27 March 2025
EMA/PRAC/583624/2024 Rev.1[1]
Human Medicines Division

Pharmacovigilance Risk Assessment Committee (PRAC)

Minutes of PRAC meeting on 28-31 October 2024

Chair: Ulla Wändel Liminga – Vice-Chair: Liana Martirosyan

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).

[1] '12.1.3. PRAC working group - Best practice guide on using PRAC plenary time efficiently and effectively – update on the implementation of quantitative goals – Q3 2024' added

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1. Introduction

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

The Chairperson opened the 28-31 October 2024 meeting by welcoming all participants. The meeting was held remotely.

In accordance with the Agency's policy on handling of declarations of interests of scientific Committees' members and experts, based on the declarations of interest submitted by the Committee members, alternates[2] 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.

1.2. Agenda of the meeting on 28 - 31 October 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 30 September – 03 October 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 30 September – 03 October 2024 were published on the EMA website on 27 November 2024 (EMA/PRAC/532125/2024).

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

2.1. Newly triggered procedures

None

2.2. Ongoing procedures

None

[2] No alternates for COMP

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[3]

None

3.5. Others

None

4. Signals assessment and prioritisation[4]

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

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

See also Annex I 14.1.

4.1.1. Avelumab – BAVENCIO (CAP); atezolizumab – TECENTRIQ(CAP); cemiplimab - LIBTAYO(CAP); dostarlimab – JEMPERLI(CAP); durvalumab – IMFINZI(CAP); ipilimumab – YERVOY(CAP); nivolumab - OPDIVO, OPDUALAG (CAP); pembrolizumab – KEYTRUDA (CAP); retifanlimab – ZYNYZ (CAP); tislelizumab – TEVIMBRA (CAP); toripalimab – LOQTORZI (CAP); tremelimumab – IMJUDO (CAP); durvalumab – IMFINZI (CAP)

Applicant: AstraZeneca AB (Imfinzi, Imjudo), Beigene Ireland Limited (Tevimbra), Bristol-Myers Squibb Pharma EEIG (Yervoy, Opdivo, Opdualag), GlaxoSmithKline (Ireland) Limited

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

(Jemperli), Incyte Biosciences Distribution B.V. (Zynyz), Merck Europe B.V. (Bavencio), Merck Sharp & Dohme B.V. (Keytruda), Regeneron Ireland Designated Activity Company (DAC) (Libtayo), Roche Registration GmbH (Tecentriq), TMC Pharma (EU) Limited (Loqtorzi)

PRAC Rapporteur: David Olsen

Scope: Signal of scleroderma, systemic scleroderma, morphea

EPITT 20119 – New signal

Background

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

During routine signal detection activities, a signal of scleroderma, systemic scleroderma and morphea was identified by EMA, based on 1 case of systemic sclerosis with durvalumab retrieved in the literature and 4 cases (suggestive of causality) with duvalumab retrieved from EudraVigilance. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by PRAC.

Discussion

Having considered the available evidence from the literature and the case reports in EudraVigilance, PRAC agreed that further evaluation on the signal of scleroderma, systemic scleroderma and morphea following administration of immune-check inhibitors is warranted.

PRAC appointed David Olsen as Rapporteur for the signal.

Summary of recommendation(s)

- The MAHs for Opdivo and Opdualag (nivolumab), Keytruda (pembrolizumab), Imfinzi (durvalumab), Bavencio (avelumab), Tecentriq (atezolizumab), Libtayo (cemiplimab), Jemperli (dostarlimab), Tevimbra (tislelizumab), Yervoy (ipilimumab), Imjudo (tremelimumab) and ZYNYZ (retifanlimab) should submit to EMA, within 60 days, a cumulative review of all cases of scleroderma including but not be limited to the following MedDRA PTs: "Scleroderma", "Systemic Scleroderma" and "Morphea". This analysis should include a review of the published literature, data from spontaneous reports and reports from studies including all cases in EudraVigilance database, as well as a discussion on possible biological plausibility and mechanism of this association. The MAHs should also discuss the need for any potential amendment to the product information (PI) and/or RMP.
- A 90-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.1.2. Ixekizumab – TALTZ (CAP)

Applicant: Eli Lilly and Co (Ireland) Limited

PRAC Rapporteur: Gabriele Maurer

Scope: Signal of demyelinating disorders

EPITT 20124 – New signal

Background

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

During routine signal detection activities, a signal of demyelinating disorders was identified by EMA, based on 1 case retrieved in the literature (article by *Marangi A. et al.*[5]), as well as cases retrieved in EudraVigilance for the following MedDRA PTs: myelitis, myelitis transverse, Guillain-Barre syndrome, demyelinating polyneuropathy and multiple sclerosis. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by PRAC.

Discussion

Having considered the available evidence from case reports in EudraVigilance and the literature, PRAC has agreed that further evaluation of the signal of demyelinating disorders associated with ixekizumab treatment is warranted.

Summary of recommendation(s)

- The MAH for Taltz (ixekizumab) should submit to EMA, within 60 days, a cumulative review of cases of demyelinating disorders, including data from literature, spontaneous reports and clinical trials, as well as a discussion on possible biological plausibility and mechanism of this association. The MAH's search should include the MedDRA PTs: myelitis, myelitis transverse, Guillain-Barré syndrome, demyelinating polyneuropathy, multiple sclerosis, but also other reactions belonging to the Standardised MedDRA Queries: demyelination, Guillain-Barré syndrome, or peripheral neuropathy. Based on this review, the MAH should discuss the need for an amendment to the PI and/or to the RMP.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.2. Signals follow-up and prioritisation

4.2.1. Angiotensin II receptor blockers: amlodipine, valsartan - COPALIA (CAP) - EMEA/H/C/000774/SDA/021, DAFIRO (CAP) - EMEA/H/C/000776/SDA/020, EXFORGE (CAP) - EMEA/H/C/000716/SDA/020; amlodipine, valsartan, hydrochlorothiazide - COPALIA HCT (CAP) - EMEA/H/C/001159/SDA/010, EXFORGE HCT (CAP) - EMEA/H/C/001068/SDA/010; azilsartan medoxomil - EDARBI (CAP) - EMEA/H/C/002293/SDA/013, NAP; candesartan (NAP); eprosartan (NAP); irbesartan - APROVEL (CAP) - EMEA/H/C/000141/SDA/023, IFIRMASTA (CAP) - EMEA/H/C/000962/SDA/015, IRBESARTAN TEVA (CAP) - EMEA/H/C/001093/SDA/006, IRBESARTAN ZENTIVA (CAP) - EMEA/H/C/000785/SDA/014, KARVEA (CAP) - EMEA/H/C/000142/SDA/023, NAP; irbesartan, hydrochlorothiazide - COAPROVEL (CAP) - EMEA/H/C/000222/SDA/011, IFIRMACOMBI (CAP) – EMEA/H/C/002302/SDA/004, IRBESARTAN HYDROCHLOROTHIAZIDE ZENTIVA (CAP) - EMEA/H/C/000783/SDA/012, IRBESARTAN/HYDROCHLOROTHIAZIDE TEVA (CAP) - EMEA/H/C/001112/SDA/009, KARVEZIDE (CAP) - EMEA/H/C/000221/SDA/011; losartan (NAP); olmesartan (NAP); telmisartan, sacubitril, valsartan - ENTRESTO (CAP) - EMEA/H/C/004062/SDA/012; telmisartan - KINZALMONO (CAP) - EMEA/H/C/000211/SDA/031, MICARDIS (CAP) - EMEA/H/C/000209/SDA/032, PRITOR (CAP) - EMEA/H/C/000210/SDA/025, TELMISARTAN ACTAVIS (CAP) -

[5] Marangi A, Benvenuti F, Mazzai L, Riva G, Polo D, Franceschetti I, De Sandre P, Zanusso MA, Scanelli G, Perini F. Cerebral tumefactive iLesion occurrence during ixekizumab treatment in a patient with active psoriatic arthritis. Neurologist. 2024;29(4):246-249; doi: 10.1097/NRL.0000000000000551.

EMEA/H/C/001168/SDA/007, TOLURA (CAP) - EMEA/H/C/001196/SDA/009; telmisartan, amlodipine - TWYNSTA (CAP) - EMEA/H/C/001224/SDA/013; telmisartan, hydrochlorothiazide - ACTELSAR HCT (CAP) - EMEA/H/C/002676/SDA/002, KINZALKOMB (CAP) - EMEA/H/C/000415/SDA/031, MICARDISPLUS (CAP) - EMEA/H/C/000413/SDA/030, PRITORPLUS (CAP) - EMEA/H/C/000414/SDA/031, TOLUCOMBI (CAP) – EMEA/H/C/002549/SDA/002; sacubitril, valsartan - NEPARVIS (CAP) - EMEA/H/C/004343/SDA/010; other relevant fixed dose combinations containing angiotensin II receptor blockers (NAP)

Applicant(s): Actavis Group PTC ehf. (Actelsar HCT, Telmisartan Actavis), Bayer AG (Kinzalkomb, Kinzalmono, Pritor, PritorPlus), Boehringer Ingelheim International (Micardis, MicardisPlus, Twynsta), KRKA, d.d., Novo mesto (Ifirmacombi, Ifirmasta, Tolucombi, Tolura), Novartis Europharm Limited (Copalia, Copalia HCT, Dafiro, Entresto, Exforge HCT, Neparvis), Sanofi Winthrop Industrie (Aprovel, Coaprovel, Karvea, Karvezide), Takeda Pharma A/S (Edarbi), Teva B.V. (Irbesartan Teva, Irbesartan/Hydrochlorothiazide Teva), Zentiva, k.s. (Irbesartan Hydrochlorothiazide Zentiva, Irbesartan Zentiva), various

PRAC Rapporteur: Martin Huber

Scope: Signal of intestinal angioedema

EPITT 20104 – Follow-up to Month July 2024

Background

For background information, see PRAC minutes July 2024.

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

Discussion

Having considered the available evidence in EudraVigilance, including the responses submitted by the MAHs, PRAC concluded that there is sufficient evidence to establish a causal association between angiotensin II receptor agonists and intestinal angioedema. Therefore, the product information for olmesartan-, irbesartan-, valsartan-, losartan-, candesartan-, azilsartan-, eprosartan- and telmisartan-containing products (mono-substances and fixed-dose combinations) should be updated to add intestinal angioedema as a warning and as an undesirable effect.

Summary of recommendation(s)

- The MAHs for olmesartan-, irbesartan-, valsartan-, losartan-, candesartan-, azilsartan-, eprosartan- and telmisartan-containing products (mono-substances and fixed-dose combinations) should submit to national competent authorities and EMA, as applicable, within 60 days, a variation to amend the product information[6], taking into account the already existing wording in some nationally authorised products where the text needs to be adapted by MAHs to individual products.

4.2.2. Eptinezumab - VYEPTI (CAP) - EMEA/H/C/005287/SDA/008; erenumab - AIMOVIG (CAP) - EMEA/H/C/004447/SDA/007; fremanezumab - AJOVY (CAP) -

[6] Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly.

EMEA/H/C/004833/SDA/010; galcanezumab - EMGALITY (CAP) - EMEA/H/C/004648/SDA/007

Applicant(s): H. Lundbeck A/S (Vyepti), Novartis Europharm Limited (Aimovig), TEVA GmbH (Ajovy), Eli Lilly Nederland B.V. (Emgality)

PRAC Rapporteur: Terhi Lehtinen

Scope: Signal of insomnia

EPITT 20077 – Follow-up to Month May 2024

Background

For background information, see PRAC minutes May 2024.

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

Discussion

Having considered the available evidence in EudraVigilance, literature and the responses from the MAHs, PRAC concluded that the current evidence is insufficient to establish a causal relationship between erenumab, fremanezumab, galcanezumab or eptinezumab and insomnia to further warrant an update to the product information and/or risk management plan at present.

Summary of recommendation(s)

- The MAHs of calcitonin gene-related peptide (CGRP) receptor antagonists, Aimovig (Novartis Europharm Limited), Ajovy (TEVA GmbH), Emgality (Eli Lilly Nederland B.V.), and Vyepti (H. Lundbeck A/S) should continue to monitor cases of insomnia as part of routine pharmacovigilance.

4.2.3. Paracetamol (NAP); fixed dose combinations containing paracetamol (NAP)

Applicant: various

PRAC Rapporteur: Jean-Michel Dogné

Scope: Signal of high anion gap metabolic acidosis (HAGMA) due to pyroglutamate acidosis

EPITT 20105 – Follow-up to Month July 2024

Background

For background information, see PRAC minutes July 2024.

The MAHs replied to the request for information on the signal of HAGMA due to pyroglutamate acidosis and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence, including data from EudraVigilance, literature and the responses from the MAHs, PRAC concluded that there is sufficient evidence to establish a causal association between paracetamol and HAGMA. Therefore, the product information of all paracetamol-containing medicinal products (single-ingredient and fixed dose combinations) should be amended to provide additional clarification on the risk of HAGMA

due to pyroglutamic acidosis and to add HAGMA as undesirable effect with a frequency 'not known'.

Summary of recommendation(s)

- The MAHs for all paracetamol-containing medicinal products (single-ingredient and fixed dose combinations) should submit to national competent authorities, within 60 days, a variation to amend the product information[7], taking into account the already existing wording in some nationally authorised products where the text needs to be adapted by MAHs to individual products.

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.

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. Datopotamab (CAP MAA) - EMEA/H/C/006547

Scope (pre D-180 phase): Treatment of adult patients with inoperable or metastatic HR-positive / HER2-negative breast cancer with disease progression following chemotherapy in the metastatic setting

5.1.2. Datopotamab (CAP MAA) - EMEA/H/C/006081

Scope (pre D-180 phase): Treatment of adult patients with locally advanced or metastatic non squamous non-small cell lung cancer (NSCLC)

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.

