUSA/00000696/202311

Applicant(s): various

PRAC Lead: Nathalie Gault

Scope: Evaluation of a PSUSA procedure

16.3.2. Bromocriptine (NAP) - PSUSA/00000438/202310

Applicant(s): various

PRAC Lead: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

16.3.3. Citric acid, potassium salts, potassium citrate (NAP) - PSUSA/00000783/202311

Applicant(s): various

PRAC Lead: Polona Golmajer

Scope: Evaluation of a PSUSA procedure

16.3.4. Drospirenone (NAP) - PSUSA/00010853/202311

Applicant(s): various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.3.5. Etifoxine (NAP) - PSUSA/00001321/202310

Applicant(s): various

[41] Subcutaneous and intravenous uses only

PRAC Lead: Maria Popova-Kiradjieva

Scope: Evaluation of a PSUSA procedure

16.3.6. Flutamide (NAP) - PSUSA/00001453/202310

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.3.7. Hydroxyzine, hydroxyzine combination (NAP) - PSUSA/00001696/202311

Applicant(s): various

PRAC Lead: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

16.3.8. Ketotifen[42] (NAP) - PSUSA/00001813/202310

Applicant(s): various

PRAC Lead: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.3.9. Methacholine (NAP) - PSUSA/00010891/202310

Applicant(s): various

PRAC Lead: Jana Lukacisinova

Scope: Evaluation of a PSUSA procedure

16.3.10. Tetrabenazine (NAP) - PSUSA/00002911/202310

Applicant(s): various

PRAC Lead: Eamon O'Murchu

Scope: Evaluation of a PSUSA procedure

16.4. Follow-up to PSUR/PSUSA procedures

16.4.1. Human C1-esterase inhibitor - CINRYZE (CAP) - EMEA/H/C/001207/LEG 022

Applicant: Takeda Manufacturing Austria AG

PRAC Rapporteur: Gabriele Maurer

Scope: MAH's response to questions raised during procedure PSUSA/00010104/202306 (cumulative review):
Periodic Safety Update Report (16 June 2021 to 15 June 2023)
Issue to be addressed as a post authorisation measure: The case related to "Creutzfeldt-

[42] Oral formulation(s) only

Jakob disease" needs to be further assessed. The MAH is therefore requested to submit within 1 month a comprehensive presentation of this case (incl. CJD subtype, patient details, batch number, follow-up information, medical reports, etc.), a causality assessment and a justified evaluation of any potential implication(s) on the benefit-risk balance of Cinryze

16.4.2. Piperaquine tetraphosphate, Artenimol - EURARTESIM (CAP) - EMEA/H/C/001199/LEG 018.2

Applicant: Alfasigma S.p.A.

PRAC Rapporteur: Martin Huber

Scope: MAH's response to LEG 018.1 [the issue of autoimmune haemolytic anaemia] RSI as adopted in February 2024

An updated assessment report was adopted via written procedure on 19 July 2024.

16.4.3. Venetoclax - VENCLYXTO (CAP) - EMEA/H/C/004106/LEG 017.3

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Eva Jirsová

Scope: From II-0031
Interim Report for period covering 05 June 2023 - 04 December 2023
The MAH shall provide targeted tumour lysis syndrome (TLS) assessment reports on a biannual basis (submitted annually within the PSUR, and 6 months after the PSUR submission in a separate report) through 2023, and annually thereafter, as per the RMP v8.0.

These biannual assessment reports ensure close monitoring of the important identified risk of TLS, and the evaluation of the impact of newly implemented risk minimisation measures for TLS, on adherence to both already existing and updated recommendation added to the SmPC, the impact of the DHPC distributed to haematologists, and the patient card

16.5. Variation procedure(s) resulting from PSUSA evaluation

16.5.1. Fingolimod - GILENYA (CAP) - EMEA/H/C/002202/II/0090/G

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Tiphaine Vaillant

Scope: Grouped application comprising two variations as follows:
Type II (C.I.3.b) - Update of sections 4.3 and 4.4 of the SmPC in order to add history of progressive multifocal leukoencephalopathy (PML) as a new contraindication and to amend an existing warning on PML and to update the educational material to improve the general readability of these documents and better address key messages and recommendations for healthcare professionals following the assessment of procedure PSUSA/00001393/202302. The package leaflet and Annex II are updated accordingly. The RMP version 20.0 has also been submitted.
Type IA (A.6) - To change the ATC Code of Fingolimod from L04AA27 to L04AE01

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. Voretigene neparvovec - LUXTURNA (CAP) - EMEA/H/C/PSA/S/0114

Applicant: Novartis Europharm Ltd, ATMP

PRAC Rapporteur: Gabriele Maurer

Scope: Substantial amendment to a post-authorisation observational study to collect long-term safety information (i.e., for 5 years after treatment) associated with voretigene neparvovec (vector and/or transgene), its subretinal injection procedure, the concomitant use of corticosteroids, or a combination of these procedures and products

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

17.2.1. Brexucabtagene autoleucel - TECARTUS (CAP) - EMEA/H/C/005102/ANX 011.2

Applicant: Kite Pharma EU B.V., ATMP[46]

PRAC Rapporteur: Bianca Mulder

Scope: **REVISED PROTOCOL combining STUDY No. KTE-EU-472-6036 & KT-EU-474-6644**
From Initial MAA
ANX 002: Study No. KTE-EU-472-6036:
KT-EU-472-6036: Long-term, non-interventional study of recipients of Tecartus for treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL)

From II-008-G
ANX 011: KT-EU-474-6644: Long-term, non-interventional study of the treatment by Tecartus of adult patients with relapsed or refractory (r/r) B-cell precursor acute lymphoblastic leukemia (ALL)

MAH Response to ANX 011.1 as adopted in December 2023:
Joint protocol combining studies KTE-EU-472-6036 & KT-EU-474-6644 as follows:

