29 February 2024
EMA/PRAC/68905/2024
Human Medicines Division

Pharmacovigilance Risk Assessment Committee (PRAC)

Minutes of PRAC meeting on 08-11 January 2024

Chair: Sabine Straus – Vice-Chair: Martin Huber

Disclaimers

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

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

Note on access to documents

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

1. Introduction

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

The Chairperson opened the 08-11 January 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[1] and experts and on the topics in the agenda of the meeting, the Committee Secretariat announced the restricted involvement of some Committee members, alternates and experts for concerned agenda topics. Participants were asked to declare any changes, omissions or errors to their declared interests concerning the matters for discussion. No new or additional competing interests were declared. Restrictions applicable to this meeting are captured in the List of participants included in the minutes.

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

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

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

1.2. Agenda of the meeting on 08-11 January 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 27-30 November 2023

The minutes were adopted with some amendments received during the consultation phase and will be published on the EMA website.

Post-meeting note: the PRAC minutes of the meeting held on 27-30 November 2023 were published on the EMA website on 01 February 2024 (EMA/PRAC/25440/2024).

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

2.1. Newly triggered procedures

None

[1] No alternates for COMP

2.2. Ongoing procedures

None

2.3. Procedures for finalisation

None

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

3.1. Newly triggered procedures

None

3.2. Ongoing procedures

None

3.2.1. Hydroxyprogesterone (NAP) - EMEA/H/A-31/1528

Applicant(s): various

PRAC Rapporteur: Amelia Cupelli; PRAC Co-rapporteur: Nathalie Gault

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

Background

A referral procedure under Article 31 of Directive 2001/83/EC is ongoing for hydroxyprogesterone caproate (17-OHPC). The review was initiated following the results of a pharmacoepidemiological study by *Murphy et al*[2] that showed that in utero exposure to 17-OHPC may be associated with a higher risk of cancer in the offspring. In addition, the results from another study by *Blackwell et al*[3] suggested that 17-OHPC is no more effective than placebo in preventing recurrent premature birth or medical complications due to prematurity in the new-born infant. For further background, see PRAC minutes May 2023 and PRAC minutes October 2023.

Summary of recommendation(s)/conclusions

- PRAC adopted a revised timetable for the procedure (EMA/PRAC/194263/2023 rev.2) to introduce the date of the ad-hoc expert meeting (AHEG) scheduled on 22 January 2024.
- PRAC discussed the list of participants (LoP) for the AHEG.

Post-meeting note: On 19 February 2024, PRAC adopted the LoP for the AHEG via written procedure.

[2] Murphy CC, et al. In utero exposure to 17α-hydroxyprogesterone caproate and risk of cancer in offspring. Am J Obstet Gynecol. 2022 Jan;226(1):132.e1-132.e14. doi:10.1016/j.ajog.2021.10.035
[3] Blackwell, S. C. et al. 17-OHPC to prevent recurrent preterm birth in singleton gestations (PROLONG Study): A multicenter, international, randomied double-blind trial. Am J Perinatol. 2020 Jan;37(2):127-136. doi:10.1055/s-0039-3400227

3.3. Procedures for finalisation

None

3.4. Re-examination procedures[4]

None

3.5. Others

None

4. Signals assessment and prioritisation[5]

4.1. New signals detected from EU spontaneous reporting systems

See also Annex I 14.1.

4.1.1. Aflibercept – EYLEA (CAP), YESAFILI (CAP); ranibizumab – LUCENTIS (CAP)

Applicant(s): Bayer AG (Eylea), Biosimilar Collaborations Ireland Limited (Yesafili), Novartis Europharm Limited (Lucentis)

PRAC Rapporteur: Nathalie Gault

Scope: Signal of nephropathy toxic after intravitreal administration

EPITT 20024 – 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 nephropathy toxic after intravitreal administration was identified by EMA, based on 194 cases for aflibercept retrieved from EudraVigilance and on cases for aflibercept and ranibizumab issued from literature. The Rapporteurs 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 agreed that further evaluation on the signal of nephropathy toxic after intravitreal administration of aflibercept is warranted. PRAC also recommended no further action other than routine pharmacovigilance for other intravitreal vascular endothelial growth factor (VEGF) inhibitors.

PRAC appointed Nathalie Gault as the lead Rapporteur for the signal.

[4] Re-examination of PRAC recommendation under Article 32 of Directive 2001/83/EC
[5] Each signal refers to a substance or therapeutic class. The route of marketing authorisation is indicated in brackets (CAP for Centrally Authorised Products; NAP for Nationally Authorised Products including products authorised via Mutual Recognition Procedures and Decentralised Procedure). Product names are listed for reference Centrally Authorised Products (CAP) only. PRAC recommendations will specify the products concerned in case of any regulatory action required

Summary of recommendation(s)