[7] Update of SmPC sections 4.4, 4.5, 4.8. The package leaflet is updated accordingly.

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. Avacopan - TAVNEOS (CAP) - PSUSA/00010967/202403

Applicant: Vifor Fresenius Medical Care Renal Pharma France

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 Tavneos, a centrally authorised medicine containing avacopan 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 Tavneos (avacopan) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the existing warning on hepatotoxicity to add information on the frequency of monitoring for hepatic transaminases and total bilirubin in the first 6 months after treatment initiation. Therefore, the current terms of the marketing authorisation(s) should be varied[8].
- In the next PSUR, the MAH should include a reflection/summary of cumulative post-marketing data in the relevant PSUR sub-section 'characterisation of risks' for all important and potential risks.

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

6.1.2. Belimumab - BENLYSTA (CAP) - PSUSA/00009075/202403

Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Karin Bolin

Scope: Evaluation of a PSUSA procedure

Background

[8] Update of SmPC section 4.4. 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 Benlysta, a centrally authorised medicine containing belimumab 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 Benlysta (belimumab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add serious cutaneous adverse reactions (SCAR) (Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)) as a warning and undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[9].
- In the next PSUR, the MAH should provide a review of the available safety data on 'pancreatitis' including any potential new cases and cases from clinical studies, post-marketing and spontaneous sources, as well as the literature.

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

6.1.3. Ixekizumab - TALTZ (CAP) - PSUSA/00010493/202403

Applicant: Eli Lilly and Co (Ireland) Limited

PRAC Rapporteur: Gabriele Maurer

Scope: Evaluation of a PSUSA procedure

Background

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Taltz, a centrally authorised medicine containing ixekizumab 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 Taltz (ixekizumab) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAH should provide cumulative and interval data of fatal outcomes in the clinical development programme and in the post-marketing setting, as well as to provide cumulative reviews on cases of 'paradoxical psoriasis' and 'worsening of psoriasis', 'alopecia areata', 'pyoderma gangrenosum' and 'interstitial lung disease' with ixekizumab, using data from clinical trials, post-marketing sources and scientific literature, and discuss the need to update of the product information and/or the risk management plan as warranted. In addition, the MAH should continue to present data on lack of efficacy and to sub-differentiate between different tumour entities regarding the important potential risk 'malignancies'.

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

- The MAH should submit to EMA, within 6 months, a cumulative review on major adverse cerebro-cardiovascular events with data from clinical trials, post-marketing sources and literature and discuss any update on the product information and/or the risk minimisation plan, 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. Ocrelizumab - OCREVUS (CAP) - PSUSA/00010662/202403

Applicant: Roche Registration GmbH

PRAC Rapporteur: Gabriele Maurer

Scope: Evaluation of a PSUSA procedure

Background

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Ocrevus, a centrally authorised medicine containing ocrelizumab 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 Ocrevus (ocrelizumab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the information on contraception by updating the minimum period for women of childbearing potential to use contraception after the last administered dose of ocrelizumab. Therefore, the current terms of the marketing authorisation(s) should be varied[10].
- In the next PSUR, the MAH should provide an updated review on (non-infectious) colitis, cumulative review of interstitial lung disease (SMQ), of psoriasis and related terms including but not limited to the MedDRA HLT psoriatic condition, and of cases reporting serum sickness following treatment with ocrelizumab including a discussion on possible pathophysiologic mechanisms. The MAH should also continue to closely monitor drug-induced liver injury events and provide a review of all pruritus cases (clinical trials, post-marketing sources, literature) occurred later than 24 hours after administration of ocrelizumab, including a causality assessment. The MAH should discuss the need to update the product information (PI) and/or the risk management plan (RMP), as warranted. In addition, the MAH should report the number of questionnaires sent out on progressive multifocal leukoencephalopathy (PML), and pregnancy and breastfeeding, and to summarise the information obtained from these questionnaires. Finally, the MAH should provide an overview on cases from all sources reporting concomitant treatment with two or more disease modifying treatments (DMTs) and discuss whether the pattern of reported adverse reactions differs from that of patients treated with ocrelizumab as a monotherapy, the reasons for such non-guideline-compliant treatments, and whether risk minimisation measures are warranted.

[10] Update of SmPC section 4.6. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion.

- The MAH should submit to EMA, within 4 months, a cumulative review of all cases (clinical trials, post-marketing and literature) of the MedDRA PTs 'febrile neutropenia' and 'agranulocytosis', as well as to discuss the need to update the PI and/or the RMP, as warranted. In addition, the MAH should provide information on alopecia events from the controlled treatment periods of the OPERA I/II and ORATORIO studies and on well documented cases which report alopecia and are not confounded by other risk factors for alopecia or concomitant treatment with drugs known to cause alopecia.

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. Risankizumab - SKYRIZI (CAP) - PSUSA/00010765/202403

Applicant: AbbVie Deutschland GmbH & Co. KG

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 Skyrizi, a centrally authorised medicine containing risankizumab 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 Skyrizi (risankizumab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the existing warning on hypersensitivity regarding anaphylactic reactions and to add anaphylactic reactions as an undesirable event with a frequency 'rare'. Therefore, the current terms of the marketing authorisation(s) should be varied[11].
- In the next PSUR, the MAH should provide a cumulative review of cases of hepatotoxicity including also the MedDRA preferred terms (PTs) hepatitis acute, hepatic fibrosis, and autoimmune hepatitis.

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. Siponimod - MAYZENT (CAP) - PSUSA/00010818/202403

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

Background

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

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Mayzent, a centrally authorised medicine containing siponimod 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 Mayzent (siponimod) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add immune reconstitution inflammatory syndrome (IRIS) syndrome and malignant melanoma as warnings and undesirable effects with frequency 'rare' and 'uncommon' respectively. Therefore, the current terms of the marketing authorisation(s) should be varied[12].
- In the next PSUR, the MAH should provide a cumulative review of the cases of status epilepticus that occurred in patient with pre-existing seizures and/or seizure lowering therapy versus cases occurred without these underlying conditions, and of cryptococcal pneumonia cases discussing the need for any potential amendment to the product information and/or the RMP to broaden the important potential risk 'opportunistic infections other that cryptococcal meningitis' to cryptococcal infections. In addition, the MAH should provide information about medication error, discuss the safety results of the study by *Regner-Nelke et al., 2022* [13] clarifying if the study is part of the AMASIA study, and describe the serious cases of herpes zoster or the cases of herpes zoster disseminated. The MAH should also continue to monitor cases of basal cell carcinoma (BCC) with underlying risk factors and stopping treatment, the serious events of bradyarrhythmia other than syncope occurred after the step-up dose period attributed to other conditions, the cases with several recurrences of the same type of skin cancer as well as the occurrence of the different types of skin cancer, the cases of MS relapses especially regarding MRI findings or follow-up, and the hepatic events other than increase of transaminases, while severe liver injury should be included as important potential risk in the PSUR. Finally, the MAH should continue to provide literature review on COVID-19 vaccine response.
- The MAH should also add IRIS in the description of the important identified risk progressive multifocal leukoencephalopathy (PML) in the RMP and update Annex 6 accordingly. In addition, 'safety in patients over 60 years-old' and 'use during lactation' should be removed from the missing information, while melanoma should be included as important identified risk in the RMP.

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.

6.1.7. Vardenafil - LEVITRA (CAP) - PSUSA/00003098/202403

Applicant: Bayer AG

PRAC Rapporteur: Maria del Pilar Rayon

[12] Update of SmPC sections 4.4 and 4.8. The package leaflet and Annex IID are updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion.
[13] Regner-Nelke L, Pawlitzki M, Willison A, et al. Real-world evidence on siponimod treatment in patients with secondary progressive multiple sclerosis. Neurol Res Pract. 2022 Nov 7;4(1):55. doi: 10.1186/s42466-022-00219-3. PMID: 36336685; PMCID: PMC9639325

Scope: Evaluation of a PSUSA procedure

Background

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Levitra, a centrally authorised medicine containing vardenafil 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 Levitra (vardenafil) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) and central serous chorioretinopathy as warnings and undesirable effects with frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[14].
- In the next PSUR, the MAH should provide a cumulative review of cases of atrial fibrillation, while serious cardiac events due to QT prolonged interval, central serous retinopathy and other chorioretinal disorders (i.e. retinal vascular occlusion) should be followed as important potential risks. In addition, the MAH should provide all cases of off-label use split by indication, as well as describe the off-label use in patients with left ventricular assist device (LVAD). Finally, the MAH should closely monitor cases of interaction with anticoagulants as rivaroxaban and apixaban.

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. Esomeprazole - NEXIUM CONTROL (CAP); NAP - PSUSA/00001269/202403

Applicant(s): GlaxoSmithKline Dungarvan Ltd (Nexium Control), various

PRAC Rapporteur: Rugile Pilviniene

Scope: Evaluation of a PSUSA procedure

Background

Esomeprazole is a proton pump inhibitors indicated for the treatment of gastroesophageal reflux disease (GERD) including erosive reflux oesophagitis, of pathological hypersecretory conditions including Zollinger-Ellison syndrome, and the prevention of relapse of GERD in patients with healed oesophagitis, healing/prevention of Helicobacter pylori-associated duodenal/peptic ulcers (in combination with appropriate antibiotics), of ulcers associated with non-steroidal anti-inflammatory drug (NSAID) therapy, of re-bleeding in patients following therapeutic endoscopy for acute bleeding gastric or duodenal ulcers (I.V.), of re-bleeding of

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

gastric or duodenal ulcers following treatment with intravenous esomeprazole (oral), and of low-dose acetylsalicylic acid (ASA) associated gastroduodenal lesions and upper GI symptoms, as warranted.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of Nexium Control, (a) centrally authorised medicine(s) containing esomeprazole, and nationally authorised medicines containing esomeprazole 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 esomeprazole-containing product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add a warning regarding severe cutaneous adverse reactions (SCARs) and to add drug reaction with eosinophilia and systemic symptoms (DRESS) as an undesirable effect with a frequency 'very rare'. Therefore, the current terms of the marketing authorisations should be varied[15].
- In the next PSUR, the originator MAHs should provide a review of acute generalised exanthematous pustulosis (AGEP) cases from clinical trials, literature and post marketing sources, and should closely monitor the risk of drug-drug interaction (DDI) with pemetrexed, as well as discuss the need to update the product information as warranted. In addition, the originator MAHs should provide all literature data on epidemiologic studies regarding the consequences of off label and long-term use of high doses of PPIs related to risk of pancreatic and gastric cancers. Finally, all MAHs should provide a safety review on the risk of the DDI between levothyroxine-based medicines and esomeprazole, and discuss the need to update the product information, as warranted by the PSUSA for levothyroxine (PSUSA/00001860/202201) adopted by PRAC.

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

6.2.2. Spironolactone - QAIALDO (CAP); NAP - PSUSA/00002780/202403

Applicant(s): Nova Laboratories Ireland Limited (Qaialdo), various

PRAC Rapporteur: Terhi Lehtinen

Scope: Evaluation of a PSUSA procedure

Background

Spironolactone is a non-selective competitive receptor antagonist of aldosterone indicated for the treatment of essential hypertension, short-term preoperative treatment of patients with primary hyperaldosteronism, congestive heart failure (alone or in combination with standard therapy) including severe heart failure (New York Heart Association [NYHA] Class III-IV) to increase survival and reduce the risk of hospitalization when used in addition to standard therapy, in conditions in which secondary hyperaldosteronism may be present including liver cirrhosis accompanied by oedema and/or ascites, nephrotic syndrome, and other

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

oedematous conditions (alone or in combination with standard therapy), of diuretic-induced hypokalaemia/hypomagnesaemia as adjunctive therapy, as well as establishing a diagnosis of primary hyperaldosteronism and management of hirsutism, as warranted.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of Qaialdo, (a) centrally authorised medicine(s) containing spironolactone, and nationally authorised medicines containing spironolactone 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 spironolactone-containing product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add a warning on the fact that spironolactone may reduce mitotane plasma levels in adrenocortical carcinoma patients treated with mitotane. Therefore, the current terms of the marketing authorisations should be varied[16].
- In the next PSUR, the MAH should provide cumulative reviews of intrauterine growth impairment associated with exposure to spironolactone during pregnancy and any data available of use during lactation, and of cases of cardiac arrythmias including bradycardia and premature ventricular complexes, as well as discuss whether this concern relates to other populations or only to patients on haemodialysis. The MAHs should also discuss the need to update the product information as warranted.

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

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

See also Annex I 16.2.1.

6.3.1. Bilastine (NAP) - PSUSA/00003163/202403

Applicant(s): various

PRAC Lead: Roxana Dondera

Scope: Evaluation of a PSUSA procedure

Background

Bilastine is an antihistaminic indicated for the symptomatic treatment of allergic rhino-conjunctivitis (seasonal and perennial) and urticaria, as well as for treatment of ocular signs and symptoms of seasonal and perennial allergic conjunctivitis, as warranted.

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

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of bilastine-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information of bilastine-containing products indicated for oral administration should be updated to add a warning regarding QT prolongation/Torsades de pointes. In addition, the product information should be updated to reflect that cases of 'electrocardiogram QT interval prolonged' have also been reported in the post-marketing setting. ITherefore, the current terms of the marketing authorisation(s) should be varied[17].
- In the next PSUR, the MAHs should provide a cumulative review of cases with PTs grouped into MedDRA HLT Bladder and urethral symptoms as well as HLT Hallucination (excluding sleep-related), including any data from published literature and clinical trials, along with discussion on a possible mechanism. The MAHs should also discuss the need to update the product information as warranted.