[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] 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
[46] Advanced therapy medicinal product

KT-EU-472-6036: Long-term, non-interventional study of recipients of Tecartus for treatment of adult patients with relapsed or refractory (r/r) mantle cell lymphoma (MCL) or adult patients with r/r B-cell precursor acute lymphoblastic leukemia (ALL)

17.2.2. Dexmedetomidine - DEXDOR (CAP) - EMEA/H/C/002268/LEG 016.6

Applicant: Orion Corporation

PRAC Rapporteur: Ulla Wändel Liminga

Scope: ***Protocol Study***
Draft Study Title: Post-hoc analysis of the SPICE III (academic) trial dataset to address the risk of increased mortality among patients ≤65y sedated with dexmedetomidine. (category 3 study)

17.2.3. Efgartigimod alfa - VYVGART (CAP) - EMEA/H/C/005849/MEA 007.1

Applicant: Argenx

PRAC Rapporteur: Rhea Fitzgerald

Scope: From MEA 002.1
**REVISED PROTOCOL (ver. 0.5) for PASS (non-imposed/non-interventional/Cat. 3) Evaluation of long-term risk of malignancies in patients with myasthenia gravis (MG) treated with efgartigimod compared to MG patients on any other MG therapy and who do not have malignancy history in the look back period.

MAH Response to MEA 007 as adopted in January 2024:
A revised protocol for the non-imposed non-interventional PASS should be submitted by 02.04.2024 taking into account the comments included in section 4 overall conclusion of EMEA/H/C/005849/MEA/007 procedure

17.2.4. Ipilimumab - YERVOY (CAP) - EMEA/H/C/002213/MEA 036.7

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Bianca Mulder

Scope: **PASS Protocol Study no.: CA184557**
Title: Long-term Follow-up of Nivolumab and Ipilimumab (as Monotherapy and as Combination Therapy)-treated Pediatric Patients Enrolled in the Dutch Melanoma Treatment Registry (DMTR).

MAH Response to MEA 036.6 as adopted in January 2024:
1. The MAH is requested to provide an update on whether they are aware of any other registry that has the infrastructure and resources to collect long-term follow-up of paediatric melanoma patients in the capacity of DMTR.
2. The MAH is requested to provide an update on the patient enrolment for patients treated with ipilimumab monotherapy and discuss the impact of the current landscape on the patient enrolment for the added treatment options.
3. The MAH amended al mention of the grade 3 and 4 AEs to grade 3 and 4 treatment related AEs. No further justification is provided. It remains unclear if the amendment concerns a change in the DMTR protocol. The MAH is requested to provide a proper

justification for this amendment and clarify if the DMTR collects all reported AEs or only treatment related AEs

17.2.5. Inotersen - TEGSEDI (CAP) - EMEA/H/C/004782/MEA 001.11

Applicant: Akcea Therapeutics Ireland Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: ***REVISED PROTOCOL for PASS Study TEG4001*** (Version 4.1)
A Prospective, Non-interventional, Long-term, Multinational Cohort Safety Study of Patients with Hereditary Transthyretin Amyloidosis with Polyneuropathy (hATTR-PN).

17.2.6. Linzagolix choline - YSELTY (CAP) - EMEA/H/C/005442/MEA 002.3

Applicant: Theramex Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: From Initial MAA:
REVISED PROTOCOL (ver. 4) for PASS YSELTY (NI/NI/RMP/Cat. 3)
A multinational PASS on real-world treatment in patients receiving YSELTY® (linzagolix choline) for moderate to severe symptoms of uterine fibroids, to evaluate routinely collected data on bone mineral density and to assess safety during long term (>12 months) use for linzagolix 200mg (with ABT) and 100mg (with and without ABT) dosing regimen

17.2.7. Nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/MEA 057.1

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Martin Huber

Scope: ***PASS Study no.: CA184557***
Title: Long-term Follow-up of Nivolumab and Ipilimumab (as Monotherapy and as Combination Therapy)-treated Pediatric Patients Enrolled in the Dutch Melanoma Treatment Registry (DMTR).

MAH Response to MEA 057 as adopted in January 2024:
A revised protocol for the non-imposed non-interventional PASS should be submitted by 25 March 2024 taking into account the comments below:
As it is not acceptable, that long-term safety data in pediatric patients < 12 years of age will be collected as a separate off-label use cohort, the MAH is asked to make the changes in the protocol accordingly

17.2.8. Omaveloxolone - SKYCLARYS (CAP) - EMEA/H/C/006084/MEA 002

Applicant: Reata Ireland Limited

PRAC Rapporteur: Amelia Cupelli

Scope: From initial MAA
PROTOCOL (ver. 3) for PASS 296FA401 (408-C-2301)
An observational, multinational, post-marketing registry of omaveloxolone-treated patients with Friedreich's ataxia

17.2.9. Pegvaliase - PALYNZIQ (CAP) - EMEA/H/C/004744/MEA 005.9

Applicant: BioMarin International Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: From Initial MAA:
REVISED PROTOCOL (Version 5) for Study 165-504
A prospective global pregnancy observational safety surveillance study. A global multicentre study to assess maternal, fetal and infant outcomes of exposure to Palynziq (pegvaliase-pqpz) during pregnancy.