- The MAHs for the aflibercept-containing medicinal products intravitreal injections Eylea and Yesafili, should submit to EMA, within 60 days, a cumulative review of all cases of renal toxicity (e.g. using SMQ broad 'acute renal failure') from clinical trials, the post-marketing setting, and the literature, discussing also possible aetiologies for renal toxicity due to VEGF blockage, risk and confounding factors for each case along with a potential mechanism of action and non-clinical data as appropriate. The MAHs should also discuss the need for any potential amendment to the product information (PI) and/ or the risk management plan (RMP) as warranted.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.1.2. Axicabtagene ciloleucel – YESCARTA (CAP); idecabtagene vicleucel – ABECMA (CAP); lisocabtagene maraleucel – BREYANZI (CAP); ciltabtagene autoleucel – CARVYKTI (CAP); tisagenlecleucel – KYMRIAH (CAP); brexucabtagene autoleucel – TECARTUS (CAP)

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

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of secondary malignancy of T-cell origin

EPITT 20040 – 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 secondary malignancy of T-cell origin was identified by EMA, based on 23 cases retrieved from EudraVigilance for Yescarta (axicabtagene ciloleucel), Abecma (idecabtagene vicleucel), Breyanzi (lisocabtagene maraleucel), Carvykti (ciltacabtagene autoleucel), Kymriah (tisagenlecleucel). The Rapporteurs confirmed that the signal needed initial analysis and prioritisation by PRAC.

Discussion

Having considered the available evidence from case reports in EudraVigilance, PRAC agreed that further evaluation on the signal of secondary malignancy of T-cell origin following administration of CAR-T cell products is warranted.

PRAC appointed Ulla Wändel Liminga as lead Rapporteur for the signal.

Summary of recommendation(s)

- The MAHs for Yescarta (axicabtagene ciloleucel), Abecma (idecabtagene vicleucel), Breyanzi (lisocabtagene maraleucel), Carvykti (ciltabtagene autoleucel), Kymriah (tisagenlecleucel) and Tecartus (brexucabtagene autoleucel) should submit to EMA, within 30 days, a cumulative review of the signal, including an analysis of all case reports from the literature, data from spontaneous reports and reports from studies

presenting cases of T-cell lymphoma/leukaemia/lymphoproliferative disorders (data lock point: 11 January 2024) with at least the following search terms: HLGT Lymphomas non-Hodgkin's T-cell; HLT Leukaemias chronic T-cell, PT T-cell type acute leukaemia, PT Lymphoproliferative disorder, PT Lymphocytic leukaemia. In addition, the MAHs should specifically provide the cumulative exposure for each substance by region and EU Member State, causality assessment, information on the background occurrence stratified by indications, discussion on causality and possible mechanism of actions including risk for insertional mutagenesis and/or other mechanisms. The MAHs should also discuss the need for any potential amendment to the product information (PI) and/ or the risk management plan (RMP) or educational material, as well as other measures such as direct healthcare professional communication (DHPC) as warranted.

- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.2. New signals detected from other sources

See also Annex I 14.2.

4.2.1. Baricitinib – OLUMIANT (CAP)

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Signal of hypoglycaemia in diabetic patients

EPITT 20038 – 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 hypoglycaemia in diabetic patients was identified by EMA, based on data from clinical trial conducted by *Waibel M et al*[6] and on literature publications by *van Lint JA et al* [7], *Fujita Y et al*[8], as well as on 17 cases retrieved from EudraVigilance. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by PRAC.

Discussion

Having considered the available evidence from case reports in EudraVigilance, the literature and in the study by *Waibel et al* as well as the labelled hypoglycaemic effect in the class of JAK inhibitors, PRAC agreed that further evaluation on the signal hypoglycaemia in diabetic patients following treatment with baricitinib is warranted.

[6] Waibel M, Wentworth JM, So M, Couper JJ, Cameron FJ, MacIsaac RJ, et al. Baricitinib and β-Cell Function in Patients with New-Onset Type 1 Diabetes. N Engl J Med 2023;389:2140–50. https://doi. org/10.1056/NEJMoa2306691
[7] van Lint JA, van Hunsel FPAM, Tas SW, Vonkeman HE, Hoentjen F, van Doorn MBA, et al. Hypoglycaemia following JAK inhibitor treatment in patients with diabetes. Ann Rheum Dis 2022;81:597– 9. https://doi.org/10.1136/annrheumdis-2021-221840
[8] Fujita Y, Nawata M, Nagayasu A, Someya K, Saito K, Tanaka Y. Fifty-Two-Week Results of Clinical and Imaging Assessments of a Patient with Rheumatoid Arthritis Complicated by Systemic Sclerosis with Interstitial Pneumonia and Type 1 Diabetes despite Multiple Disease-Modifying Antirheumatic Drug Therapy That Was Successfully Treated with Baricitinib: A Novel Case Report. Case Rep Rheumatol 2019;2019:5293981. https://doi.org/10.1155/2019/5293981

Summary of recommendation(s)

- The MAH for Olumiant (baricitinib) should submit to EMA, within 60 days, a cumulative review of cases of hypoglycaemia in diabetic patients, including an overview of patients treated with baricitinib currently on insulin therapy or other anti-diabetic medicinal products, considering the time to onset to hypoglycaemia, as well as any changes to their medications. The MAH should also discuss the effect and mechanism of action of baricitinib revealed in the *Waibel et al* study. Finally, the MAH should also discuss the need for any potential amendment to the product information (PI) and/ or the risk management plan (RMP), as warranted.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.2.2. Canagliflozin – INVOKANA (CAP); Dapagliflozin – EDISTRIDE (CAP), FORXIGA (CAP), NAP; Empagliflozin – JARDIANCE (CAP); Empagliflozin, metformin – SYNJARDY (CAP), NAP

Applicant(s): AstraZeneca AB (Forxiga, Edistride), Boehringer Ingelheim International GmbH (Jardiance, Synjardy), Janssen-Cilag International N.V. (Invokana), various

PRAC Rapporteur: Mari Thorn

Scope: Signal of polycythaemia

EPITT 20019 – 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.