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

6.3.2. Chlorphenamine maleate, paracetamol (NAP) - PSUSA/00000703/202403

Applicant(s): various

PRAC Lead: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

Background

Chlorphenamine maleate is an antihistamine medicine. Paracetamol is non-opioid analgesic and antipyretic agent. Chlorphenamine maleate/paracetamol as a combination is indicated for the treatment of flu and cold symptoms in adults.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing chlorphenamine maleate/paracetamol 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 chlorphenamine maleate/paracetamol-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add information on the use in patients with G6PD deficiency and add information on disseminated intravascular coagulation following overdose of paracetamol. Therefore, the current terms of the marketing authorisation(s) should be varied[18].

[17] 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.
[18] Update of SmPC sections 4.4 and 4.9. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position.

- In the next PSUR, the MAHs should provide a cumulative review of cases of major cardiovascular events (hypertensive crisis, arterial thromboembolism, cardiac arrest etc.), of asthma exacerbation and bronchospasm. The MAHs should also discuss the need to update the product information as warranted. The MAH Zentiva should also follow-up on abdominal pain/distension cases.

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. Lanthanum (NAP) - PSUSA/00003175/202403

Applicant(s): various

PRAC Lead: Mari Thorn

Scope: Evaluation of a PSUSA procedure

Background

Lanthanum is a phosphate binding agent indicated for the treatment of hyperphosphatemia associated with chronic kidney disease (CKD).

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing lanthanum 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 lanthanum-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add a contraindication regarding 'bowel obstruction' and add a cross-reference to the new contraindication. Therefore, the current terms of the marketing authorisation(s) should be varied[19].
- In the next PSUR, the MAHs should provide a cumulative review of gastric malignancies limited to neoplasia in the ventricle. In addition, the MAH Viatris should provide the number of reports on off label use, misuse, overdose etc, while the MAH Takeda should provide the reported cases of serious events or medical errors.

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

6.3.4. Oxycodone (NAP) - PSUSA/00002254/202404

Applicant(s): various

PRAC Lead: Liana Martirosyan

Scope: Evaluation of a PSUSA procedure

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

Background

Oxycodone is an opioid analgesic indicated for the treatment of pain requiring the use of an opioid analgesic and of moderate to severe pain in patients with cancer and post-operative pain, as warranted.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing oxycodone 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 oxycodone-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the warning on hepatobiliary disorders and add a new black box warning about the risk of dependence and addiction in the package leaflet. Therefore, the current terms of the marketing authorisation(s) should be varied[20].
- In the next PSUR, the brand leader MAH should provide a follow-up trend analysis of oxycodone cases aggregately reported under the SMQ 'drug abuse, dependence and withdrawal', as well as cases reported under the separate MedDRA PTs of 'drug dependence', 'withdrawal syndrome', 'drug withdrawal syndrome', 'drug abuse' and 'overdose', and discuss the need to further actions as warranted.

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.

6.4. Follow-up to PSUR/PSUSA procedures

See Annex I 16.3.1.

6.5. Variation procedure(s) resulting from PSUSA evaluation

See also Annex I 16.4.1.

6.5.1. 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

[20] Update of SmPC section 4.4. The package leaflet is updated for the black box. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position.

been submitted.
Type IA (A.6) - To change the ATC Code of Fingolimod from L04AA27 to L04AE01.

Background

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

Following the evaluation of the most recently submitted PSUR(s) for the above-mentioned medicine(s), PRAC requested the MAH to submit a variation to update the product information and the educational material on PML. PRAC is responsible for adopting an outcome based on the assessment report from the PRAC Rapporteur, to be further considered at the level of CHMP, responsible for adopting an opinion on this variation. For further background, see PRAC minutes June 2024.

Summary of recommendation(s)

- Based on the available data and the Rapporteur's assessment, PRAC agreed that the product information[21] should be updated to add suspected or confirmed PML as a new contraindication, to add immune reconstitution inflammatory syndrome (IRIS) as a warning and undesirable effect with frequency 'not known', as well as to amend the existing warning on PML. In addition, the educational materials are updated to include information about the risk of IRIS and to improve the general readability of these documents and better address key messages and recommendations for healthcare professionals and for patients following the assessment of procedure PSUSA/00001393/202302.

6.5.2. Naltrexone hydrochloride, bupropion hydrochloride - MYSIMBA (CAP) - EMEA/H/C/003687/II/0063

Applicant: Orexigen Therapeutics Ireland Limited

Scope: Re-examination of variation II/63 concluded with negative PRAC recommendation in July 2024

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 recommendation for refusal of the variation EMEA/H/C/003687/II/0063 to the terms of the Marketing Authorisation adopted by PRAC in July 2024 (see PRAC minutes July 2024), the MAH submitted a request for re-examination on 09 August 2024, followed by the submission of the scientific grounds for re-examination on 25 September 2024. PRAC is responsible for adopting an outcome based on the assessment report from the PRAC Rapporteur, to be further considered at the level of CHMP, responsible for adopting an opinion on this variation. For further background, see also PRAC minutes October 2024.

Summary of recommendation(s)

[21] Update of SmPC sections 4.3, 4.4 and 4.8. The Package Leaflet and Annex II are updated accordingly.

- Based on the available data, the Rapporteur's assessment, the outcome of the AHEG meeting (held on 18 October 2024) and the totality of information provided by the MAH in writing and during the oral explanation (held on 29 October 2024), PRAC agreed that the product information[22] should be updated to amend the contraindication and add a warning on the concomitant use of opioids during treatment with Mysimba (naltrexone hydrochloride, bupropion hydrochloride). In addition, PRAC recommended that a patient card should be implemented to serve as a reminder for the patients to inform their doctors that they are using Mysimba (naltrexone hydrochloride, bupropion hydrochloride). In addition, the RMP was updated and agreed to take into account the changes above.

6.5.3. Relugolix - ORGOVYX (CAP) - EMEA/H/C/005353/II/0024

Applicant: Accord Healthcare S.L.U.

PRAC Rapporteur: Karin Erneholm

Scope: Update of section 4.8 of the SmPC in order to amend the frequency of an existing adverse drug reactions (ADRs) 'Myocardial infarction' from 'rare' to 'uncommon' following PSUSA 00010994/202401 procedure and based on the current available clinical trial data. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to add editorial changes.

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 amend the frequency of the existing undesirable effect of myocardial infarction following PSUSA 00010994/202401. PRAC is responsible for adopting an outcome based on the assessment report from the PRAC Rapporteur, to be further considered at the level of CHMP, responsible for adopting an opinion on this variation. For further background, see PRAC minutes September 2024.

Summary of recommendation(s)

- Based on the available data and the Rapporteur's assessment, PRAC agreed that the product information[23] should be updated to amend the frequency of the existing undesirable effect of myocardial infarction from 'rare' to 'uncommon'.

6.6. Expedited summary safety reviews[24]

None

[22] Update of SmPC sections 4.3, 4.4, 4.5 and 4.8. The Package Leaflet and Annex II are updated accordingly.
[23] Update of SmPC section 4.8. The Package Leaflet is updated accordingly.
[24] Submission of expedited summary safety reports for review in addition to the requirements for submission of PSUR(s) falling within the pandemic period and requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC

7. Post-authorisation safety studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)[25]

See also Annex I 17.1.

7.1.1. Valproate[26] (NAP) - EMEA/H/N/PSP/J/0108

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

PRAC Rapporteur: Liana Martirosyan

Scope: Paternal exposure to valproate, further investigation on the risk of Neuro Developmental Disorders (NDD) and Congenital Malformation (CM) in Offspring: A Non-Interventional Post-Authorization Safety Study (PASS)

Background

Valproic acid and the relates substances are antiepileptics indicated for the treatment of epilepsy, of bipolar disorders restricted to the treatment of manic episodes when lithium is contraindicated or not tolerated, and for the prophylaxis of migraine attacks, as warranted.

Further to the conclusions dated 2018 of the referral procedure under Article 31 of Directive 2001/83/EC (EMEA/H/A-31/1454) conducted by PRAC for valproate-containing medicines, the MAHs were required as a condition to the marketing authorisation(s) (Annex IV) to conduct a retrospective observational study to investigate the association between paternal exposure to valproate and the risk of congenital anomalies and neurodevelopmental disorders, including autism, in offspring. The MAH Sanofi-Aventis Recherche & Développement, on behalf of a consortium, submitted to EMA the final results of the study. See PRAC minutes May 2023, PRAC minutes June 2023, PRAC minutes July 2023, PRAC minutes October 2023[27], PRAC minutes November 2023[28] and PRAC minutes December 2023[29].

The current submission is requested as a condition to marketing authorization following completion of a first post authorisation safety study (PASS) Paternal study on medicinal product(s) containing valproate and related substances (EMEA/H/N/PSR/J/0043). For further background information, see PRAC minutes January 2024. Thus, the MAH Sanofi-Aventis Recherche & Développement, on behalf of a consortium, submitted to EMA a PASS protocol version 1.0 for medicinal products containing valproate and related substances for a study entitled 'PaTernal exposure to vAlproate, further iNvestiGation on the risk of NeuroDevelopmental Disorders (NDD) and Congenital Malformation (CM) in Offspring: A Non-Interventional PASS - (TANGO)' for review by PRAC. PRAC is responsible for evaluating the PASS protocol.

Endorsement/Refusal of the protocol

- Having considered the draft protocol version 1.0 in accordance with Article 107n of Directive 2001/83/EC, PRAC objected to the draft protocol for the above listed medicinal

[25] In accordance with Article 107n of Directive 2001/83/EC
[26] Valproic acid, sodium valproate, valproate pivoxil, valproate semisodium, valpromide, valproate bismuth, calcium valproate, valproate magnesium
[27] Held 25-28 September 2023
[28] Held 23-26 October 2023
[29] Held 27-30 November 2023

product(s), as the Committee considered that the design of the study did not fulfil the study objectives at this stage.

- PRAC recommended that further revisions are needed regarding the proposed data sources, the study design, objectives, duration and size, the data management and analyses, the potential risk factors and confounders, as well as the definition of outcomes and of exposure.
- The MAH should submit a revised PASS protocol within 90 days to EMA. A 60 days-assessment timetable will be followed.

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

See Annex I 17.1.1.

7.3. Results of PASS imposed in the marketing authorisation(s)[31]

None

7.4. Results of PASS non-imposed in the marketing authorisation(s)[32]

See also Annex I 17.4.

7.4.1. Dolutegravir - TIVICAY (CAP) - EMEA/H/C/002753/WS2620/0092; Dolutegravir, lamivudine - DOVATO (CAP) - EMEA/H/C/004909/WS2620/0047; Dolutegravir, rilpivirine - JULUCA (CAP) - EMEA/H/C/004427/WS2620/0056; Dolutegravir, abacavir, lamivudine - TRIUMEQ (CAP) - EMEA/H/C/002754/WS2620/0118

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Martin Huber

Scope: Update of section 4.6 of the SmPC in order to update information about the use of DTG-containing regimens in pregnancy and at conception based on final results from non-interventional Tsepamo study and the Eswatini Birth Outcomes Surveillance study. In addition, data from other cohort studies and pregnancy registries, including the APR, DOLOMITE-EPPICC (Study 208613) and DOLOMITE-NEAT-ID Network study (Study 208759) both listed as category 3 studies in the RMP; and the US Chart Review (Study 212976) as well as data from literature are included. DOLOMITE-EPPICC (Study 208613) is a s a non-interventional study to Assess "real-world" maternal and foetal outcomes following DTG use during pregnancy and to describe patterns of DTG utilization; DOLOMITE NEAT ID Network Study (208759) is a non-interventional, multi-site observational study to define the safety and effectiveness of Dolutegravir use in HIV positive pregnant women. The Package Leaflet is updated accordingly. The RMP version 19 has also been submitted. In addition, the MAH took the opportunity to implement editorial changes to sections 4.4 and 4.5 of the SmPC

Background

[30] 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
[31] In accordance with Article 107p-q of Directive 2001/83/EC
[32] 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

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

As stated in the RMP of Tivicay (dolutegravir), RMP of Dovato (dolutegravir/lamivudine), RMP of Juluca (dolutegravir/rilpivirine) and RMP of Triumeq (dolutegravir/abacavir/lamivudine) the MAH conducted/conducts the PASS DOLOMITE-EPPICC (Study 208613), as well as the ongoing DOLOMITE-NEAT-ID Network study (Study 208759) to assess the safety and effectiveness of dolutegravir in pregnancy, especially regarding neural tube defects. Furthermore, the MAH evaluated the data of the non-imposed non-interventional Tsepamo study, as well as the ongoing Eswatini Birth Outcome Surveillance study, the APR and other studies.

The Rapporteur assessed the MAH´s final study report and his evaluation of data from the other studies in addition to the MAH´s answers to the request for supplementary information (RSI)The Rapporteur assessed the MAH's study report in addition to the MAH's answers to the request for supplementary information (RSI). For further background, see PRAC minutes February 2024, PRAC minutes May 2024 and PRAC minutes October 2024[33].

Summary of advice

- Based on the available data, the MAH's responses to the requests for supplementary information (RSIs) and the Rapporteur's review, PRAC considered that the ongoing variation assessing the final study report could be recommended for approval.
- PRAC agreed with the update of the product information[34] to reflect the new data about the use of dolutegravir-containing medicinal products in pregnancy and at conception. In addition, PRAC agreed with the update of the RMPs, but recommended that these should be further updated in the next regulatory opportunity with the 2024 APR data.

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

See Annex I 17.4.1.

7.6. Others

See Annex I 17.5.1.

7.7. New Scientific Advice

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

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.

[33] Held 30 September – 3 October 2024
[34] Update of SmPC section 4.6. The Package Leaflet is updated accordingly.

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 18.1.1.

8.3. Renewals of the marketing authorisation

See Annex I 18.2.1.