MAH Response to MEA 005.7 as adopted in February 2024:
1. Adequately justify the purpose of the change in enrolment method.
2. Clarify if HCP initiated enrolment or enrolment via HCP has been in use to enrol subjects at any time point since the start of data collection.
3. Discuss how the change in enrolment method may impact on the number of subjects enrolled.
4. Discuss the limitations of the proposed enrolment method and how the MAH proposes to address these limitations.
5. Add detail to the protocol on how potential subjects are being encouraged to participate in the study and are being made aware of the existence of the study.
6. Add a description of any mechanisms and procedures to ensure data quality and integrity of data obtained and recorded by the co-ordinating centres and/or the MAH.
7. Update the milestones in appendix 3 of the protocol

17.2.10. Respiratory syncytial virus vaccine (bivalent, recombinant) - ABRYSVO (CAP) - EMEA/H/C/006027/MEA 003

Applicant: Pfizer Europe Ma EEIG

PRAC Rapporteur: Liana Martirosyan

Scope: From initial MAA
PROTOCOL FOR PASS NO. C3671026 (NINI/RMP/Cat. 3)
A post-authorisation safety study (PASS) of ABRYSVO (respiratory syncytial virus stabilised prefusion F subunit vaccine) in pregnant women and their offspring in a real world setting in Europe and UK

17.2.11. Respiratory syncytial virus vaccine (bivalent, recombinant) - ABRYSVO (CAP) - EMEA/H/C/006027/MEA 004

Applicant: Pfizer Europe Ma EEIG

PRAC Rapporteur: Liana Martirosyan

Scope: From initial MAA
PROTOCOL PASS NO. C3671038 (NINI/RMP/Cat. 3)
A PASS of ABRYSVO in immunocompromised, or renally or hepatically impaired older adults aged 60 years and older in a real world setting in Europe and UK

17.2.12. Risankizumab - SKYRIZI (CAP) - EMEA/H/C/004759/MEA 009.2

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Liana Martirosyan

Scope: From X/0020/G:
REVISED PROTOCOL FOR PASS No. P23-653 (non-imposed/non-interventional) Pregnancy Exposure and Outcomes for Women with Crohn's Disease Treated with Risankizumab.
A comparative cohort study to describe risankizumab exposure in pregnant patients with Crohn's disease, and compare pregnancy and infant outcomes to pregnant patients with Crohn's disease who were treated with alternative therapies (e.g., biologics). In addition, descriptive analyses of pregnancy outcomes in patients with Crohn's disease without exposure to any treatments under investigation will also be conducted

MAH Response to MEA 009.1 as adopted in December 2023:
A revised protocol for the non-imposed non-interventional PASS should be submitted by 6 February 2024 taking into account the comments included in the AR section 4

17.2.13. Ritlecitinib - LITFULO (CAP) - EMEA/H/C/006025/MEA 001

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Adam Przybylkowski

Scope: From intial MAA:
DRAFT PROTOCOL FOR PASS B7981101 (Cat. 3/RMP/NINI)
Active Surveillance Study to Monitor the Real-World Safety of Ritlecitinib Among Patients with Alopecia Areata in Europe

17.2.14. Ritlecitinib - LITFULO (CAP) - EMEA/H/C/006025/MEA 002

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Adam Przybylkowski

Scope: From intial MAA:
DRAFT PROTOCOL FOR PASS B7981092 (Cat. 3/RMP/NINI)
Prospective Active Surveillance Study to Monitor the Real-World Safety of Ritlecitinib Among Adolescents with Alopecia Areata

17.2.15. Ritlecitinib - LITFULO (CAP) - EMEA/H/C/006025/MEA 003

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Adam Przybylkowski

Scope: From intial MAA:
Study B7981102 - A Drug Utilization Study to Evaluate Indicators of Adherence to the Risk Minimization Measures for Ritlecitinib Using Electronic Healthcare Data in Denmark, France, and Sweden
Protocol Study B7981102

17.2.16. Tirzepatide - MOUNJARO (CAP) - EMEA/H/C/005620/MEA 002.2

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Bianca Mulder

Scope: MAH's responses to MEA 002.1 [8B-MC-B011] RSI as adopted in November 2023:
A revised protocol for the non-imposed non-interventional PASS should be submitted within 4 months of CHMP opinion taking into account the comments raised in the AR. The review of the revised protocol will follow a 74-day timeline

17.2.17. Tirzepatide - MOUNJARO (CAP) - EMEA/H/C/005620/MEA 005.2

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Bianca Mulder

Scope: MAH's responses to MEA 005.1 [(IBF-MC-B014 (formerly IBF-MC-B013)] RSI adopted in November 2023:
A revised protocol for the non-imposed non-interventional PASS should be submitted within 4 months of CHMP opinion taking into account the comments raised in the AR. The review of the revised protocol will follow a 74-day timeline

17.2.18. Ublituximab - BRIUMVI (CAP) - EMEA/H/C/005914/MEA 001.2

Applicant: Neuraxpharm Pharmaceuticals S.L.

PRAC Rapporteur: Liana Martirosyan

Scope: ***Revised PASS Protocol / Study TG1101-RMS402 (ENLIGHTEN) (cat. 3)***
Final protocol submission of the Study entitled "Evaluating Long-Term Safety of BRIUMVI in Patients with Relapsing Multiple Sclerosis (RMS) in a Real-World Setting from Registry Data"

17.2.19. Ublituximab - BRIUMVI (CAP) - EMEA/H/C/005914/MEA 002.1

Applicant: Neuraxpharm Pharmaceuticals S.L.

PRAC Rapporteur: Liana Martirosyan

Scope: From initial MAA
PASS No TG1101-RMS403, NI/NI, cat. 3
Final protocol submission of the BRIUMVI Pregnancy Registry: A Prospective Registry Study of Pregnancy and Infant Outcomes in Patients Treated with BRIUMVI

17.2.20. Ublituximab - BRIUMVI (CAP) - EMEA/H/C/005914/MEA 003.1

Applicant: Neuraxpharm Pharmaceuticals S.L.