Following the publication by *Gangat N, et al.*[9], a signal of polycythaemia was identified by EMA during routine signal detection activities, as well as based on 20 cases retrieved from EudraVigilance. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by PRAC.

Discussion

Having considered the available evidence from case reports in the literature and the EudraVigilance, PRAC agreed that further evaluation on the signal of polycythaemia is warranted for dapagliflozin-containing medicinal products.

PRAC also agreed that the information included in the product information[10] on haematocrit increase of canagliflozin- and empagliflozin-containing medicinal products is sufficient, thus a further review in this case is not warranted.

PRAC appointed Mari Thorn as Rapporteur for the signal.

Summary of recommendation(s)

[9] Gangat N, Alkhateeb H, Reichard K, Tefferi A. Sodium-glucose co-transporter-2 inhibitor therapy and unmasking of JAK2-mutated myeloproliferative neoplasm: A Mayo Clinic series of nine consecutive cases. Am J Hematol. 2023 Oct;98(10):E276-E280. doi: 10.1002/ajh.27034. Epub 2023 Jul 20. PMID: 37470368
[10] Sections 4.4 and 4.8 of the SmPC

- In the context of the ongoing PSUR[11], the MAH of Forxiga and Edistride, centrally authorised medicines containing dapagliflozin should submit to EMA a cumulative review of cases of polycythaemia, including data from the published literature, from spontaneous reports and reports from studies, as well as a discussion on possible biological plausibility and mechanism of this association. In addition, the MAH, should discuss the need to strengthen the wording in the product information[12] to reflect that close monitoring and investigation in patients with elevated haematocrit is warranted. Regarding the canagliflozin and empagliflozin- containing products, PRAC agreed that the information regarding the haematocrit increase in the product information is sufficient, therefore no further reviews are needed.
- PRAC will assess the cumulative review within the PSUR procedure PSUSA/00010029/202310.

4.3. Signals follow-up and prioritisation

4.3.1. Amphotericin B (NAP)

Applicant(s): various

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Signal of hyperkalaemia

EPITT 19966 – Follow-up to September 2023

Background

For background information, see PRAC minutes September 2023.

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

Discussion

Having considered the available evidence in EudraVigilance, literature and responses submitted by the MAHs, PRAC agreed that no further action is deemed warranted at this stage for amphotericin B as non-lipid formulations, as the product information already includes information about hyperkalaemia. However, PRAC agreed that the product information for amphotericin B as lipid formulations should be amended to add hyperkalaemia as a warning and an undesirable effect with frequency 'common', as applicable, taking into account the already existing wording in some nationally authorised medicinal products.

Summary of recommendation(s)

- The MAHs for amphotericin B-containing medicinal products as lipid formulations i.e. AmBisome 50mg, powder for dispersion for infusion and Abelcet 5mg/ml concentrate for suspension for infusion should submit to EMA, within 60 days, a variation to amend[13] the product information.

[11] Submission date: 13 December 2023
[12] Section 4.4 of the SmPC
[13] Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly.

For the full PRAC recommendation, see EMA/PRAC/2748/2024 published on 05 February 2024 on the EMA website.

4.3.2. Avatrombopag – DOPTELET (CAP) – EMEA/H/C/004722/SDA/006

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Monica Martinez Redondo

Scope: Signal of antiphospholipid syndrome

EPITT 19954 – Follow-up to September 2023

Background

For background information, see PRAC minutes September 2023.

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

Discussion

Having considered the available evidence in EudraVigilance, literature and the responses submitted by the MAH, PRAC agreed that there is insufficient evidence to establish a causal relationship between Doptelet (avatrombopag) and antiphospholipid syndrome; however, it was considered warranted to advise about the possible increase in the risk of thrombotic events in patients with antiphospholipid syndrome. Therefore, the product information for Doptelet (avatrombopag) should be amended to add a warning on acquired risk factors (e.g. antiphospholipid syndrome).

Summary of recommendation(s)

- The MAH for Doptelet (avatrombopag) should submit to EMA, within 60 days, a variation to amend[14] the product information.
- In the next PSUR, the MAH should monitor the topics of antiphospholipid syndrome /catastrophic antiphospholipid syndrome including all cases under the MedDRA HLGT 'Autoimmune disorders', 'Embolism and thrombosis', 'Coagulopathies and bleeding diatheses (excluding thrombocytopenic)' and 'Immune system disorders' that could be related to antiphospholipid syndrome according to the recently released 2023 American College of Rheumatology (ACR) and European Alliance of Associations for Rheumatology (EULAR) antiphospholipid syndrome classification criteria.