9. Product related pharmacovigilance inspections

9.1. List of planned pharmacovigilance inspections

9.1.1. Risk-based programme for routine pharmacovigilance inspections of marketing authorisation holders connected with human centrally authorised products

Scope: Pharmacovigilance inspection programme 2024-2027 (2024 revision)

The EMA Secretariat presented the programme on pharmacovigilance inspections covering the period 2024-2027. PRAC provided comments for improvement as currently it was considered difficult to navigate the document in order to identify the relevant products, the reasoning for the proposed date and any findings of previous inspections and inconsistencies. The EMA Secretariat confirmed that there is an improvement plan ongoing and the Committee will be updated on the new process as warranted.

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. Levothyroxine (NAP) - FR/H/xxxx/WS/388

Applicant: IBSA PHARMA SAS

PRAC Lead: Tiphaine Vaillant

Scope: PRAC consultation on a worksharing variation procedure to revise, in the product information of levothyroxine-containing medicinal products (soft capsules and oral solution), the information regarding the drug-drug interaction (DDI) between levothyroxine and proton-pump inhibitors (PPIs) agreed in the last PSUSA procedure (PSUSA/00001860/202201) adopted by PRAC in October 2022, following results of 2 drug interaction studies, on request for France

Background

Levothyroxine is a synthetic thyroid hormone indicated in adults and children for the treatment of a number of conditions associated with hypothyroidism, as well as in suppression therapy for thyroid carcinoma and for diagnostic use for thyroid suppression testing.

In the context of the evaluation of a work sharing variation procedure on amendment of the product information of levothyroxine-containing medicinal products (soft capsules and oral solution) regarding the DDI between levothyroxine and PPIs, France requested PRAC advice on its assessment. For further background, see PRAC minutes October 2022[35].

[35] Held 26-29 September 2022

Summary of advice

- Based on the review of the final results of the PK interaction study (19CDN-T409) and of the clinical DDI efficacy study (13US-T404), PRAC supported the revisions of the SmPC section 4.5 of levothyroxine oral solution and soft capsules: to amend the DDI statement introduced as an outcome of the 2022 levothyroxine PSUSA (PSUSA/00001860/202201). The amendment concerns factually describing the two study findings, while keeping the actionable recommendation for biological and clinical monitoring of the thyroid function during concomitant use with PPIs, since for some patients, a DDI may be possible for both formulations. PRAC also supported that the current statement in SmPC section 5.2 (Tcaps – soft capsules) and the statement initially proposed by the MAH for both formulations, informing that the absorption of levothyroxine is not affected by co-administration with PPIs, are not warranted, and thus the current mention for Tcaps should be removed from the SmPC. PRAC agreed also that there is no need to update the package leaflet in light of the current knowledge. Finally, PRAC considered that the proposed conclusions of the current work-sharing variation (FR/H/xxxx/WS/388) including amendments to the product information, would be relevant for the other levothyroxine products, not involved in the procedure, with the same formulations (i.e. soft capsules, oral solution).

11.2. Other requests

None

12. Organisational, regulatory and methodological matters

12.1. Mandate and organisation of PRAC

12.1.1. PRAC membership

None

12.1.2. Vote by proxy

None

12.1.3. PRAC working group - Best practice guide on using PRAC plenary time efficiently and effectively – update on the implementation of quantitative goals – Q3 2024

In line with the adopted PRAC best practice guidance (BPG) on Committee efficiency (see PRAC minutes May 2016 and PRAC minutes June 2018) and the adopted implementation plan for the BPG including goals to measure compliance with the recommendations (see PRAC minutes June 2016 and PRAC minutes June 2018), PRAC was informed on the quantitative measures collected for Q3 2024 of PRAC meetings during the organisational, regulatory and methodological matters (ORGAM) meeting on 14 November 2024. For previous update, see PRAC minutes September 2024.

12.2. Coordination with EMA Scientific Committees or CMDh-v

None

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

None

12.4. Cooperation within the EU regulatory network

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

The topic was postponed for the PRAC December 2024 plenary meeting.

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

12.7.1. PRAC work plan 2025

PRAC lead: Ulla Wändel Liminga, Liana Martirosyan

The EMA Secretariat provided an overview of planned topics to be included in the PRAC work plan 2025 which is planned to be adopted in December 2024.

12.8. Planning and reporting

12.8.1. EU Pharmacovigilance system - quarterly workload measures and performance indicators – Q3 2024 and predictions

At the organisational, regulatory and methodological matters (ORGAM) meeting on 14 November 2024, the EMA Secretariat presented to PRAC an overview of the quarterly figures on the EMA pharmacovigilance system-related workload and performance indicators. The EMA Secretariat also informed PRAC on the ongoing exercise to review the workload measures and pharmacovigilance indicators and change the periodicity from quarterly to annual reporting. PRAC will be kept informed about the outcome of the exercise and the final agreed indicators.

12.8.2. PRAC workload statistics – Q3 2024

The EMA secretariat informed PRAC about the quarterly and cumulative figures to estimate the evolution of the PRAC workload for Q3 2024, by reflecting on the number of procedures and agenda items covered at each PRAC plenary meeting.

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 single assessment (PSUSA) – reminder session on agreed approach post pilot on Section 6 "Other Considerations" of the PSUSA assessment report

PRAC lead: Ulla Wändel Liminga, Liana Martirosyan

The EMA Secretariat provided to PRAC a reminder session on the agreed approach following the end of the pilot phase in July 2024 to remove the 'other considerations' section (section 6) from the PSUSA assessment report (AR) for all PSUSA types (CAP only, mix CAP/NAP and NAPs only). For further background, see PRAC July 2024 minutes. The topic will be further presented and disseminated in the context of an upcoming assessors' training organised by EMA.

12.10.2. Periodic safety update reports

None

12.10.3. Granularity and Periodicity Advisory Group (GPAG)

PRAC lead: Jana Lukacisinova

The topic was postponed for PRAC December 2024 plenary meeting.

12.10.4. PSURs repository

None

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

PRAC endorsed the draft revised EURD list, version November 2024, reflecting PRAC's comments impacting on the data lock point (DLP) and PSUR submission frequencies of the substances/combinations. PRAC endorsed the newly allocated Rapporteurs for upcoming PSUSAs in accordance with the principles previously endorsed by PRAC (see PRAC minutes April 2013).

Post-meeting note: following the PRAC meeting of November 2024, the updated EURD list was adopted by CHMP and CMDh at their November 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)

12.11. Signal management

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

PRAC lead: Martin Huber

The topic was postponed for PRAC December 2024 plenary meeting.

12.12. Adverse drug reactions reporting and additional monitoring

12.12.1. Management and reporting of adverse reactions to medicinal products

None

12.12.2. Additional monitoring

None

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

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

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

12.13. EudraVigilance database

12.13.1. Activities related to the confirmation of full functionality

None

12.14. Risk management plans and effectiveness of risk minimisations

12.14.1. Risk management systems

None

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

None

12.15. Post-authorisation safety studies (PASS)

12.15.1. Post-authorisation Safety Studies – imposed PASS

None

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

None

12.16. Community procedures

12.16.1. Referral procedures for safety reasons

None

12.17. Renewals, conditional renewals, annual reassessments

None

12.18. Risk communication and transparency

12.18.1. Public participation in pharmacovigilance

None

12.18.2. Safety communication

None

12.19. Continuous pharmacovigilance

12.19.1. Incident management

None

12.20. Impact of pharmacovigilance activities

12.20.1. Draft PRAC Interest Group (IG) Impact workplan 2025/2026

PRAC lead: Liana Martirosyan

The EMA Secretariat provided PRAC with an overview of the activities related to the PRAC Impact Strategy, including key objectives. The EMA Secretariat also presented to PRAC the new PRAC IG biannual workplan for endorsement. The PRAC members were invited to send their comments by 12 November 2024.

Post meeting note: At the ORGAM meeting held on 14 November 2024, PRAC endorsed the PRAC IG workplan 2025/2026. In addition, a call for expressions of interest by 6 December 2024 was launched for PRAC members, alternates and national experts to participate and contribute to the PRAC IG activities.

12.20.2. Good Pharmacovigilance Practices (GVP) module XVI – Addendum on pregnancy - update

PRAC lead: Ulla Wändel Liminga

The topic was postponed for the PRAC December 2024 plenary meeting.

12.20.3. Impact study on the dissemination of additional risk minimisation measures (RMM) for patients and healthcare professionals in EU Member States

PRAC lead: Liana Martirosyan

The EMA Secretariat presented to PRAC the background, rationale, research question and objectives for a qualitative study on the dissemination of additional RMM for patients and healthcare professionals to be commissioned under framework contract EMA/2020/46/TDA. The study's aim is to gain a better understanding on how additional RMM materials for patients and healthcare professionals are disseminated by different stakeholders in clinical practice across EU Member States, to help inform regulatory decision-making on the selection of additional RMM tools and on evaluating their overall effectiveness. The PRAC members were invited to send their comments on the draft technical specifications (TS) for tender by 12 November 2024.

Post meeting note: At the ORGAM meeting held on 14 November 2024, PRAC endorsed the draft technical specifications (TS) for tender for the impact study.

12.21. Others

12.21.1. Draft template for qualification of patient registries

The EMA Secretariat presented to PRAC a draft of a briefing book for qualification requests on patient registries, developed in the frame of the Multistakeholder workshop on Patient Registries and aiming to guide the structure and content of qualification applications on patient registries. PRAC members were invited to send their comments on the draft document by 29 November 2024.

12.21.2. EMA-HMA catalogues of real-world data sources and non-interventional studies

The EMA Secretariat presented to PRAC an update on the ongoing activities and future developments related to the HMA-EMA Catalogues of real-world data sources and studies, after their launch in February 2024. The EMA Secretariat also flagged the upcoming survey aiming to collect feedback on the RWD Catalogues' usability and insights on potential improvements that could enhance the RWD Catalogues and users experience. The PRAC members were invited to share information about the Catalogues to the relevant colleagues in the EU network and to participate in future webinars showing the usability of the Catalogues. PRAC noted the information.

12.21.3. IRIS training plan

The EMA Secretariat presented to PRAC an update on the training activities for network users to prepare for go-live of post-authorisation procedures in IRIS, as well as on the network users' support plan after the go-live in January 2025. PRAC noted the information.

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

The EMA Secretariat presented to PRAC an update on RWE and DARWIN EU activities, including the progress on the growth of the network of data partners and an update regarding the ongoing and finalised RWD studies. Moreover, the EMA Secretariat presented a list of ongoing and proposed studies to be performed in the context of upcoming PSUSA procedures due in 2025. PRAC was also informed about the upcoming events related to RWE organised by EMA.

12.21.5. Comparative effectiveness and safety studies using the target trial emulation and estimand frameworks

The EMA Secretariat presented to PRAC an overview of the target trial emulation and estimand framework, as well as the objectives, deliverables and timelines for a research project aiming to develop a clear and detailed overview about the advantages and challenges of combining the target trial emulation with the estimand framework for comparative efficacy and safety studies. PRAC will be kept informed about further developments.

13. Any other business

None

14. Annex I – Signals assessment and prioritisation[36]

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[37].

14.1. New signals detected from EU spontaneous reporting systems

14.1.1. Domperidone (NAP)

Applicant(s): various

PRAC Rapporteur: Jean-Michel Dogné

Scope: Signal of hypertension in patients with a phaeochromocytoma

EPITT 20106– New signal

14.1.2. Tegafur, gimeracil, oteracil – TEYSUNO (CAP)

Applicant: Nordic Group B.V.

[36] 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

[37] 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

PRAC Rapporteur: Bianca Mulder

Scope: Signal of hyperammonaemia

EPITT 20115 – New signal

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 - EMEA/H/C/006339

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

15.1.2. Aflibercept - EMEA/H/C/006551

Scope (pre D-180 phase): Treatment of age-related macular degeneration (AMD) and visual impairment, treatment of age-related macular degeneration (AMD), visual impairment and retinopathy of prematurity (ROP)

15.1.3. Denosumab - EMEA/H/C/006398

Scope (pre D-180 phase): Prevention of skeletal related events with advanced malignancies

15.1.4. Denosumab - EMEA/H/C/006157

Scope (pre D-180 phase): Prevention of skeletal related events with advanced malignancies

15.1.5. Denosumab - EMEA/H/C/006399

Scope (pre D-180 phase): Treatment of osteoporosis and bone loss

15.1.6. Denosumab - EMEA/H/C/006156

Scope (pre D-180 phase): Treatment of osteoporosis and bone loss

15.1.7. Pegfilgrastim - EMEA/H/C/006407

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

15.1.8. Tocilizumab - EMEA/H/C/006196

Scope (pre D-180 phase): Treatment of rheumatoid arthritis (RA)

15.1.9. Ustekinumab - EMEA/H/C/006444

Scope (pre D-180 phase): For the treatment of Crohn's disease and ulcerative colitis

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. Afamelanotide - SCENESSE (CAP) - EMEA/H/C/002548/II/0053, Orphan

Applicant: Clinuvel Europe Limited

PRAC Rapporteur: Martin Huber

Scope: Submission of an updated RMP version 9.12 to include changes made to the pharmacokinetic study CUV052 including the inclusion of adolescent patients in the protocol. CUV052 is an interventional study to evaluate the pharmacokinetics of afamelanotide in patients with Erythropoietic Protoporphyria (EPP)

15.2.2. Alendronic acid, colecalciferol - ADROVANCE (CAP) - EMEA/H/C/000759/WS2696/0055; Alendronic acid, colecalciferol - FOSAVANCE (CAP) - EMEA/H/C/000619/WS2696/0058; Alendronic acid, colecalciferol - VANTAVO (CAP) - EMEA/H/C/001180/WS2696/0045

Applicant: Organon N.V.