PRAC Rapporteur: Liana Martirosyan

Scope: From initial MAA
PASS No TG1101-RMS404, NI/NI, cat. 3
Final protocol submission of the Post-Authorisation Study to Characterize the Safety of Briumvi Use in Pregnant Patients with Multiple Sclerosis Using Data from a US Administrative Healthcare Claims Database

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

None

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

17.4.1. Baricitinib - OLUMIANT (CAP) - EMEA/H/C/004085/II/0047

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Submission of the final report from non-interventional Study I4V-MC-B012 listed as a category 3 study in the RMP. This is a post-marketing safety surveillance of baricitinib in three European registries. The RMP version 23.1 has also been submitted

17.4.2. Tozinameran - COMIRNATY (CAP) - EMEA/H/C/005735/II/0206/G

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Liana Martirosyan

Scope: A grouped application comprised of 3 Type II variations as follows:

C.I.13: Submission of the final report from study C4591012 listed as a category 3 study in the RMP. This is a non-interventional Post-Emergency Use Authorisation active safety surveillance study among individuals in the Veteran's Affairs health system receiving Pfizer-BioNTech Coronavirus Disease 2019 (COVID-19) vaccine. The RMP version 11.2 has also been submitted.

C.I.11.b: Submission of an updated RMP version 11.2 in order to implement changes to an agreed post-authorisation study (C4591052 protocol amendments 1 & 2) in the RMP, where there is an impact on the description of the study.

C.I.11.b: Submission of an updated RMP version 11.2 in order to implement changes to an agreed post-authorisation study (C4591021 protocol amendment 4) in the RMP, where there is an impact on the description of the study.

In addition, the MAH took the opportunity to update the milestones for the two studies C4591022 and C4591051 in the RMP

17.4.3. Elasomeran - SPIKEVAX (CAP) - EMEA/H/C/005791/II/0131

Applicant: Moderna Biotech Spain S.L.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Submission of the final report from study mRNA-1273-919 - An Observational Study to Assess Maternal and Infant Outcomes Following Exposure to Spikevax During Pregnancy, listed as a category 3 study in the RMP

[47] In accordance with Article 107p-q of Directive 2001/83/EC
[48] In accordance with Article 61a (6) of Regulation (EC) No 726/2004, in line with the revised variations regulation for any submission as of 4 August 2013

17.4.4. Denosumab - PROLIA (CAP) - EMEA/H/C/001120/II/0100

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Mari Thorn

Scope: Submission of the final report from the postmarketing observational study 20090522, listed as a category 3 study in the RMP. This is a denosumab global safety assessment among women with postmenopausal osteoporosis (PMO), men with osteoporosis, and men and women who receive Prolia with glucocorticoid exposure in multiple observational databases

17.4.5. Dimethyl fumarate - TECFIDERA (CAP) - EMEA/H/C/002601/WS2587/0085; Diroximel fumarate - VUMERITY (CAP) - EMEA/H/C/005437/WS2587/0015

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Martin Huber

Scope: Submission of the final report from study 109MS401, a multicenter, global, observational study to collect information on safety and to document the drug utilization of Tecfidera (Dimethyl Fumarate) when used in routine medical practice in the treatment of Multiple Sclerosis (ESTEEM), listed as a category 3 study in the RMP (MEA007.6). The RMPs version 16.1 for Tecfidera and version 2.1 for Vumerity, have also been submitted

17.4.6. Empagliflozin, linagliptin - GLYXAMBI (CAP) - EMEA/H/C/003833/WS2571/0055; Empagliflozin - JARDIANCE (CAP) - EMEA/H/C/002677/WS2571/0082; Empagliflozin, metformin - SYNJARDY (CAP) - EMEA/H/C/003770/WS2571/0076

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Submission of the final report from study 1245-0201. This is an observational post-authorisation safety study (PASS) to assess the risk of acute pancreatitis in type 2 diabetes mellitus (T2DM) patients newly initiating empagliflozin compared to other oral non-incretin/non-sodium glucose co-transporter-2 inhibitors (SGLT2i)-containing glucose lowering drugs. The RMP versions 22.0, 15.0 and 10.0 have also been submitted for Jardiance, Synjardy and Glyxambi, respectively

17.4.7. Inotuzumab ozogamicin - BESPONSA (CAP) - EMEA/H/C/004119/II/0028, Orphan

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Gabriele Maurer

Scope: Submission of the final report from study B1931028; this is a non-interventional post-authorisation safety study (PASS) of inotuzumab ozogamicin to characterize complications post-hematopoietic stem cell transplantation (HSCT) following inotuzumab ozogamicin treatment in adult and pediatric patients with B-cell precursor acute lymphoblastic leukemia (ALL). The RMP version 3.0 has also been submitted

17.4.8. Selexipag - UPTRAVI (CAP) - EMEA/H/C/003774/II/0045

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Nathalie Gault

Scope: Submission of the final report from study 67896049PAH0002 (EXTRACT) and interim report for study AC-065A401 (EXPOSURE), listed as a category 3 study in the RMP. EXTRACT is a Retrospective Medical Chart Review of Patients with PAH newly treated with either Uptravi (selexipag) or any other PAH-specific therapy. EXPOSURE is an observational cohort study of PAH patients newly treated with either Uptravi (selexipag) or any other PAH-specific therapy, in clinical practice

17.4.9. Tafamidis - VYNDAQEL (CAP) - EMEA/H/C/002294/II/0091/G, Orphan

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Tiphaine Vaillant

Scope: A grouped application comprised of two Type II Variations, as follows:

C.I.4: Update of the Annex II based on final results from study B3461001 (THAOS) listed as a category 3 study in the RMP. This is a global, multi-center, longitudinal, observational survey of patients with documented transthyretin gene mutations or wild-type transthyretin amyloidosis.

C.I.13: Submission of the final report from study B3461042 listed as a category 3 study in the RMP. This is a post-marketing safety surveillance study in Japanese patients with AATR-PN.