For the full PRAC recommendation, see EMA/PRAC/2748/2024 published on 05 February 2024 on the EMA website.

4.3.3. Cefotaxime (NAP)

Applicant(s): various

PRAC Rapporteur: Sonja Hrabcik

Scope: Signal of drug reaction with eosinophilia and systemic symptoms (DRESS)

EPITT 19960 – Follow-up to September 2023

[14] Update of SmPC section 4.4. The package leaflet is updated accordingly.

Background

For background information, see PRAC minutes September 2023.

The MAH(s) replied to the request for information on the signal of DRESS and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence in EudraVigilance, literature and the responses submitted by the MAH(s), PRAC agreed that there is sufficient evidence to establish a causal relationship between cefotaxime and DRESS. Therefore, the product information for cefotaxime-containing medicinal products should be amended to add DRESS as an undesirable effect with frequency 'not known' as well as a warning on severe cutaneous adverse reactions (SCARs) including acute generalized exanthematous pustulosis (AGEP), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and DRESS as applicable, taking into account the already existing wording in some nationally authorised products.

Summary of recommendation(s)

- The MAHs for cefotaxime-containing medicinal products should submit to EMA, within 60 days, a variation to amend[15] the product information.

For the full PRAC recommendation, see EMA/PRAC/2748/2024 published on 05 February 2024 on the EMA website.

4.3.4. Cobimetinib – COTELLIC (CAP) - EMEA/H/C/003960/SDA/006; Vemurafenib – ZELBORAF (CAP) - EMEA/H/C/002409/SDA/039

Applicant: Roche Registration GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of aphthous ulcer, mouth ulceration, stomatitis

EPITT 19961 – Follow-up to September 2023

Background

For background information, see PRAC minutes September 2023.

The MAH replied to the request for information on the signal of aphthous ulcer, mouth ulceration, stomatitis and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence in EudraVigilance, clinical studies and the literature, as well as the responses submitted by the MAH, PRAC agreed there is sufficient evidence to establish a causal relationship between aphthous ulcer, mouth ulceration, stomatitis and treatment with cobimetinib and vemurafenib administered in combination. Therefore, the product information for Cotellic (cobimetinib) and Zelboraf (vemurafenib) should be amended to add stomatitis as an undesirable effect with frequency 'very common' and 'common' respectively.

Summary of recommendation(s)

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

- The MAH for Cotellic (cobimetinib) and Zelboraf (vemurafenib) should submit to EMA, within 60 days, a variation to amend[16] the product information.

For the full PRAC recommendation, see EMA/PRAC/2748/2024 published on 05 February 2024 on the EMA website.

4.4. Variation procedure(s) resulting from signal evaluation

None

5. Risk management plans (RMPs)

5.1. Medicines in the pre-authorisation phase

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

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

See also Annex I 15.1.

5.1.1. Efanesoctocog alfa - EMEA/H/C/005968, Orphan

Applicant: Swedish Orphan Biovitrum AB (publ)

Scope: Treatment and prophylaxis of bleeding in patients with haemophilia A

5.1.2. Sotatercept - EMEA/H/C/005647, PRIME, Orphan

Applicant: Merck Sharp & Dohme B.V.

Scope: treatment of pulmonary arterial hypertension in adults

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

See Annex I 15.2.

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

See also Annex I 15.3.

5.3.1. Denosumab - PROLIA (CAP) - EMEA/H/C/001120/II/0099

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Mari Thorn

Scope: Update of sections 4.4 and 4.8 of the SmPC in order to update a warning regarding hypocalcaemia and to include reports of life-threatening events and fatal cases occurred in

[16] Update of SmPC section 4.8. The package leaflet is updated accordingly.

the post marketing setting, particularly in patients with severe renal impairment, receiving dialysis or treatment with other calcium lowering drugs based on the cumulative review of MAH safety database and literature. The package leaflet (PL) is updated accordingly. The RMP version 32.0 has also been submitted

Background

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

CHMP is evaluating a type II variation for Prolia, a centrally authorised product containing denosumab, to update the product information in order to amend the warning regarding hypocalcaemia and to update the important identified risk 'hypocalcaemia' and to include reports of life-threatening events and fatal cases particularly in patients with severe renal impairment, receiving dialysis or treatment with other calcium lowering drugs. PRAC is responsible for providing advice to CHMP on the necessary updates to the RMP to support this procedure. For further background, see PRAC minutes November 2023.

Summary of advice

- The RMP version 32.0 for Prolia (denosumab) in the context of the variation under evaluation by CHMP is not considered acceptable. Therefore, RMP version 31.0 remains as the latest approved.
- PRAC agreed that hypocalcaemia continues to be a serious safety concern following treatment with denosumab. However, since the risk of hypocalcaemia with denosumab is well-known and measurements of serum calcium is recommended in all patients before each dose and in patients predisposed to hypocalcaemia also within 2 weeks after the first dose, PRAC considered that the effectiveness of extended monitoring of calcium levels in all patients as a measure to decrease the number of serious events of hypocalcaemia is questionable and that the present data might not be sufficient to justify increased monitoring of serum calcium. Therefore, PRAC agreed that only minor changes are needed to the product information in order to update the existing warning regarding hypocalcaemia and to include reports of life-threatening events and fatal cases occurred in the post marketing setting. Finally, PRAC noted that the issue will be further addressed as part of the separate procedure (EMEA/H/C/001120/II/0100) assessing the final results of the post marketing observational study 20090522, listed as a category 3 study in the RMP.