PRAC Rapporteur: Jan Neuhauser

Scope: Submission of an updated RMP version 8.0 following the assessment outcome from procedure WS/2467 to reclassify the risk of atypical femoral fracture from "important potential risk" to "important identified risk" and to extend the risk of "atypical femoral fracture" to "atypical fractures of long bones"

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 post-authorisation safety study: PASS-TachoSil Evaluation (PasTel)

15.2.4. Niraparib - ZEJULA (CAP) - EMEA/H/C/004249/II/0055, Orphan

Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Jan Neuhauser

Scope: Submission of an updated RMP version 8.0 in order to remove the category 3 PASS 3000-04-002/ GSK 214708; this is an integrated meta-analysis of MDS/AML and other SPM incidence in patients with ovarian cancer who have been treated with niraparib

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. Afamelanotide - SCENESSE (CAP) - EMEA/H/C/002548/II/0052, Orphan

Applicant: Clinuvel Europe Limited

PRAC Rapporteur: Martin Huber

Scope: Update of section 4.2 of the SmPC in order to update the posology recommendations by removing the current recommendation of a maximum of four implants per year, based on a literature review and analysis of safety data. The Package Leaflet is updated accordingly. The RMP version 9.8 has also been submitted. In addition, the MAH took the opportunity to introduce a minor editorial change to the Product Information

15.3.2. Avacopan - TAVNEOS (CAP) - EMEA/H/C/005523/II/0015, Orphan

Applicant: Vifor Fresenius Medical Care Renal Pharma France

PRAC Rapporteur: Liana Martirosyan

Scope: Update of sections 4.5 and 5.2 of the SmPC based on final results from study CL020_168; this is an open-label, phase 1 study to evaluate the effect of repeated oral doses of avacopan on the pharmacokinetics of a single dose of simvastatin in healthy volunteers; the Package Leaflet is updated accordingly. The updated RMP version 2.0 has also been submitted. In addition, the MAH took the opportunity to implement editorial changes to the SmPC

15.3.3. Avelumab - BAVENCIO (CAP) - EMEA/H/C/004338/II/0046/G

Applicant: Merck Europe B.V.

PRAC Rapporteur: Karin Erneholm

Scope: A grouped application consisting of:
C.I.4: Update of sections 4.2, 4.4, 4.6 and 4.8 of the SmPC in order to add the immune-mediated adverse reactions sclerosing cholangitis, arthritis, polymyalgia rheumatica, and Sjogren's syndrome based on post-marketing data and literature. The Package Leaflet is updated accordingly. The RMP version 7.3 has also been submitted.

C.I.4: Update of section 4.8 of the SmPC in order to update the immunogenicity information based on results from studies EMR100070-003, B9991003 and 100/B9991001. Study EMR100070-003 is a Phase 2, single-arm, open label, multicenter study to investigate the clinical activity and safety of avelumab in patients with mMCC. T. Study B9991003 is a Phase 3 multinational, multicenter, randomized (1:1), open-label, parallel 2 - arm study of

avelumab in combination with axitinib versus sunitinib monotherapy in the 1L treatment of participants with aRCC. Study 100/B9991001 is a Phase 3, multicenter, multinational, randomized, open-label, parallel-arm efficacy and safety study of avelumab plus best supportive care (BSC) versus BSC alone as a maintenance treatment in adult participants with locally advanced or metastatic UC whose disease did not progress after completion of 1L platinum-containing chemotherapy

15.3.4. Baloxavir marboxil - XOFLUZA (CAP) - EMEA/H/C/004974/X/0022

Applicant: Roche Registration GmbH

PRAC Rapporteur: Sonja Hrabcik

Scope: Extension application to add a new pharmaceutical form (granules) associated with three new strengths (10, 30 and 40 mg) packaged in sachet (PET/alu/PET)

15.3.5. Bimekizumab - BIMZELX (CAP) - EMEA/H/C/005316/II/0029

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Liana Martirosyan

Scope: Submission of the final report from study PS0014 (BE BRIGHT) listed as a category 3 study in the RMP. This is a multicenter, open-label extension (OLE) study to assess the long-term safety, tolerability, and efficacy of bimekizumab in adult study participants with moderate to severe plaque PSO who completed 1 of the 3 completed feeder studies. The RMP version 2.2 has also been submitted

15.3.6. Bulevirtide - HEPCLUDEX (CAP) - EMEA/H/C/004854/II/0034, Orphan

Applicant: Gilead Sciences Ireland Unlimited Company

PRAC Rapporteur: Adam Przybylkowski

Scope: Update of section 4.8 of the SmPC in order to update safety information based on final results from study MYR204 listed as a category 3 study in the RMP; this is a multicenter, open-label, randomized Phase 2b clinical study to assess efficacy and safety of bulevirtide in combination with pegylated interferon alfa-2a in patients with chronic hepatitis delta. The RMP version 4.2 has also been submitted

15.3.7. Canagliflozin - INVOKANA (CAP) - EMEA/H/C/002649/II/0069

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Martin Huber

Scope: Extension of indication to include treatment of paediatric patients with type 2 diabetes mellitus aged 10 years old and older for INVOKANA, based on final results from study JNJ-28431754DIA3018 as well as study JNJ-28431754DIA1055. Study JNJ-28431754DIA3018 is a double-blind, placebo-controlled, 2-arm, parallel-group, multicenter Phase 3 study in participants with T2DM >10 and <18 years of age who had inadequate glycemic control (ie, HbA1c of >6.5% to <11.0%). As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 13.1 of the RMP has also been submitted. In addition, the Marketing

authorisation holder (MAH) took the opportunity to introduce minor changes to the PI and update the list of local representatives in the Package Leaflet

15.3.8. Canakinumab - ILARIS (CAP) - EMEA/H/C/001109/II/0085

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Gabriele Maurer

Scope: 1. Type II (B.II.e.1.b.2) - Change in the immediate packaging of the biological finished product Ilaris .
The updated RMP version 14.0 has also been submitted

15.3.9. Capivasertib - TRUQAP (CAP) - EMEA/H/C/006017/II/0001

Applicant: AstraZeneca AB

PRAC Rapporteur: Sonja Hrabcik

Scope: Update of sections 4.2, 4.4 and 4.8 of the SmPC in order to update the posology recommendation and the warning regarding Diabetic Ketoacidosis (DKA) and add it to the list of adverse drug reactions (ADRs) with frequency uncommon based on a safety review. The Package Leaflet is updated accordingly. The RMP version 2 has also been submitted. In addition, the MAH took the opportunity to remove post authorisation measures which were added to Annex II in error, to update the list of local representatives in the Package Leaflet and to bring the PI in line with the latest QRD template version 10.4

15.3.10. Casirivimab, Imdevimab - RONAPREVE (CAP) - EMEA/H/C/005814/II/0017

Applicant: Roche Registration GmbH

PRAC Rapporteur: Mari Thorn

Scope: Extension of indication to include treatment of paediatric patients from 2 to less than 12 years old, weighing at least 10kg, who do not require supplemental oxygen and who are at increased risk of progression to severe COVID-19 for Ronapreve, based on final results from study COV-2067; this was a seamless, adaptive, Phase 3, randomized, double-blinded, placebo-controlled, multi-center study to evaluate the efficacy, safety, and tolerability of casirivimab+imdevimab combination therapy in paediatric and adult outpatients with mild to moderate COVID-19. As a consequence, sections 4.1, 4.2, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated. The Package Leaflet is updated in accordance.
Version 4.0 of the RMP has also been submitted

15.3.11. Efgartigimod alfa - VYVGART (CAP) - EMEA/H/C/005849/II/0022/G, Orphan

Applicant: Argenx

PRAC Rapporteur: Rhea Fitzgerald

Scope: 1. Type II (B.II.e.1.b.2) An updated RMP version 2.6 has also been submitted
2. Type IB (B.II.e.5.a.2)
3. Type II (B.II.a.3.b.5)
4. Type II (B.II.a.5) .
5. Type II (B.II.b.1.c)

6. Type IA (B.II.b.2.a)
7. Type II (B.I.a.1.e)
8. Type II (B.I.a.1.j)
9. Type II (B.I.z)

15.3.12. Evinacumab - EVKEEZA (CAP) - EMEA/H/C/005449/II/0015

Applicant: Ultragenyx Germany GmbH

PRAC Rapporteur: Mari Thorn

Scope: Extension of indication for EVKEEZA to include the treatment of paediatric patients with homozygous familial hypercholesterolaemia aged 6 months to less than 5 years, based on the results of population PK and population PK/PD model-based extrapolation reports (R1500-PM-23202-SR-01V2 and R1500-PM-23089-SR-01V2). As a consequence, sections 4.1, 4.2, 4.8, 5.1, and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 2.0 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to implement minor changes to sections 4.2, 4.4, and 4.7 of the SmPC, along with editorial changes to the SmPC

15.3.13. Glofitamab - COLUMVI (CAP) - EMEA/H/C/005751/II/0005, Orphan

Applicant: Roche Registration GmbH

PRAC Rapporteur: Jana Lukacisinova

Scope: Extension of indication to include in combination with gemcitabine and oxaliplatin the treatment of adult patients with relapse or refractory diffuse large B-cell lymphoma not otherwise specified (DLBCL NOS) who are not candidates for autologous stem cell transplant (ASCT) for COLUMVI, based on results of primary and updated analyses from study GO41944 (STARGLO) listed as a Specific Obligation in the Annex II of the Product Information, as well supportive data from the Phase Ib study GO41943. Study GO41944 (STARGLO) is a Phase III, open-label, multicenter, randomized study of glofitamab in combination with GemOx (Glofit-GemOx) vs. rituximab in combination with GemOx (R-GemOx) in patients with R/R DLBCL. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The Annex II and Package Leaflet are updated in accordance. Version 2.0 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the PI and update the list of local representatives in the Package Leaflet. As part of the application, the MAH is requesting a 1-year extension of the market protection

15.3.14. Human normal immunoglobulin - HYQVIA (CAP) - EMEA/H/C/002491/II/0102

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Gabriele Maurer

Scope: Submission of the final report from study 161505; this is a Phase 3b, open-label, non-controlled, multicenter study to assess the long-term tolerability and safety of immune globulin infusion 10% (human) with recombinant human hyaluronidase (HYQVIA/HyQvia) for the treatment of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). The RMP version 16.0 has also been submitted

15.3.15. Influenza quadrivalent vaccine (rDNA[38]) - SUPEMTEK (CAP) - EMEA/H/C/005159/II/0021/G

Applicant: Sanofi Pasteur

PRAC Rapporteur: Tiphaine Vaillant

Scope: Grouped application comprising two type II variations as follows:
C.I.6.a – Extension of indication to include the treatment of children 9 years of age and older for Supemtek, based on final results from study VAP00027; this is a Phase III, non-randomized, open-label, uncontrolled study to demonstrate the non-inferior HAI immune response of RIV4 for the 4 strains in participants aged 9 to 17 years vs participants aged 18 to 49 years; As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 2.0 of the RMP has also been submitted.
C.I.4 - Update of sections 4.8 and 5.1 of the SmPC in order to update paediatric information based on final results from study VAP00026; this is a Phase III, randomized, modified double-blind, active-controlled 2-arm to demonstrate the non-inferior HAI immune response of RIV4 vs licensed IIV4 for the 4 strains based on the egg-derived antigen in all participants. Version 2.0 of the RMP has also been submitted

15.3.16. Influenza vaccine (surface antigen, inactivated, prepared in cell cultures) - FLUCELVAX TETRA (CAP) - EMEA/H/C/004814/II/0047

Applicant: Seqirus Netherlands B.V.

PRAC Rapporteur: Gabriele Maurer

Scope: Extension of indication to include treatment of adults and children from 6 months of age and older for FLUCELVAX TETRA based on final results from study V130_14. This is a phase 3, randomized, observer-blind, multicenter study to evaluate the efficacy, immunogenicity, and safety of Seqirus' Cell-Based Quadrivalent Subunit Influenza Virus Vaccine (QIVc) compared to a non-influenza vaccine when administrated in healthy subjects aged 6 months through 47 months. As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 3.3 of the RMP has also been submitted

15.3.17. 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

[38] Ribosomal deoxyribonucleic acid

15.3.18. Ivacaftor, tezacaftor, elexacaftor - KAFTRIO (CAP) - EMEA/H/C/005269/II/0056, Orphan

Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Martin Huber

Scope: Update of sections 4.8 and 5.1 of the SmPC in order to update safety and efficacy data based on final results from study VX19-445-107 (Study 107); this is a Phase 3, Open-label Study Evaluating the Long-term Safety and Efficacy of ELX/TEZ/IVA Combination Therapy in Subjects With Cystic Fibrosis Who Are 6 Years of Age and Older. The RMP version 9.2 has also been submitted

15.3.19. Ixekizumab - TALTZ (CAP) - EMEA/H/C/003943/II/0053

Applicant: Eli Lilly and Co (Ireland) Limited

PRAC Rapporteur: Gabriele Maurer

Scope: Extension of indication to include treatment of juvenile idiopathic arthritis for TALTZ, based on week 16 results from study I1F-MC-RHCG; this is a multicenter, open-label, efficacy, safety, tolerability, and pharmacokinetic study (COSPIRIT-JIA) of subcutaneous ixekizumab with adalimumab reference arm, in children from 2 to less than 18 years of age with juvenile idiopathic arthritis subtypes of enthesitis-related arthritis (including juvenile-onset ankylosing spondylitis) and juvenile psoriatic arthritis was performed to evaluate the efficacy and safety of ixekizumab for 16 weeks after treatment initiation. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 8.1 of the RMP has also been submitted. Furthermore, the PI is in line with the latest QRD template version 10.4

15.3.20. Liraglutide - SAXENDA (CAP) - EMEA/H/C/003780/II/0042

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Bianca Mulder

Scope: Extension of indication to include the use of SAXENDA for weight management in children from the age of 6 years to less than 12 years based on results from study NN8022-4392; this is a 56-week, double-blind, randomised, placebo-controlled study investigating safety and efficacy of liraglutide on weight management in children with obesity aged 6 to <12 years. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 34.0 of the RMP has also been submitted

15.3.21. Lisocabtagene maraleucel - BREYANZI (CAP) - EMEA/H/C/004731/II/0043/G

Applicant: Bristol-Myers Squibb Pharma EEIG, ATMP

PRAC Rapporteur: Gabriele Maurer

Scope: A grouped application consisting of:
C.I.6 (Type II): Extension of indication for Breyanzi to include treatment of adult patients with 3rd line + follicular lymphoma (FL) based on final results from the pivotal study JCAR017-FOL-001 (FOL-001, TRANSCEND-FL). This is a phase 2, open-label, single-arm,

multicohort, multicenter study to evaluate efficacy and safety of JCAR017 in adult subjects with relapsed or refractory (r/r) follicular Lymphoma (FL) or marginal zone lymphoma (MZL). As a consequence, sections 4.1, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 5.0 of the RMP is being submitted. Furthermore, as part of the application the MAH is requesting a 1-year extension of the market protection.