The RMP version 10.0 has also been submitted. In addition, the MAH took the opportunity to provide B3461028 Clinical Study Report (CSR) Errata

17.4.10. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/II/0062

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Martirosyan

Scope: Submission of the final report from study A3921203 (Tofacitinib Pregnancy Exposure Registry OTIS Autoimmune Diseases in Pregnancy Project) listed as a category 3 study in the RMP; this is a prospective, observational cohort study of pregnancy outcomes in women with a disease for which tofacitinib had an approved indication

17.4.11. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/II/0100

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: Update of section 4.6 of the SmPC in order to update information on pregnancy based on the final synoptic report from study CNTO1275PSO4037 (OTIS); this is a pregnancy exposure registry for Stelara. The package leaflet is updated accordingly. The RMP version 26.2 has also been submitted

17.4.12. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/II/0104

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: Submission of the final report from study RRA-20745 listed as a category 3 study in the RMP. This is an observational post-authorisation safety study (PASS) to describe the safety of ustekinumab and other Crohn's disease treatments in a cohort of patients with Crohn's disease. The RMP version 27.2 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. Arsenic trioxide - TRISENOX (CAP) - EMEA/H/C/000388/MEA 050.6

Applicant: Teva B.V.

PRAC Rapporteur: Tiphaine Vaillant

Scope: From II/0058:
PASS to assess the long-term safety of ATRA+ATO in newly diagnosed low to intermediate risk APL patients in a real-world clinical practice setting
Study Title: A post-authorisation long term safety cohort study in acute promyelocytic leukaemia (APL) patients treated with Trisenox
*** FORTH ANNUAL INTERIM REPORT***/ PASS C18477-ONC-50025

17.5.2. Bimekizumab - BIMZELX (CAP) - EMEA/H/C/005316/MEA 005.2

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Liana Martirosyan

Scope: From Initial MAA:
Study PS0014:
A multicenter, open-label study to assess the long-term safety, tolerability, and efficacy of bimekizumab in adult study participants with moderate-to-severe chronic plaque PSO. Assess the safety and efficacy of long-term use of bimekizumab.

MAH Response to MEA 005.1 as adopted in March 2024:
There are two outstanding issues requiring further discussion. Both issues are related to the uncertainties regarding the effect of ADA and nAb status on bimekizumab efficacy

17.5.3. Cabotegravir - VOCABRIA (CAP) - EMEA/H/C/004976/ANX 002.1

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Martin Huber

Scope: From initial MAA:
SECOND INTERIM REPORT FOR PASS NO. 215161 (Cat. 1)
The MAH will conduct a real-world five-year Drug Utilisation Study (DUS). This observational cohort study will aim to better understand the patient population receiving cabotegravir long acting injection and/or rilpivirine long acting injection containing regimens

in routine clinical practice. The study will assess usage patterns, adherence, and post marketing clinical effectiveness of these regimens and monitor for resistance among virologic failures for whom data on resistance testing are available.

17.5.4. Cabotegravir - VOCABRIA (CAP) - EMEA/H/C/004976/MEA 004.4

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Martin Huber

Scope: ***Second annual interim report of a category 3***
Non-interventional study aiming to monitor for hepatotoxicity and discontinuation of the regimen due to liver-related adverse events (AEs) following initiation of CAB+RPV including the month of oral lead-in, followed by injectable long-acting CAB+RPV. The MAH is requested to submit annual interim reports and a final report as agreed in the pharmacovigilance plan

17.5.5. Ciltacabtagene autoleucel - CARVYKTI (CAP) - EMEA/H/C/005095/ANX 003.2

Applicant: Janssen-Cilag International NV, ATMP

PRAC Rapporteur: Jo Robays

Scope: MAH Response to ANX 003.1 [PASS Study 68284528MMY4004] RSI as adopted in January 2024.
Title: An Observational Post-authorisation Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel

17.5.6. Filgrastim - FILGRASTIM HEXAL (CAP) - EMEA/H/C/000918/MEA 007.15

Applicant: Hexal AG

PRAC Rapporteur: Bianca Mulder

Scope: ***Thirteenth Interim Report / SMART Study no. EP06-501***
Title: Non-interventional, prospective, long-term observational study to assess the safety and effectiveness of Zarzio/Filgrastim HEXAL administered to healthy unrelated stem cell donors for peripheral blood progenitor cell mobilization. The primary objective of this non-interventional study (NIS) is to evaluate the occurrence of adverse events (AEs) suspected to be drug-related

17.5.7. Filgrastim - ZARZIO (CAP) - EMEA/H/C/000917/MEA 007.15

Applicant: Sandoz GmbH

PRAC Rapporteur: Bianca Mulder

Scope: **13th Interim Report / SMART Study no. EP06-501**
Title: Non-interventional, prospective, long-term observational study to assess the safety and effectiveness of Zarzio/Filgrastim HEXAL administered to healthy unrelated stem cell donors for peripheral blood progenitor cell mobilization. The primary objective of this non-interventional study (NIS) is to evaluate the occurrence of adverse events (AEs) suspected to be drug-related

17.5.8. Mercaptamine - CYSTADROPS (CAP) - EMEA/H/C/003769/MEA 001.5

Applicant: Recordati Rare Diseases

PRAC Rapporteur: Maria del Pilar Rayon

Scope: From Initial MAA:
THIRD INTERIM REPORT for PASS No. CYT-DS-001 (Categ. 3)
Open-label longitudinal Post Authorisation safety Study to assess safety of Cystadrops in paediatric and adult cystinosis patients in long term use

17.5.9. Ofatumumab - KESIMPTA (CAP) - EMEA/H/C/005410/MEA 003.3

Applicant: Novartis Ireland Limited

PRAC Rapporteur: Amelia Cupelli

Scope: ***ALITHIOS Study COMB157G2399***
An open-label, single arm, multi-center extension study evaluating long-term safety, tolerability and effectiveness of ofatumumab in subjects with relapsing multiple sclerosis (Categ. 3)
THIRD INTERIM ANNUAL REPORT

17.5.10. Rilpivirine - REKAMBYS (CAP) - EMEA/H/C/005060/ANX 002.1

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Liana Martirosyan

Scope: ***Second annual interim report of a category 1 imposed study***
Imposed study aiming to assess usage patterns, adherence, post marketing clinical effectiveness and to monitor for resistance among virologic failure. The MAH is requested to submit annual interim reports and a final report to fulfil its obligations as agreed in the pharmacovigilance plan.