6. Periodic safety update reports (PSURs)

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

See also Annex I 16.1.

6.1.1. Binimetinib - MEKTOVI (CAP) - PSUSA/00010717/202306

Applicant: Pierre Fabre Medicament

PRAC Rapporteur: Carla Torre

Scope: Evaluation of a PSUSA procedure

Background

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

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Mektovi, a centrally authorised medicine containing binimetinib 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 Mektovi (binimetinib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include tumour lysis syndrome as a warning and as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[17].
- In the next PSUR, the MAH should provide a cumulative review of cases of stomatitis and ulceration associated with use of binimetinib, including data from clinical trials, post-marketing reports and scientific literature, and discuss a possible biological plausibility and mechanism, as well as the need to update the product information if warranted.

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

6.1.2. Elasomeran (Spikevax), elasomeran, imelasomeran (Spikevax bivalent Original/Omicron BA.1), elasomeran, davesomeran (Spikevax bivalent Original/Omicron BA.4-5), andusomeran (Spikevax XBB.1.5) - SPIKEVAX (CAP) - PSUSA/00010897/202306

Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Evaluation of a PSUSA procedure

Background

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

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Spikevax elasomeran (Spikevax), elasomeran, imelasomeran (Spikevax bivalent Original/Omicron BA.1), elasomeran, davesomeran (Spikevax bivalent Original/Omicron BA.4-5), andusomeran (Spikevax XBB.1.5)), a centrally authorised medicine and issued a recommendation on their marketing authorisation(s).

[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 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 Spikevax (elasomeran (Spikevax), elasomeran, imelasomeran (Spikevax bivalent Original/Omicron BA.1), elasomeran, davesomeran (Spikevax bivalent Original/Omicron BA.4-5), andusomeran (Spikevax XBB.1.5)) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add chronic urticaria as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[18].
- In the next PSUR, the MAH should provide a cumulative review of autoimmune hepatitis with elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran or andusomeran, including data from literature, spontaneous case reports, clinical trials and non-interventional studies, as well as a causality assessment of cases, and discuss a potential mechanism of action and the need for an update of the product information, if warranted. The MAH should also comment on the publication by *Premec H et al*[19] concerning the potential risk of secondary hemophagocytic lymphohistiocytosis (sHLH), including a discussion on the potential mechanism of action. The MAH should also comment on the publications by *Tv P et al*[20] and *Gómez-Moyano E et al*[21] concerning the potential risk of postural orthostatic tachycardia syndrome (POTS), including a discussion on the potential mechanism of action.

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. Encorafenib - BRAFTOVI (CAP) - PSUSA/00010719/202306

Applicant: Pierre Fabre Medicament

PRAC Rapporteur: Rugile Pilviniene

Scope: Evaluation of a PSUSA procedure

Background

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

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

[19] Premec H, Živko M, Mijić M, Jelić-Puškarić B, Lalovac M, Filipec Kanižaj T, Sobočan N. Acute Liver Failure Caused by Secondary Hemophagocytic Lymphohistiocytosis After COVID-19 Vaccination - Case Report and Literature Review. Int Med Case Rep J. 2023 Aug 7;16:449-455. doi: 10.2147/IMCRJ.S417347. PMID: 37577009; PMCID: PMC10416787

[20] Tv P, Tran TT, Hao HT, Hau NTH, Jain N, Reinis A. Postural orthostatic tachycardia syndrome-like symptoms following COVID-19 vaccination: An overview of clinical literature. Hum Antibodies. 2023;31(1-2):9-17. doi: 10.3233/HAB-220013. PMID: 37248893; PMCID: PMC10357168

[21] Gómez-Moyano E, Rodríguez-Capitán J, Gaitán Román D, Reyes Bueno JA, Villalobos Sánchez A, Espíldora Hernández F, González Angulo GE, Molina Mora MJ, Thurnhofer-Hemsi K, Molina-Ramos AI, Romero-Cuevas M, Jiménez-Navarro M, Pavón-Morón FJ. Postural orthostatic tachycardia syndrome and other related dysautonomic disorders after SARS-CoV-2 infection and after COVID-19 messenger RNA vaccination. Front Neurol. 2023 Aug 16;14:1221518. doi: 10.3389/fneur.2023.1221518. PMID: 37654428; PMCID: PMC10467287

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Braftovi, a centrally authorised medicine containing encorafenib 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 Braftovi (encorafenib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include tumour lysis syndrome as a warning and as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[22].
- In the next PSUR, the MAH should provide a cumulative review of cases of stomatitis and ulceration associated with use of encorafenib, including data from clinical trials, post-marketing reports and scientific literature, and discuss a possible biological plausibility and mechanism, as well as the need to update the product information if 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. Fenfluramine - FINTEPLA (CAP) - PSUSA/00010907/202306

Applicant: UCB Pharma SA

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

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

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Fintepla, a centrally authorised medicine containing fenfluramine 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 Fintepla (fenfluramine) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the current warning on valvular heart disease and pulmonary arterial hypertension and to add pulmonary arterial hypertension as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[23].