B.II.d.1.e (Type II)
B.II.d.1.a (Type IB)
B.II.d.1.a (Type IB)

15.3.22. Nintedanib - OFEV (CAP) - EMEA/H/C/003821/X/0057/G

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Barbara Kovacic Bytyqi

Scope: Extension application to add a new strength of 25 mg hard capsules, grouped with an extension of indication (C.I.6.a) to include treatment of fibrosing Interstitial Lung Diseases (ILDs) in children and adolescents from 6 to 17 years of age for Ofev, following the assessment of procedure X/0052/G, based on final results from study 1199-0337 (A Double Blind, Randomised, Placebo-controlled Trial to Evaluate the Dose-exposure and Safety of Nintedanib Per os on Top of Standard of Care for 24 Weeks, Followed by Open Label Treatment With Nintedanib of Variable Duration, in Children and Adolescents (6 to 17 Year-old) With Clinically Significant Fibrosing Interstitial Lung Disease), which is supplemented by the currently ongoing prospective Phase III extension trial 1199-0378 (An Open-label Trial of the Long-term Safety and Tolerability of Nintedanib Per os, on Top of Standard of Care, Over at Least 2 Years, in Children and Adolescents With Clinically Significant Fibrosing Interstitial Lung Disease). The main objective of the study 1199-0337 was to evaluate dose-exposure and safety of nintedanib in children and adolescents with fibrosing Interstitial Lung Disease (ILD). As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet and Labelling are updated in accordance. Version 12.0 of the RMP has also been submitted

15.3.23. Olipudase alfa - XENPOZYME (CAP) - EMEA/H/C/004850/II/0012/G, Orphan

Applicant: Sanofi B.V.

PRAC Rapporteur: Martin Huber

Scope: A grouped application consisting of:
C.I.4: Update of sections 4.4 and 4.8 of the SmPC in order to update safety information based on final results from study DFI12712 ASCEND, listed as a category 3 study in the RMP; this is a Phase 2/3, multicenter, randomised, double-blinded, placebo-controlled, repeat-dose study to evaluate the efficacy, safety, pharmacodynamics and pharmacokinetics of olipudase alfa in patients with AMSD. The Package Leaflet is updated accordingly. The RMP version 3.0 has also been submitted. In addition, the MAH took the opportunity to bring the PI in line with the latest QRD template version 10.4 and to implement editorial changes to the SmPC.

C.I.4: Update of sections 4.4 and 4.8 of the SmPC in order to update safety information

based on final results from study LTS13632 listed as a category 3 study in the RMP; this is a long-term study the ongoing safety and efficacy of olipudase alfa in patients with ASMD. The Package Leaflet is updated accordingly. The RMP version 3.0 has also been submitted

15.3.24. Rozanolixizumab - RYSTIGGO (CAP) - EMEA/H/C/005824/II/0006, Orphan

Applicant: UCB Pharma

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Update of section 5.1 of the SmPC based on final results from study MG0007 listed as a specific a category 3 study in the RMP; this is a randomized, open-label extension study to evaluate the long-term safety, tolerability, and efficacy of repeated 6-week treatment cycles of rozanolixizumab based on myasthenia gravis worsening in adult study participants with generalized myasthenia gravis. The RMP version 1.1 has also been submitted. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet, to bring the PI in line with the latest QRD template version 10.4 and to update the PI in accordance with the latest EMA excipients guideline

15.3.25. Trastuzumab - ENHERTU (CAP) - EMEA/H/C/005124/II/0048

Applicant: Daiichi Sankyo Europe GmbH

PRAC Rapporteur: Carla Torre

Scope: Extension of indication to include treatment of adult patients with unresectable or metastatic HER2-low or HER2-ultralow breast cancer (BC) who have received at least one endocrine therapy in the metastatic setting for ENHERTU, based on results from study D9670C00001 (DESTINY-Breast06); this is a phase 3, randomized, multicentre, open-label study of trastuzumab deruxtecan (DS-8201a) compared with investigator's choice chemotherapy in, hormone receptor-positive, HER2-low and HER2-ultralow BC patients whose disease has progressed on endocrine therapy in the metastatic setting. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 8.1 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce editorial changes to the PI, to update the list of local representatives in the Package Leaflet and to update the PI according to the Excipients Guideline

15.3.26. Trastuzumab emtansine - KADCYLA (CAP) - EMEA/H/C/002389/II/0071/G

Applicant: Roche Registration GmbH

PRAC Rapporteur: Karin Erneholm

Scope: A grouped application consisting of:
C.I.4 (Type II): 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 BO27938 (KATHERINE) listed as a PAES in the Annex II and as a category 3 study in the RMP. This is a Randomized, Multicenter, Open Label Phase III Study to Evaluate the Efficacy and Safety of Trastuzumab Emtansine Versus Trastuzumab as Adjuvant Therapy for Patients with HER2-Positive Primary Breast Cancer who have Residual Tumor Present Pathologically in the Breast or Axillary Lymph Nodes Following Preoperative Therapy. The Package Leaflet is updated in accordance. The RMP version 16.0 has also been submitted. In addition, the MAH took the

opportunity to update the list of local representatives in the Package Leaflet, to bring the PI in line with the latest QRD template version 10.4, to update the PI in accordance with the latest EMA excipients guideline, and to implement editorial changes to the PI. Furthermore, the MAH took the opportunity to update Annex II-D and to implement editorial changes to the Labelling section.
A.4 (Type I)

15.3.27. Ustekinumab - PYZCHIVA (CAP) - EMEA/H/C/006183/II/0005/G

Applicant: Samsung Bioepis NL B.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: Type II B.IV.1.c
Type IB C.I.2.a To update section 4.6 Fertility, Pregnancy and lactation of the SmPC to update information on pregnancy following assessment of the same change for the reference product Stelara (EMEA/H/C/000958).
An updated RMP (version 4.0) is provided

15.3.28. Ustekinumab - WEZENLA (CAP) - EMEA/H/C/006132/II/0003/G

Applicant: Amgen Technology (Ireland) Unlimited Company

PRAC Rapporteur: Rhea Fitzgerald

Scope: B.IV.1.c (Type II)
B.IV.1.c (Type II)

The RMP version 1.0 has also been submitted

15.3.29. Valoctocogene roxaparvovec - ROCTAVIAN (CAP) - EMEA/H/C/005830/II/0014, Orphan

Applicant: BioMarin International Limited, ATMP

PRAC Rapporteur: Bianca Mulder

Scope: Update of the Annex II in order to propose changes to the current marketing authorisation obligations for ROCTAVIAN. The RMP version 1.3 has also been submitted

15.3.30. Velaglucerase alfa - VPRIV (CAP) - EMEA/H/C/001249/II/0063

Applicant: Takeda Pharmaceuticals International AG Ireland Branch

PRAC Rapporteur: Martin Huber

Scope: Update of section 4.2 of the SmPC in order to add information to support at-home self-administration of VPRIV by a trained patient and/or a caregiver based on post-marketing data and literature. The Package Leaflet and Annex IID are updated accordingly. The updated RMP version 13.0 has also been submitted

15.3.31. Zanubrutinib - BRUKINSA (CAP) - EMEA/H/C/004978/X/0023

Applicant: BeiGene Ireland Ltd

PRAC Rapporteur: Bianca Mulder

Scope: Extension application to introduce a new pharmaceutical form associated with new strength (160 mg film-coated tablets)

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. 5-aminolevulinic acid[39] - GLIOLAN (CAP) - PSUSA/00000009/202403

Applicant: Photonamic GmbH & Co. KG

PRAC Rapporteur: Carla Torre

Scope: Evaluation of a PSUSA procedure

16.1.2. Aprepitant - EMEND (CAP) - PSUSA/00000229/202403

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Mari Thorn

Scope: Evaluation of a PSUSA procedure

16.1.3. Atogepant - AQUIPTA (CAP) - PSUSA/00000100/202403

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Rugile Pilviniene

Scope: Evaluation of a PSUSA procedure

16.1.4. Bosutinib - BOSULIF (CAP) - PSUSA/00010073/202403

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

[39] Glioma indication only

16.1.5. COVID-19 Vaccine (recombinant, adjuvanted) - BIMERVAX (CAP) - PSUSA/00011045/202403

Applicant: Hipra Human Health S.L.

PRAC Rapporteur: Zane Neikena

Scope: Evaluation of a PSUSA procedure

16.1.6. Dupilumab - DUPIXENT (CAP) - PSUSA/00010645/202403

Applicant: Sanofi Winthrop Industrie

PRAC Rapporteur: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

16.1.7. Duvelisib - COPIKTRA (CAP) - PSUSA/00010939/202403

Applicant: Secura Bio Limited

PRAC Rapporteur: Petar Mas

Scope: Evaluation of a PSUSA procedure

16.1.8. Enalapril maleate[40] - AQUMELDI (CAP) - PSUSA/00000201/202403

Applicant: Proveca Pharma Limited

PRAC Rapporteur: Mari Thorn

Scope: Evaluation of a PSUSA procedure

16.1.9. Etrasimod - VELSIPITY (CAP) - PSUSA/00000273/202404

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Karin Bolin

Scope: Evaluation of a PSUSA procedure

16.1.10. Filgotinib - JYSELECA (CAP) - PSUSA/00010879/202403

Applicant: Alfasigma S.p.A.

PRAC Rapporteur: Petar Mas

Scope: Evaluation of a PSUSA procedure

16.1.11. Fluticasone furoate, umeclidinium, vilanterol - ELEBRATO ELLIPTA (CAP); TRELEGY ELLIPTA (CAP) - PSUSA/00010653/202403

Applicant: GlaxoSmithKline Trading Services Limited

PRAC Rapporteur: Mari Thorn

[40] Centrally authorised product for use in children below the age of 18 only

Scope: Evaluation of a PSUSA procedure

16.1.12. Fosaprepitant - IVEMEND (CAP) - PSUSA/00001471/202403

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Mari Thorn

Scope: Evaluation of a PSUSA procedure

16.1.13. Fostamatinib - TAVLESSE (CAP) - PSUSA/00010819/202404

Applicant: Instituto Grifols, S.A.

PRAC Rapporteur: Bianca Mulder

Scope: Evaluation of a PSUSA procedure

16.1.14. Futibatinib - LYTGOBI (CAP) - PSUSA/00000068/202403

Applicant: Taiho Pharma Netherlands B.V.

PRAC Rapporteur: Mari Thorn

Scope: Evaluation of a PSUSA procedure

16.1.15. Glofitamab - COLUMVI (CAP) - PSUSA/00000067/202403

Applicant: Roche Registration GmbH

PRAC Rapporteur: Jana Lukacisinova

Scope: Evaluation of a PSUSA procedure

16.1.16. Guanfacine - INTUNIV (CAP) - PSUSA/00010413/202403

Applicant: Takeda Pharmaceuticals International AG Ireland Branch

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

16.1.17. Human coagulation factor X - COAGADEX (CAP) - PSUSA/00010481/202403

Applicant: BPL Bioproducts Laboratory GmbH

PRAC Rapporteur: Bianca Mulder

Scope: Evaluation of a PSUSA procedure

16.1.18. Idecabtagene vicleucel - ABECMA (CAP) - PSUSA/00010954/202403

Applicant: Bristol-Myers Squibb Pharma EEIG, ATMP

PRAC Rapporteur: Mari Thorn

Scope: Evaluation of a PSUSA procedure

16.1.19. Ipilimumab - YERVOY (CAP) - PSUSA/00009200/202403

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Bianca Mulder

Scope: Evaluation of a PSUSA procedure

16.1.20. Lasmiditan - RAYVOW (CAP) - PSUSA/00011011/202404

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Anna Mareková

Scope: Evaluation of a PSUSA procedure

16.1.21. Lutetium (^{177}LU) vipivotide tetraxetan - PLUVICTO (CAP) - PSUSA/00011031/202403

Applicant: Novartis Europharm Limited

PRAC Rapporteur: John Joseph Borg

Scope: Evaluation of a PSUSA procedure

16.1.22. Maralixibat - LIVMARLI (CAP) - PSUSA/00011032/202403

Applicant: Mirum Pharmaceuticals International B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.23. Mirikizumab - OMVOH (CAP) - PSUSA/00000049/202403

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Sonja Hrabcik

Scope: Evaluation of a PSUSA procedure

16.1.24. Naldemedine - RIZMOIC (CAP) - PSUSA/00010753/202403

Applicant: Shionogi B.V.

PRAC Rapporteur: Eamon O'Murchu

Scope: Evaluation of a PSUSA procedure

16.1.25. Nintedanib[41] - OFEV (CAP) - PSUSA/00010319/202404

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Barbara Kovacic Bytyqi

Scope: Evaluation of a PSUSA procedure

[41] Respiratory indication only

16.1.26. Niraparib - ZEJULA (CAP) - PSUSA/00010655/202403

Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.1.27. Olipudase alfa - XENPOZYME (CAP) - PSUSA/00011003/202403

Applicant: Sanofi B.V.