17.5.11. Sarilumab - KEVZARA (CAP) - EMEA/H/C/004254/MEA 002.7

Applicant: Sanofi Winthrop Industrie

PRAC Rapporteur: Monica Martinez Redondo

Scope: From initial MAA
FOURTH INTERMIM REPORT FOR PASS "Safety surveillance program using existing European Rheumatoid Arthritis Registries"
This study is conducted in 4 countries: Germany (OBS15180), Spain (OBS16829), Sweden (OBS15220) and UK (OBS16828)

17.5.12. Tozinameran - COMIRNATY (CAP) - EMEA/H/C/005735/MEA 017.9

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Liana Martirosyan

Scope: Interim study report for study C4591021 (formerly named ACCESS/VAC4EU) - Assessment of potential increased risk of adverse events of special interest (AESI),

including
myocarditis/pericarditis after being vaccinated with COVID-19 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 vaccination
Fifth Interim Report / Study C4591021 (former ACCESS/VAC4EU)

17.5.13. Upadacitinib - RINVOQ (CAP) - EMEA/H/C/004760/MEA 005.4

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Petar Mas

Scope: From initial MAA
ANNUAL PROGRESS REPORT for PASS P20-199
Drug utilisation study of upadacitinib (Rinvoq) in Europe to evaluate the effectiveness of additional risk minimisation measures among patients with Rheumatoid Arthritis

17.5.14. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/MEA 044.18

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: FROM II 0042 & II-0073
SIXTH ANNUAL REPORT FOR PASS No. CNTO1275PSO4056 (Cat. 3)
Adolescent Registry: An Observational PASS of Ustekinumab in the Treatment of Pediatric Patients Aged 12 Years and Older With Moderate to Severe Plaque Psoriasis

17.5.15. Venetoclax - VENCLYXTO (CAP) - EMEA/H/C/004106/MEA 002.11

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Eva Jirsová

Scope: **6TH PROGRESS REPORT for Registry Study Cohort No P16-562 (RMP)
Prospective observational study to assess the long-term safety profile of venetoclax in a Swedish cohort of Chronic Lymphocytic Leukaemia (CLL) patients

17.5.16. Venetoclax - VENCLYXTO (CAP) - EMEA/H/C/004106/MEA 015.2

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Eva Jirsová

Scope: From II/0031
FIRST ANNUAL UPDATE REPORT for PASS NO. P22-907 (NI/NI/RMP/Cat. 3)
Cross-sectional Study Evaluating the Effectiveness of Venetoclax Risk-Minimisation Measures Among Haematologists in Europe

17.5.17. Venetoclax - VENCLYXTO (CAP) - EMEA/H/C/004106/MEA 016.2

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Eva Jirsová

Scope: From II/0031
FIRST ANNUAL UPDATE REPORT for PASS NO. P22-905 (NI/NI/RMP/Cat. 3)
Cross-sectional Study Evaluating the Effectiveness of the Venetoclax Patient Card Among Adult Patients in Europe

17.5.18. Voretigene neparvovec - LUXTURNA (CAP) - EMEA/H/C/004451/ANX 011.1

Applicant: Novartis Europharm Limited, ATMP

PRAC Rapporteur: Gabriele Maurer

Scope: **FOURTH INTERIM ANALYSIS for PASS CLTW888A12401 (PERCEIVE)**
A Post-Authorisation, Multicenter, Multinational, Longitudinal, Observational Safety Registry Study for Patients Treated with Voretigene Neparvovec
The objective of this post-authorisation observational study is to collect long-term safety information (i.e. for 5 years after treatment) associated with voretigene neparvovec (vector and/or transgene), its subretinal injection procedure, the concomitant use of corticosteroids, or a combination of these procedures and products

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.

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. Clofarabine - EVOLTRA (CAP) - EMEA/H/C/000613/S/0081 (with RMP)

Applicant: Sanofi B.V.

PRAC Rapporteur: Tiphaine Vaillant

Scope: Annual reassessment of the marketing authorisation

18.1.2. Velmanase alfa - LAMZEDE (CAP) - EMEA/H/C/003922/S/0035 (without RMP)

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Jan Neuhauser

Scope: Annual reassessment of the marketing authorisation

18.2. Conditional renewals of the marketing authorisation

18.2.1. Pirtobrutinib - JAYPIRCA (CAP) - EMEA/H/C/005863/R/0004 (with RMP)

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Bianca Mulder

Scope: Conditional renewal of the marketing authorisation

18.2.2. Valoctocogene roxaparvovec - ROCTAVIAN (CAP) - EMEA/H/C/005830/R/0011 (with RMP)

Applicant: BioMarin International Limited, ATMP[49]

PRAC Rapporteur: Bianca Mulder

Scope: Conditional renewal of the marketing authorisation

18.3. Renewals of the marketing authorisation

18.3.1. Clopidogrel, acetylsalicylic acid - CLOPIDOGREL/ACETYLSALICYLIC ACID VIATRIS (CAP) - EMEA/H/C/004996/R/0012 (with RMP)

Applicant: Viatris Limited

PRAC Rapporteur: Carla Torre

Scope: 5-year renewal of the marketing authorisation

18.3.2. Delafloxacin - QUOFENIX (CAP) - EMEA/H/C/004860/R/0026 (without RMP)

Applicant: A. Menarini Industrie Farmaceutiche Riunite s.r.l.