[22] 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
[23] Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly. Annex II D -Conditions or restrictions with regard to the safe and effective use of the medicinal product is also updated. PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion

- In the next PSUR, the MAH should provide a cumulative review of cases of growth retardation along with data provided within the register, including a discussion on the need for an update of the product information and/or RMP. The MAH should also provide a cumulative review of cases of insomnia following treatment with fenfluramine in patients with Lennox Gastaut syndrome (LGS), including a causality assessment.

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. Fluciclovine (^{18}F) - AXUMIN (CAP) - PSUSA/00010594/202305

Applicant: Blue Earth Diagnostics Ireland Limited

PRAC Rapporteur: Rugile Pilviniene

Scope: Evaluation of a PSUSA procedure

Background

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

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Axumin, a centrally authorised medicine containing fluciclovine (^{18}F) 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 Axumin (fluciclovine (^{18}F) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- The MAH should submit to EMA, within 4 months, a cumulative review of case reports of PET imaging interpretation errors with a particular focus on false positive and false negative results, as well as a discussion of related literature and any further evidence available as part of a post-authorisation measure. In addition, data on the implementation of the self-training programme in the EU member states should be provided. Based on the above, a discussion should be provided on whether the data warrants further regulatory action.

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. Follitropin beta - PUREGON (CAP) - PSUSA/00001465/202305

Applicant: Organon N.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

Background

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

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Puregon, a centrally authorised medicine containing follitropin beta 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 Puregon (follitropin beta) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add the anaphylactic reaction as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[24].

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

6.1.7. Hydroxycarbamide[25] - SIKLOS (CAP); XROMI (CAP) - PSUSA/00001692/202306

Applicant: Theravia (Siklos), Nova Laboratories Ireland Limited (Xromi)

PRAC Rapporteur: Jo Robays

Scope: Evaluation of a PSUSA procedure

Background

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

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Siklos and Xromi, centrally authorised medicines containing hydroxycarbamide 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 Siklos and Xromi (hydroxycarbamide) 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 a cumulative review of cases of myelodysplastic syndrome, including data from clinical trials and relevant literature, including a causality assessment.

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.

[24] Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion
[25] For centrally authorised product only

6.1.8. Ixazomib - NINLARO (CAP) - PSUSA/00010535/202305

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

Background

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

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Ninlaro, a centrally authorised medicine containing ixazomib and issued a recommendation on its marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Ninlaro (ixazomib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include toxic epidermal necrolysis as a warning and as an undesirable effect with a frequency 'rare'. In addition, the product information should be updated to add anaphylactic reaction and angioedema as undesirable effects with frequency 'rare'. Therefore, the current terms of the marketing authorisation(s) should be varied[26].
- In the next PSUR, the MAH should provide a cumulative review of cases of arthralgia, pyrexia and fatigue after treatment initiation, from all relevant sources, including a causality assessment, and a discussion on the need for an update of the product information, if 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. The frequency of submission of the subsequent PSURs should be changed from 6-monthly to two-yearly and the list of Union reference dates (EURD list) will be updated accordingly.

6.1.9. Lumacaftor, ivacaftor - ORKAMBI (CAP) - PSUSA/00010455/202305

Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Eamon O'Murchu

Scope: Evaluation of a PSUSA procedure

Background

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

[26] 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 Orkambi, a centrally authorised medicine containing lumacaftor/ivacaftor 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 Orkambi (lumacaftor/ivacaftor) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add depression as a warning and as an undesirable effect with a frequency 'not known'. In addition, the product information should be updated to amend the existing wording regarding breastfeeding. Therefore, the current terms of the marketing authorisation(s) should be varied[27].
- In the next PSUR, the MAH should provide a cumulative review of cases of acute pancreatitis, including data from literature, post-marketing setting and clinical trials, along with a discussion on the need for an update of the product information, as warranted. In addition, the MAH should provide a review of cases of anaphylaxis and discuss the need for an update of the product information, if warranted, as well as a review of cases of cataract and related terms in the infant following both in utero exposure, and exposure via breastfeeding to cystic fibrosis transmembrane conductance regulator (CTFR) modulators including Orkambi.

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.

6.1.10. Mosunetuzumab - LUNSUMIO (CAP) - PSUSA/00010999/202306

Applicant: Roche Registration GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

Background

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

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Lunsumio, a centrally authorised medicine containing mosunetuzumab 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 Lunsumio (mosunetuzumab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include haemophagocytic lymphohistiocytosis (HLH) as a warning and as an undesirable effect with a frequency

[27] Update of SmPC sections 4.4, 4.6 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion

'uncommon' (both for all grades, and grade 3-4). Therefore, the current terms of the marketing authorisation(s) should be varied[28].