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.28. Pemigatinib - PEMAZYRE (CAP) - PSUSA/00010923/202404

Applicant: Incyte Biosciences Distribution B.V.

PRAC Rapporteur: Bianca Mulder

Scope: Evaluation of a PSUSA procedure

16.1.29. Selinexor - NEXPOVIO (CAP) - PSUSA/00010926/202403

Applicant: Stemline Therapeutics B.V.

PRAC Rapporteur: Bianca Mulder

Scope: Evaluation of a PSUSA procedure

16.1.30. Selumetinib - KOSELUGO (CAP) - PSUSA/00010936/202404

Applicant: AstraZeneca AB

PRAC Rapporteur: Mari Thorn

Scope: Evaluation of a PSUSA procedure

16.1.31. Tepotinib - TEPMETKO (CAP) - PSUSA/00010979/202403

Applicant: Merck Europe B.V.

PRAC Rapporteur: Bianca Mulder

Scope: Evaluation of a PSUSA procedure

16.1.32. Tucatinib - TUKYSA (CAP) - PSUSA/00010918/202404

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

16.1.33. Velmanase alfa - LAMZEDE (CAP) - PSUSA/00010677/202403

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.1.34. Zilucoplan - ZILBRYSQ (CAP) - PSUSA/00000169/202403

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Karin Erneholm

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. Colesevelam - CHOLESTAGEL (CAP); NAP - PSUSA/00000864/202403

Applicant(s): CHEPLAPHARM Arzneimittel GmbH (Cholestagel), various

PRAC Rapporteur: Bianca Mulder

Scope: Evaluation of a PSUSA procedure

16.2.2. Dexmedetomidine - DEXDOR (CAP); NAP - PSUSA/00000998/202403

Applicant(s): Orion Corporation, various

PRAC Rapporteur: Karin Bolin

Scope: Evaluation of a PSUSA procedure

16.2.3. Gozetotide - LOCAMETZ (CAP); NAP - PSUSA/00011030/202403

Applicant(s): Novartis Europharm Limited, various

PRAC Rapporteur: John Joseph Borg

Scope: Evaluation of a PSUSA procedure

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

16.3.1. Barnidipine (NAP) - PSUSA/00000300/202403

Applicant(s): various

PRAC Lead: Bianca Mulder

Scope: Evaluation of a PSUSA procedure

16.3.2. Calcium chloride, glutamic acid, glutathione, histidine, lactobionic acid, magnesium chloride, mannitol, potassium chloride, sodium hydroxide (NAP) - PSUSA/00009162/202403

Applicant(s): various

PRAC Lead: Maria Popova-Kiradjieva

Scope: Evaluation of a PSUSA procedure

16.3.3. Erythromycin[42] (NAP) - PSUSA/00010809/202403

Applicant(s): various

PRAC Lead: Eamon O'Murchu

Scope: Evaluation of a PSUSA procedure

16.3.4. Ezetimibe, simvastatin (NAP) - PSUSA/00001347/202403

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.3.5. Fluorodopa (^{18}F) (NAP) - PSUSA/00010002/202403

Applicant(s): various

PRAC Lead: John Joseph Borg

Scope: Evaluation of a PSUSA procedure

16.3.6. Fluprednidene (NAP) - PSUSA/00010097/202403

Applicant(s): various

PRAC Lead: Jana Lukacisinova

Scope: Evaluation of a PSUSA procedure

16.3.7. Fluprednidene, gentamicin (NAP) - PSUSA/00010098/202403

Applicant(s): various

PRAC Lead: Jana Lukacisinova

Scope: Evaluation of a PSUSA procedure

16.3.8. Highly refined fish oil, glycerol, purified egg phosphatide (NAP) - PSUSA/00010802/202403

Applicant(s): various

PRAC Lead: Polona Golmajer

[42] Topical use only

Scope: Evaluation of a PSUSA procedure

16.3.9. Human anti-d immunoglobulin (NAP) - PSUSA/00001614/202403

Applicant(s): various

PRAC Lead: Gabriele Maurer

Scope: Evaluation of a PSUSA procedure

16.3.10. Metamizole (NAP) - PSUSA/00001997/202403

Applicant(s): various

PRAC Lead: Melinda Palfi

Scope: Evaluation of a PSUSA procedure

16.3.11. Nitrazepam (NAP) - PSUSA/00002170/202403

Applicant(s): various

PRAC Lead: Karin Erneholm

Scope: Evaluation of a PSUSA procedure

16.3.12. Olodaterol (NAP) - PSUSA/00010245/202403

Applicant(s): various

PRAC Lead: Bianca Mulder

Scope: Evaluation of a PSUSA procedure

16.4. Follow-up to PSUR/PSUSA procedures

16.4.1. Tenofovir disoproxil - VIREAD (CAP) - EMEA/H/C/000419/LEG 279.1

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Tiphaine Vaillant

Scope: MAH's responses to LEG 279 [Cumulative safety review on dental disorders, increased parathyroid hormone and congenital anomalies] RSI as adopted in May 2024

16.5. Variation procedure(s) resulting from PSUSA evaluation

16.5.1. Fenfluramine - FINTEPLA (CAP) - EMEA/H/C/003933/II/0025, Orphan

Applicant: UCB Pharma SA

PRAC Rapporteur: Martin Huber

Scope: Update of section 4.8 of the SmPC in order to propose a combined Adverse Drug Reaction table for Dravet Syndrome and Lennox-Gastaut syndrome following PSUSA procedure EMEA/H/C/PSUSA/00010907/202306. The package leaflet is updated accordingly

16.5.2. Ivacaftor, tezacaftor, elexacaftor - KAFTRIO (CAP) - EMEA/H/C/005269/II/0055, Orphan

Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Martin Huber

Scope: Update of section 4.6 of the SmPC in order to amend the existing wording on exposure during pregnancy following PSUR procedure (EMEA/H/C/PSUSA/00010868/202310)

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. Exagamglogene autotemcel - CASGEVY (CAP) - EMEA/H/C/PSA/S/0113.1

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) [MAH's response to PSA/S/0113]

17.1.2. Valproate (NAP)- EMEA/H/N/PSP/J/0094.5

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

PRAC Rapporteur: Liana Martirosyan

Scope: Progress report & substantial amendment: Characterization of neurodevelopmental disorders in children exposed in utero to valproate and/or other antiepileptic drugs with long-term follow up: retrospective study of multiple European data sources

[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

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

17.2.1. Abrocitinib - CIBINQO (CAP) - EMEA/H/C/005452/MEA 006

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Petar Mas

Scope: ***Study Protocol B7451120***
Title: A Prospective Active Surveillance Study to Monitor Growth, Development, and Maturation Among Adolescents with Atopic Dermatitis Exposed to Abrocitinib" (as listed in PART III of the EU Risk Management Plan (Version 4.4) agreed during the Type II Variation (Procedure No. EMEA/H/C/005452/II/0010)

17.2.2. Atogepant - AQUIPTA (CAP) - EMEA/H/C/005871/MEA 003.1

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Rugile Pilviniene

Scope: MAH's responses to MEA 003 [***Atogepant pregnancy exposure registry: Study P22-392***] RSI as adopted in May 2024
Study P22-392 aims to prospectively evaluate maternal, fetal, and infant outcomes through 12 months of age among women exposed to atogepant during pregnancy
Protocol and Interim Study Result

17.2.3. Atogepant - AQUIPTA (CAP) - EMEA/H/C/005871/MEA 004.1

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Rugile Pilviniene

Scope: MAH's responses to MEA 004 [***Study P22-419***/ Pregnancy Study] RSI as adopted in 30 May 2024.
Study P22-419 aims to describe and compare the incidence of pregnancy outcomes in women with migraine who are exposed to atogepant during pregnancy
Protocol and Interim Study

17.2.4. Efgartigimod alfa - VYVGART (CAP) - EMEA/H/C/005849/MEA 007.2

Applicant: Argenx

PRAC Rapporteur: Rhea Fitzgerald

Scope: MAH's responses to MEA 007.1 [***Revised Protocol***] as adopted in June 2024.
To Evaluate the Risk of Malignancies in Patients with Myasthenia Gravis (MG) Treated with Efgartigimod

17.2.5. Exagamglogene autotemcel - CASGEVY (CAP) - EMEA/H/C/005763/MEA 011

Applicant: Vertex Pharmaceuticals (Ireland) Limited, ATMP

[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

PRAC Rapporteur: Bianca Mulder

Scope: ***Protocol v. 1.0 / Study no VX24-290-102***
Title: Healthcare Professional Survey (HCP) to Assess the Effectiveness of the Additional Risk Minimization Measures (aRMM) for Casgevy (exagamglogene autotemcel)

17.2.6. Inotersen - TEGSEDI (CAP) - EMEA/H/C/004782/MEA 001.12

Applicant: Akcea Therapeutics Ireland Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: ***REVISED PROTOCOL for PASS Study TEG4001*** (Version 4.2)
A Prospective, Non-interventional, Long-term, Multinational Cohort Safety Study of Patients with Hereditary Transthyretin Amyloidosis with Polyneuropathy (hATTR-PN)

17.2.7. Linaclotide - CONSTELLA (CAP) - EMEA/H/C/002490/MEA 009.8

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Martin Huber

Scope: ***Amended PASS Protocol (v 13.2) / Study number: EVM-18888***
Title: Linaclotide Safety Study for the Assessment of Diarrhoea Complications and Associated Risk Factors in Selected European Populations with Irritable Bowel Syndrome with Constipation (IBS-C)

17.2.8. Mirikizumab - OMVOH (CAP) - EMEA/H/C/005122/MEA 001.2

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Sonja Hrabcik

Scope: MAH's response to questions regarding MEA 001.1 and a Revised Protocol [***Protocol I6T-MC-B003***] as adopted in July 2024.
Observational Study of Pregnancy and Infant Outcomes Among Women Exposed to Mirikizumab During Pregnancy in US-based Administrative Claims Data. (RMP v.0.4)

17.2.9. Plasmodium falciparum and hepatitis B vaccine (recombinant, adjuvanted) - MOSQUIRIX (Art 58[46]) - EMEA/H/W/002300/MEA 003.11

Applicant: GlaxoSmithkline Biologicals SA

PRAC Rapporteur: Jean-Michel Dogné

Scope: MAH's response to MEA 003.10 [Amended Protocol (version 3) for PASS EPI-MALARIA-003] RSI as adopted in July 2024.
Phase IV prospective observational study to evaluate the safety, effectiveness and impact of the RTS,S/AS01E vaccine in young children in sub-Saharan Africa

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

17.3. 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. Adalimumab - HUMIRA (CAP) - EMEA/H/C/000481/II/0219

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Karin Bolin

Scope: Submission of the final report from study P10-262 listed as a category 3 study in the RMP. This is a long-term, multi-center, longitudinal, post-marketing observational registry to assess long-term safety and effectiveness of Humira (adalimumab) in children with moderately to severely active polyarticular or polyarticular-course juvenile idiopathic arthritis (JIA). The RMP version 16.1 has also been submitted

17.4.2. Lenvatinib - LENVIMA (CAP) - EMEA/H/C/003727/II/0056

Applicant: Eisai GmbH

PRAC Rapporteur: Mari Thorn

Scope: Update of section 5.1 of the SmPC in order to update the safety and efficacy information for the current HCC indication based on final results from study E7080-M000-508 (STELLAR), listed as a category 3 PASS in the RMP; this is a multicentre non-interventional, observational Phase 4 study to evaluate the safety and tolerability of lenvatinib in patients with advanced or unresectable HCC. The RMP version 17.0 has also been submitted

17.4.3. Pasireotide - SIGNIFOR (CAP) - EMEA/H/C/002052/II/0070, Orphan

Applicant: Recordati Rare Diseases

PRAC Rapporteur: Mari Thorn

Scope: Submission of the final report from study CSOM230B2410 listed as a category 3 PASS in the RMP. This is a non-interventional, multinational, multi-centre post-marketing study to further document the safety and efficacy of pasireotide s.c. administered in routine clinical practice in patients with Cushing's disease. The RMP version 8.0 has also been submitted

17.4.4. 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

[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

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

17.5. 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 050.7

Applicant: Teva B.V.

PRAC Rapporteur: Tiphaine Vaillant

Scope: MAH's responses to MEA 050.6 [*** FORTH ANNUAL INTERIM REPORT***/ PASS C18477-ONC-50025] as adopted in June 2024.
Study Title: A post-authorisation long term safety cohort study in acute promyelocytic leukaemia (APL) patients treated with Trisenox

17.5.2. Avapritinib - AYVAKYT (CAP) - EMEA/H/C/005208/SOB 009.4

Applicant: Blueprint Medicines (Netherlands) B.V.

PRAC Rapporteur: Bianca Mulder

Scope: MAH's response to SOB 009.3 [***Study BLU-285-1406***] as adopted in July 2024:
Study BLU-285-1406 is an imposed non-interventional PASS aiming to confirm the safety and efficacy of avapritinib in the treatment of adult patients with unresectable or metastatic GIST harbouring the PDGFRA D842V mutation, given as Specific Obligation 3 (SOB3) of the Conditional Marketing Authorisation for AYVAK
The interim report should include an update of the MAH’s efforts to include data from AVIATOR2020. If the MAH has found a way to include patient data from this registry, the MAH should discuss how these data will be incorporated in study 1406, which methodological challenges are faced and how these will be addressed.
Third Progress Report / Study BLU-285-1406

17.5.3. Givosiran - GIVLAARI (CAP) - EMEA/H/C/004775/MEA 006.7

Applicant: Alnylam Netherlands B.V.