PRAC Rapporteur: Petar Mas

Scope: 5-year renewal of the marketing authorisation

[49] Advanced therapy medicinal product

18.3.3. Esketamine - SPRAVATO (CAP) - EMEA/H/C/004535/R/0023 (with RMP)

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Kirsti Villikka

Scope: 5-year renewal of the marketing authorisation

18.3.4. Glucagon - BAQSIMI (CAP) - EMEA/H/C/003848/R/0015 (without RMP)

Applicant: Amphastar France Pharmaceuticals

PRAC Rapporteur: Eamon O'Murchu

Scope: 5-year renewal of the marketing authorisation

18.3.5. Netarsudil - RHOKIINSA (CAP) - EMEA/H/C/004583/R/0022 (with RMP)

Applicant: Santen Oy

PRAC Rapporteur: Maria del Pilar Rayon

Scope: 5-year renewal of the marketing authorisation

18.3.6. Pegfilgrastim - CEGFILA (CAP) - EMEA/H/C/005312/R/0020 (with RMP)

Applicant: Mundipharma Corporation (Ireland) Limited

PRAC Rapporteur: Bianca Mulder

Scope: 5-year renewal of the marketing authorisation

18.3.7. Romosozumab - EVENITY (CAP) - EMEA/H/C/004465/R/0025 (without RMP)

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Tiphaine Vaillant

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 10-13 June 2024 PRAC meeting, which was held in-person. Participants marked with "a" attended the plenary session while those marked with "b" attended the ORGAM.

An asterisk (*) after the role, in the second column, signals that the member/alternate attended remotely. Additional experts participated in (part of) the meeting, either in person or remotely.

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Sonja Hrabcik [a]	Alternate	Austria	No interests declared	
Jean-Michel Dogné [a]	Member*	Belgium	No interests declared	
Jo Robays [a,b]	Alternate	Belgium	No interests declared	
Maria Popova-Kiradjieva [a,b]	Member	Bulgaria	No interests declared	
Petar Mas [a,b]	Member	Croatia	No interests declared	
Barbara Bytyqi [a,b]	Member	Croatia	No interests declared	
Panagiotis Psaras [a,b]	Alternate	Cyprus	No interests declared	
Eva Jirsová [a,b]	Member	Czechia	No interests declared	
Jana Lukacisinova [a,b]	Alternate	Czechia	No interests declared	
Marie Louise Schougaard Christiansen [a,b]	Member	Denmark	No interests declared	
Karin Erneholm [a,b]	Alternate	Denmark	No interests declared	
Maia Uusküla [a,b]	Member	Estonia	No interests declared	
Kirsti Villikka [a,b]	Member	Finland	No interests declared	
Kimmo Jaakkola [a,b]	Alternate	Finland	No interests declared	
Tiphaine Vaillant [a,b]	Member	France	No interests declared	
Nathalie Gault [a,b]	Alternate	France	No interests declared	
Martin Huber [a,b]	Member (Vice-Chair)	Germany	No interests declared	
Gabriele Maurer [a,b]	Alternate	Germany	No participation in discussion, final deliberations	**17.2.7.** Nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/MEA 057.1

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			and voting on:	
Sofia Trantza [a]	Member	Greece	No interests declared	
Julia Pallos [a],[b]	Member	Hungary	No participation in discussion, final deliberations and voting on:	**4.2.1**.Axicabtagene ciloleucel - YESCARTA (CAP) - EMEA/H/C/004480/SDA/015.1;Brexucabtagene autoleucel - TECARTUS (CAP) - EMEA/H/C/005102/SDA/013.1;Ciltacabtagene autoleucel - CARVYKTI (CAP) - EMEA/H/C/005095/SDA/016.1;Idecabtagene vicleucel - ABECMA (CAP) - EMEA/H/C/004662/SDA/020.1;Lisocabtagene maraleucel - BREYANZI (CAP) - EMEA/H/C/004731/SDA/019.1;Tisagenlecleucel - KYMRIAH (CAP) - EMEA/H/C/004090/SDA/024.1; **6.5.1**.Atazanavir - REYATAZ (CAP) - EMEA/H/C/000494/II/0140 **15.2.2**.Dasatinib - SPRYCEL (CAP) - EMEA/H/C/000709/II/0090; **15.2.4.** Mavacamten -

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				CAMZYOS (CAP) - EMEA/H/C/005457/II/0008 **15.3.22.** Ozanimod - ZEPOSIA (CAP) - EMEA/H/C/004835/II/0024/G **17.2.4.** Ipilimumab - YERVOY (CAP) - EMEA/H/C/002213/MEA 036.7 **17.2.7.** Nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/MEA 057.1
Melinda Palfi [a,b]	Alternate*	Hungary	No interests declared	
Guðrún Stefánsdóttir [a,b]	Member	Iceland	No participation in discussion, final deliberations and voting on:	**16.1.7.** Darbepoetin alfa - ARANESP (CAP) - PSUSA/00000932/202310 **16.1.44.** Sotorasib - LUMYKRAS (CAP) - PSUSA/00010970/202311 **17.4.4.** Denosumab - PROLIA (CAP) - EMEA/H/C/001120/II/0100
Rhea Fitzgerald [a,b]	Member	Ireland	No interests declared	
Eamon O Murchu [a,b]	Alternate	Ireland	No interests declared	
Amelia Cupelli [a,b]	Member	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 [a,b]	Member	Latvia	No interests declared	
Lina Seibokiene [a]	Alternate	Lithuania	No restrictions applicable to this meeting	
Nadine Petitpain [a,b]	Member	Luxembourg	No restrictions applicable to this meeting	
John Joseph Borg [a]	Member	Malta	No interests declared	
Liana Martirosyan [a,b]	Member	Netherlands	No interests declared	
Bianca Mulder [a,b]	Alternate	Netherlands	No interests declared	
David Olsen [a,b]	Member	Norway	No participation in discussion, final deliberations and voting on:	**6.3.6.** Nimodipine (NAP) - PSUSA/00002166/202311 **11.1.1.** Fluoroquinolones for systemic and inhalation use: ciprofloxacin (NAP); levofloxacin (NAP); lomefloxacin (NAP); moxifloxacin (NAP); norfloxacin (NAP); ofloxacin (NAP); pefloxacin (NAP); prulifloxacin (NAP); rufloxacin (NAP) - CZ/H/PSUFU/A31/1452/202210 **16.1.23.** Larotrectinib -