- In the next PSUR, the MAH should provide a cumulative review of ICANS and related cases. The case narratives with causality assessment should be also submitted, provide case narratives and causality assessment of these cases (and other cases if identified) in the next PSUR, action with mosunetuzumab treatment should be taken in case of HLH. It is obvious that treatment must be interrupted following suspicion/diagnosis of HLH; however, having considered the seriousness of the disease, it is not clear whether treatment should/must be discontinued permanently.

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.

6.1.11. Onasemnogene abeparvovec - ZOLGENSMA (CAP) - PSUSA/00010848/202305

Applicant: Novartis Europharm Limited, ATMP

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

Background

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

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Zolgensma, a centrally authorised medicine containing onasemnogene abeparvovec 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 Zolgensma (onasemnogene abeparvovec) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the existing information on hepatotoxicity and on an increased risk of AST and/or ALT elevation and thrombocytopenia observed in children weighing ≥ 8,5 kg to ≤ 21 kg compared to children < 8.5 kg, as well as about the fact that thrombocytopenia may occur within 3 weeks of administration, and to update the frequency of thrombotic microangiopathy (TMA) and acute hepatic failure as undesirable effects to 'uncommon'. Therefore, the current terms of the marketing authorisation(s) should be varied[29].
- In the next PSUR, the MAH should provide a cumulative review of cases of TMA, including data from literature, clinical trials and registries, along with a causality assessment and a discussion on the potential association between with age/weight and TMA.

[28] 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
[29] Update of SmPC sections 4.4 and 4.8. The package leaflet and Annex II-D are updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion

- The MAH should submit to EMA, within 60 days, the final reports from two studies on germline transduction, including a discussion on the need to update the product information, if warranted.
- The MAH should also revise the available follow up questionnaires (FUQs) with the aim of simplifying them, in the next RMP update submitted within an upcoming regulatory procedure affecting the RMP or at the latest by April 2023.

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.

6.1.12. Ozanimod - ZEPOSIA (CAP) - PSUSA/00010852/202305

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

Background

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

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Zeposia, a centrally authorised medicine containing ozanimod 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 Zeposia (ozanimod) in the approved indication(s) remains unchanged.
- Nevertheless, the product information (leaflet) and the educational material (patient/caregiver's guide) should be updated to include symptoms of severe liver injury. Therefore, the current terms of the marketing authorisation(s) should be varied[30].
- In the next PSUR, the MAH should provide cumulative reviews of cases of atrioventricular block, and discuss the need for an update of the product information, if warranted. In addition, the MAH should thoroughly discuss new cases of symptomatic bradycardia occurring after the initial dose escalation regimen. In addition, the MAH should provide a review of cases under SMQ[31] hepatic disorder, the sub-SMQ drug related hepatic disorders severe events only and the preferred term 'acute hepatic failure', with an active search for cases in which hepatic transplant is mentioned. Additionally, the MAH should provide a review of cases of basal cell carcinoma and melanoma, together with a critical appraisal and contextualisation in patients with multiple sclerosis and ulcerative colitis. Finally, the MAH should provide a review of

[30] Update of package leaflet and Annex II-D. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion
[31] Standardised MedDRA Queries

cases of alopecia and discuss whether an update of the product information is warranted.

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

6.1.13. Semaglutide - OZEMPIC (CAP); RYBELSUS (CAP); WEGOVY (CAP) - PSUSA/00010671/202305

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Mari Thorn

Scope: Evaluation of a PSUSA procedure

Background

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

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Ozempic, Rybelsus and Wegovy, centrally authorised medicines containing semaglutide 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 Ozempic, Rybelsus and Wegovy in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add intestinal obstruction as an undesirable effect with a frequency 'not known' and to include a drug-drug interaction between semaglutide and other coumarin derivatives. Therefore, the current terms of the marketing authorisation(s) should be varied[32].
- In the next PSUR, the MAH should provide cumulative reviews of cases of altered skin sensation following treatment with Rybelsus and of cases of hair loss for Ozempic and Rybelsus from post-marketing data. The MAH should also provide a cumulative review of cases of psychosis and psychotic disorders following concomitant treatment with semaglutide and antiparkinsonian medicines. In addition, the MAH should discuss the outcome of the mitigating actions related to the medication errors with Wegovy. Finally, the MAH, similar to other MAHs for GLP-1 agonists, should continue to closely monitor cases of thyroid cancer as part of routine pharmacovigilance and/or in the ongoing category 3 PASS studies in RMPs as relevant and report any new evidence on the association as part of their PSUR submissions.

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.

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

6.1.14. Sunitinib - SUTENT (CAP) - PSUSA/00002833/202304

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

Background

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

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Sutent, a centrally authorised medicine containing sunitinib 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 Sutent (sunitinib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include hyperammonaemic encephalopathy as a warning and as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[33].
- In the next PSUR, the MAH should provide a review of cases indicative of hearing loss, including a discussion on potential association with sunitinib treatment, as well as a review of cases of interaction between sunitinib and low molecular weight heparin (LMWH) and of hyperglycaemia, including a discussion on the need for an update of the product information. The MAH should also provide cumulative reviews of cases of retinal detachment, osteonecrosis regardless of location (hip, eardrum) apart from osteonecrosis of the jaw, skin neoplasms with a focus on basal cell carcinoma/ cutaneous squamous cell carcinoma, including data from clinical trials, post-marketing setting and scientific literature, and discuss whether a need for an update of the product information is warranted.