PRAC Rapporteur: Martin Huber

Scope: From Initial MAA:
PASS Study ALN-AS1-006
Company Sponsored AHP Registry
A global observational longitudinal prospective registry of patients with acute hepatic porphyria (AHP). [ELEVATE]
THIRD INTERIM ANNUAL REPORT

17.5.4. Linaclotide - CONSTELLA (CAP) - EMEA/H/C/002490/MEA 009.9

Applicant: AbbVie Deutschland GmbH & Co. KGGPRAC Rapporteur: Martin HuberG

Scope: ***Study Progress Report (v. 1.1) / Study no EVM-18888***
Title: Linaclotide Safety Study for the Assessment of Diarrhea Complications and Associated Risk Factors in Selected European Populations with IBS-C

17.5.5. Naloxegol - MOVENTIG (CAP) - EMEA/H/C/002810/MEA 006.16

Applicant: Gruenenthal GmbH

PRAC Rapporteur: Eamon O'Murchu

Scope: MAH Response to MEA 006.15 [Study No. D3820R00009 (EUPAS12669)] RSI as adopted in February 2024.

17.5.6. Tacrolimus - ADVAGRAF (CAP) - EMEA/H/C/000712/MEA 032.5

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Eamon O'Murchu

Scope: MAH's responses to MEA 032.4 [***Progress Report / Study No.: 2868371***] as adopted in February 2024

17.5.7. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/MEA 044.19

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: MAH's responses to MEA 044.18 [6th annual report of the observational PASS (EUPAS19506) of Ustekinumab in the treatment of paediatric patients aged 6 years and older with moderate to severe plaque psoriasis] as adopted in June 2024

17.6. Others

17.6.1. Tacrolimus - MODIGRAF (CAP) - EMEA/H/C/000954/MEA 024.5

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Mari Thorn

Scope: MAH's responses to MEA 024.4 [***Progress Report / Study No.: 2868371***] as adopted in February 2024

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. Cerliponase alfa - BRINEURA (CAP) - EMEA/H/C/004065/S/0047 (without RMP)

Applicant: BioMarin International Limited

PRAC Rapporteur: Mari Thorn

Scope: Annual reassessment of the marketing authorisation

18.1.2. Lomitapide - LOJUXTA (CAP) - EMEA/H/C/002578/S/0061 (without RMP)

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Bianca Mulder

Scope: Annual reassessment of the marketing authorisation

18.1.3. Nelarabine - ATRIANCE (CAP) - EMEA/H/C/000752/S/0068 (without RMP)

Applicant: Sandoz Pharmaceuticals d.d.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Annual reassessment of the marketing authorisation

18.1.4. Smallpox vaccine (live modified vaccinia virus Ankara) - IMVANEX (CAP) - EMEA/H/C/002596/S/0107 (with RMP)

Applicant: Bavarian Nordic A/S

PRAC Rapporteur: Gabriele Maurer

Scope: Annual reassessment of the marketing authorisation

18.1.5. Vestronidase alfa - MEPSEVII (CAP) - EMEA/H/C/004438/S/0042 (without RMP)

Applicant: Ultragenyx Germany GmbH

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Annual reassessment of the marketing authorisation

18.2. Conditional renewals of the marketing authorisation

18.2.1. Brexucabtagene autoleucel - TECARTUS (CAP) - EMEA/H/C/005102/R/0047 (with RMP)

Applicant: Kite Pharma EU B.V., ATMP

PRAC Rapporteur: Bianca Mulder

Scope: Conditional renewal of the marketing authorisation

18.2.2. Delamanid - DELTYBA (CAP) - EMEA/H/C/002552/R/0076 (with RMP)

Applicant: Otsuka Novel Products GmbH

PRAC Rapporteur: Jo Robays

Scope: Conditional renewal of the marketing authorisation

18.2.3. Selpercatinib - RETSEVMO (CAP) - EMEA/H/C/005375/R/0035 (without RMP)

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Bianca Mulder

Scope: Conditional renewal of the marketing authorisation

18.3. Renewals of the marketing authorisation

18.3.1. Arsenic trioxide - ARSENIC TRIOXIDE MYLAN (CAP) - EMEA/H/C/005235/R/0012 (without RMP)

Applicant: Mylan Ireland Limited

PRAC Rapporteur: Tiphaine Vaillant

Scope: 5-year renewal of the marketing authorisation

18.3.2. Cefiderocol - FETCROJA (CAP) - EMEA/H/C/004829/R/0022 (with RMP)

Applicant: Shionogi B.V.

PRAC Rapporteur: Martin Huber

Scope: 5-year renewal of the marketing authorisation

18.3.3. Cholera vaccine, oral, live - VAXCHORA (CAP) - EMEA/H/C/003876/R/0024 (without RMP)

Applicant: Bavarian Nordic A/S

PRAC Rapporteur: Jean-Michel Dogné

Scope: 5-year renewal of the marketing authorisation

18.3.4. Indacaterol, mometasone - ATECTURA BREEZHALER (CAP) - EMEA/H/C/005067/R/0031 (without RMP)

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Jan Neuhauser

Scope: 5-year renewal of the marketing authorisation

18.3.5. Indacaterol, mometasone - BEMRIST BREEZHALER (CAP) - EMEA/H/C/005516/R/0026 (without RMP)

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Jan Neuhauser

Scope: 5-year renewal of the marketing authorisation

18.3.6. Insulin lispro - LYUMJEV (CAP) - EMEA/H/C/005037/R/0019 (without RMP)

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Mari Thorn

Scope: 5-year renewal of the marketing authorisation

18.3.7. Isatuximab - SARCLISA (CAP) - EMEA/H/C/004977/R/0033 (without RMP)

Applicant: Sanofi Winthrop Industrie

PRAC Rapporteur: Monica Martinez Redondo

Scope: 5-year renewal of the marketing authorisation

18.3.8. Ozanimod - ZEPOSIA (CAP) - EMEA/H/C/004835/R/0028 (without RMP)

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Maria del Pilar Rayon

Scope: 5-year renewal of the marketing authorisation

18.3.9. Solriamfetol - SUNOSI (CAP) - EMEA/H/C/004893/R/0023 (with RMP)

Applicant: Atnahs Pharma Netherlands B.V.

PRAC Rapporteur: Julia Pallos

Scope: 5-year renewal of the marketing authorisation

19. Annex II – List of participants

List of participants including any restrictions with respect to involvement of members/alternates/experts following evaluation of declared interests for the 28-31 October 2024 PRAC meeting, which was held remotely. Participants marked with "a" attended the plenary session while those marked with "b" attended the ORGAM.

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Ulla Wändel Liminga [a,b]	Chair	Sweden	No interests declared	
Jan Neuhauser [a,b]	Member	Austria	No interests declared	
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 Kovacic Bytyqi [a,b]	Alternate	Croatia	No interests declared	
Elena Kaisis [a,b]	Member	Cyprus	No interests declared	
Panagiotis Psaras [a,b]	Alternate	Cyprus	No interests declared	
Eva Jirsová [a,b]	Member	Czechia	No interests declared	
Jana Lukacisinova [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	
Terhi Lehtinen [a,b]	Member	Finland	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Kimmo Jaakkola [a,b]	Alternate	Finland	No interests declared	
Tiphaine Vaillant [a,b]	Member	France	No interests declared	
Martin Huber [a]	Member	Germany	No interests declared	
Gabriele Maurer [a,b]	Alternate	Germany	No participation in final deliberations and voting on:	4.1.1 Avelumab – BAVENCIO (CAP); atezolizumab – TECENTRIQ(CAP); cemiplimab - LIBTAYO(CAP); dostarlimab – JEMPERLI(CAP); durvalumab – IMFINZI(CAP); ipilimumab – YERVOY(CAP); nivolumab - OPDIVO, OPDUALAG (CAP); pembrolizumab – KEYTRUDA (CAP); retifanlimab – ZYNYZ (CAP); tislelizumab – TEVIMBRA (CAP); tremelimumab – IMJUDO (CAP); urvalumab – IMFINZI (CAP)
Sofia Trantza [a,b]	Member	Greece	No interests declared	
Georgia Gkegka [a,b]	Alternate	Greece	No interests declared	
Julia Pallos [a,b]	Member	Hungary	No participation in discussion, final deliberations and voting on:	4.1.1. Avelumab – BAVENCIO (CAP); atezolizumab – TECENTRIQ(CAP); cemiplimab - LIBTAYO(CAP); dostarlimab –

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				JEMPERLI(CAP) ; durvalumab – IMFINZI(CAP); ipilimumab – YERVOY(CAP); nivolumab - OPDIVO, OPDUALAG (CAP); pembrolizumab – KEYTRUDA (CAP); retifanlimab – ZYNYZ (CAP); tislelizumab – TEVIMBRA (CAP); tremelimumab – IMJUDO (CAP); urvalumab – IMFINZI (CAP) 15.3.21. Lisocabtagene maraleucel - BREYANZI (CAP) - EMEA/H/C/004731/II/0043 /G 16.1.18. Idecabtagene vicleucel - ABECMA (CAP) - PSUSA/00010954/202403 16.1.19. Ipilimumab - YERVOY (CAP) - PSUSA/00009200/202403 18.3.8. Ozanimod - ZEPOSIA (CAP) - EMEA/H/C/004835/R/0028 (without RMP)
Guðrún Þengilsdóttir [a,b]	Alternate	Iceland	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Rhea Fitzgerald [a]	Member	Ireland	No interests declared	
Eamon O'Murchu [a]	Alternate	Ireland	No interests declared	
Amelia Cupelli [a,b]	Member	Italy	No interests declared	
Emilio Clementi [a,b]	Alternate	Italy	No interests declared	
Zane Neikena [a,b]	Member	Latvia	No interests declared	
Rugile Pilviniene [a,b]	Member	Lithuania	No interests declared	
Lina Seibokiene [a,b]	Alternate	Lithuania	No interests declared	
Nadine Petitpain [a,b]	Member	Luxembourg	No restrictions applicable to this meeting	
Benjamin Micallef [a]	Alternate	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:	4.2.1. Angiotensin II receptor blockers 4.2.3. Paracetamol (NAP); fixed dose combinations containing paracetamol (NAP) 6.1.7. Vardenafil - LEVITRA (CAP) - PSUSA/00003098/202403
Pernille Harg [a]	Alternate	Norway	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Adam Przybylkowski [a]	Member	Poland	No interests declared	
Katarzyna Ziolkowska [b]	Alternate	Poland	No interests declared	
Ana Sofia Diniz Martins [a]	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,b]	Alternate	Romania	No interests declared	
Anna Mareková [a,b]	Member	Slovakia	No interests declared	
Miroslava Gocova [a]	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]	Member	Spain	No interests declared	
Monica Martinez Redondo [a,b]	Alternate	Spain	No interests declared	
Mari Thorn [a,b]	Member	Sweden	No restrictions applicable to this meeting	
Karin Bolin [a,b]	Alternate	Sweden	No interests declared	
Annalisa Capuano [a]	Member	Independent scientific expert	No interests declared	
Milou-Daniel Drici [a,b]	Member	Independent scientific expert	No interests declared	
Maria Teresa Herdeiro [a,b]	Member	Independent scientific expert	No interests declared	
Patricia McGettigan [a,b]	Member	Independent scientific expert	No restrictions applicable to this meeting	
Anette Kirstine Stark [a,b]	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
Hedvig Marie Egeland Nordeng [a]	Member	Independent scientific expert	No interests declared	
Roberto Frontini [a]	Member	Healthcare Professionals' Representative	No participation in discussion, final deliberations and voting on:	16.3.9. Human anti-d immunoglobulin (NAP) - PSUSA/00001614/202403
Marko Korenjak [a]	Member	Patients' Organisation Representative	No interests declared	
Michal Rataj [a]	Alternate	Patients' Organisation Representative	No interests declared	
Laurence de Fays [a]	Expert	Belgium	No interests declared	
Behija Hudina [a]	Expert	Croatia	No restrictions applicable to this meeting	
Iva Kuliš [a]	Expert	Croatia	No interests declared	
Karina Suciu-Subert [a]	Expert	Czech Republic	No interests declared	
Frederikke Hillebrand Laustsen [a]	Expert	Denmark	No restrictions applicable to this meeting	
Emma Stadsbjerg [a]	Expert	Denmark	No restrictions applicable to this meeting	
Katia Chemala [a]	Expert	France	No interests declared	
Pauline Dayani [a]	Expert	France	No interests declared	
Camille De-Kervasdoue [a]	Expert	France	No interests declared	
Mariem Loukil [a]	Expert	France	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Sophie Teng [a]	Expert	France	No interests declared	
Muriel Uzzan [a]	Expert	France	No interests declared	
Christina Fischer [a]	Expert	Germany	No interests declared	
Jelena Katic [a]	Expert	Germany	No interests declared	
Dennis Lex [a,b]	Expert	Germany	No interests declared	
Valdas Liukaitis [a]	Expert	Lithuania	No interests declared	
Magdalena Wielowieyska [a]	Expert	Luxembourg	No restrictions applicable to this meeting	
Paul ten Berg [a]	Expert	Netherlands	No interests declared	
Louk Timmer [a]	Expert	Netherlands	No interests declared	
Inge Zomerdijk [a]	Expert	Netherlands	No interests declared	
Susanne Dertz [a]	Expert	Norway	No interests declared	
Gunnar Rimul [a]	Expert	Norway	No interests declared	
Helena Calero [a]	Expert	Spain	No restrictions applicable to this meeting	
Eva Cantarero [a]	Expert	Spain	No interests declared	
Natividad Galiana [a]	Expert	Spain	No restrictions applicable to this meeting	
María Martínez [a]	Expert	Spain	No interests declared	
Consuelo Mejías [a]	Expert	Spain	No interests declared	
Charlotte Backman [a,b]	Expert	Sweden	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Jolanta Gulbinovic [a]	Expert	Sweden	No interests declared	
A representative from the European Commission attended the meeting.				
Observers from Health Canada 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