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				VITRAKVI (CAP) - PSUSA/00010799/202311 **16.3.3**. Citric acid, potassium salts, potassium citrate (NAP) - PSUSA/00000783/202311
Pernille Harg [a,b]	Alternate	Norway	No interests declared	
Katarzyna Ziolkowska [a,b]	Alternate	Poland	No interests declared	
Ana Sofia Diniz Martins [a,b]	Member	Portugal	No interests declared	
Carla Torre [a]	Alternate	Portugal	No interests declared	
Roxana Dondera [a,b]	Member	Romania	No interests declared	
Irina Sandu [a]	Alternate*	Romania	No interests declared	
Anna Mareková [a,b]	Member*	Slovakia	No interests declared	
Miroslava Gocova [a,b]	Alternate	Slovakia	No interests declared	
Polona Golmajer [a]	Member*	Slovenia	No interests declared	
Marjetka Plementas [a,b]	Alternate	Slovenia	No interests declared	
Maria del Pilar Rayon [a,b]	Member	Spain	No interests declared	
Monica Martinez Redondo [a,b]	Alternate	Spain	No interests declared	
Ulla Wändel Liminga [a,b]	Member	Sweden	No interests declared	
Mari Thorn [a,b]	Alternate	Sweden	No restrictions applicable to this meeting	
Annalisa Capuano [a]	Member*	Independent scientific expert	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Milou-Daniel Drici [a,b]	Member	Independent scientific expert	No interests declared	
Maria Teresa Herdeiro [a,b]	Member	Independent scientific expert	No interests declared	
Patricia McGettigan [a,b]	Member	Independent scientific expert	No restrictions applicable to this meeting	
Tania Schink [a]	Member*	Independent scientific expert	No participation in discussion, final deliberations and voting on:	**18.3.7.** Romosozumab - EVENITY (CAP) - EMEA/H/C/004465/R/0025 (without RMP)
Roberto Frontini [a]	Member	Healthcare Professionals' Representative	No restrictions applicable to this meeting	
Salvatore Antonio Giuseppe Messana [a]	Alternate	Healthcare Professionals' Representative	No interests declared	
Michal Rataj [a]	Alternate	Patients' Organisation Representative	No interests declared	
Dennis Lex [a,b]	Expert	Germany	No interests declared	
Charlotte Backman [a,b]	Expert	Sweden	No interests declared	
Helene Stenbæk Hansen [a,b]	Expert	Denmark	No restrictions applicable to this meeting	
Laurence de Fays [a]	Expert	Belgium	No interests declared	
Christelle Bizimungu [a]	Expert	Belgium	No restrictions applicable to this meeting	
Els Beghein [a]	Expert	Belgium	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Piyush Jain [a]	Expert	Belgium	No interests declared	
Flora Musuamba Tshinanu [a]	Expert	Belgium	No restrictions applicable to this meeting	
Nina Lalić [a]	Expert	Croatia	No restrictions applicable to this meeting	
Ivana Ljubičić [a]	Expert	Croatia	No interests declared	
Lara Miletić [a]	Expert	Croatia	No restrictions applicable to this meeting	
Gabriela Burianová [a]	Expert	Czech Republic	No interests declared	
Jana Šípková [a]	Expert	Czech Republic	No interests declared	
Petra Vacková [a]	Expert	Czech Republic	No interests declared	
Annette Cleveland Nielsen	Expert	Denmark	No restrictions applicable to this meeting	
Kirsten Egebjerg Juul [a]	Expert	Denmark	No interests declared	
Moritz Sander [a]	Expert	Denmark	No restrictions applicable to this meeting	
Aynur Sert [a]	Expert	Denmark	No interests declared	
Per Sindahl [a,b]	Expert	Denmark	No interests declared	
Ditte Søgaard [a]	Expert	Denmark	No interests declared	
Louise Wenzel-Petersen [a]	Expert	Denmark	No interests declared	
Cécile Choquet	Expert	France	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Camille De-Kervasdoue	Expert	France	No interests declared	
Vincent Gazin	Expert	France	No interests declared	
Philipp Berg [a]	Expert	Germany	No interests declared	
Susanne Müller [a]	Expert	Germany	No interests declared	
Gabriele Ruppert-Seipp [a]	Expert	Germany	No interests declared	
Karin Seifert [a]	Expert	Germany	No interests declared	
Kevin Keohane [a]	Expert	Ireland	No interests declared	
Thijs Ambagts [a]	Expert	Netherlands	No interests declared	
Negar Babae	Expert	Netherlands	No interests declared	
Frederika Adriana Vermeij-van Nimwegen [a]	Expert	Netherlands	No restrictions applicable to this meeting	
Fokaline Vroom [a]	Expert	Netherlands	No interests declared	
Natividad Galiana [a]	Expert	Spain	No restrictions applicable to this meeting	
María Martínez[b]	Expert	Spain	No interests declared	
Consuelo Mejías [a]	Expert	Spain	No interests declared	
Marta Monreal [a]	Expert	Spain	No interests declared	
Paula Rubio Marques [a]	Expert	Spain	No interests declared	
Representatives from the European Commission attended the meeting				
Observers from Health Canada (Canada) and WHO attended the meeting.				
Meeting run with support from relevant EMA staff				

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

20. Annex III - List of acronyms and abbreviations

For a list of acronyms and abbreviations used in the PRAC minutes, see:

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: Referral procedures: human medicines | European Medicines Agency (europa.eu)

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