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

6.1.15. Trametinib - MEKINIST (CAP) - PSUSA/00010262/202305

Applicant: Novartis Europharm Limited

PRAC Rapporteur: David Olsen

Scope: Evaluation of a PSUSA procedure

Background

[33] 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

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

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Mekinist, a centrally authorised medicine containing trametinib 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 Mekinist (trametinib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include atrioventricular block as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[34].
- In the next PSUR, the MAH should provide a cumulative review of cases of QT prolongation and related terms, and cases presenting syncope for trametinib, and dabrafenib mono- and combination therapy, including data from clinical trials, post-marketing reports and scientific literature, and discuss a possible biological plausibility and mechanism, as well as the need to update the product information if warranted.

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

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

See also Annex I 16.2.

6.2.1. Fentanyl[35] - EFFENTORA (CAP); INSTANYL (CAP); PECFENT (CAP); NAP - PSUSA/00001369/202304

Applicant: Teva B.V. (Effentora), Takeda Pharma A/S (Instanyl), Kyowa Kirin Holdings B.V. (PecFent), various

PRAC Rapporteur: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

Background

Fentanyl is an opioid indicated for the treatment of breakthrough pain (BTP) in adults with cancer who are already receiving maintenance opioid therapy for chronic cancer pain.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of Effentora, Instanyl and Pecfentora, (a) centrally authorised medicine(s) containing fentanyl,

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

and nationally authorised medicines containing fentanyl[36] 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 fentanyl[37]-containing product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated in order to further minimise the risk of opioid use disorder (OUD), including by adding drug tolerance as an undesirable effect with a frequency 'not known'. Moreover, the product information should be updated to add a warning regarding the storage in a safe and secure place. In addition, the product information should be updated to add toxic leukoencephalopathy as a possible symptom of fentanyl overdose. Therefore, the current terms of the marketing authorisations should be varied[38].
- In the next PSUR, the MAH(s) should provide a detailed analysis on effectiveness of RMMs including aRMMs and comment on any further action, if necessary. Moreover, the MAH(s) should continue to closely monitor cases of cardiac arrhythmia (including cardiac arrest), interaction between fentanyl and muscle relaxants, amnesia, accidental exposure following product appearance (confusion) with fentanyl nasal sprays.

In view of available data on off-label use and opioid use disorders, including literature cases and high reporting rates of these risks in the EU, all MAHs for fentanyl-containing products[39] are encouraged to implement QR codes in the package leaflet and on the outer packaging in order to promote the use of the additional risk minimisation material for patients which has been approved by NCAs as outlined in the respective risk management plans. URL and QR codes could link to a website where the educational materials can be available and downloaded, as approved and according to national policies. The implementation of URL and QR codes should be performed in agreement with the NCAs and national requirements.

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.

6.2.2. Mycophenolate mofetil- CELLCEPT (CAP); MYCLAUSEN (CAP); MYCOPHENOLATE MOFETIL TEVA (CAP); MYFENAX (CAP); NAP; mycophenolic acid (NAP) - PSUSA/00010550/202305

Applicant: Roche Registration GmbH (CellCept), Passauer Pharma GmbH (Myclausen), Teva B.V. (Mycophenolate mofetil Teva, Myfenax), various

PRAC Rapporteur: Karin Erneholm

Scope: Evaluation of a PSUSA procedure

Background

Mycophenolate mofetil is a prodrug of mycophenolic acid, a cytostatic and immunosuppressive agent acting as a potent inhibitor of de novo synthesis of purines

[36] Transmucosal route of administration
[37] Transmucosal route of administration
[38] Update of SmPC sections 4.2, 4.4, 4.8 and 4.9. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion
[39] Transmucosal route of administration

essential for T- and B-cell proliferation. Mycophenolate mofetil or mycophenolic acid in combination with corticosteroids and either ciclosporin A or tacrolimus is indicated for the prophylaxis of acute organ rejection and for the treatment of first or refractory organ rejection in patients receiving allogeneic renal transplant, for the prophylaxis of acute organ rejection in patients receiving allogeneic cardiac transplants as well as for the prophylaxis of acute organ rejection in patients receiving allogeneic hepatic transplants.

Based on the assessment of the PSURs, PRAC reviewed the benefit-risk balance of Cellcept, Myclausen, Mycophenolate Mofetil Teva and Myfenax, centrally authorised medicines containing mycophenolate mofetil, as well as nationally authorised medicines containing mycophenolate mofetil or mycophenolic acid, and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of mycophenolate mofetil- and mycophenolic acid-containing product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the existing wording regarding breastfeeding, mentioning that limited data show that mycophenolic acid is excreted in human milk. Therefore, the current terms of the marketing authorisations should be varied[40].
- In the next PSUR, the MAHs(s) should provide a cumulative review of cases of alveolar proteinosis, including data from clinical trials, post-marketing setting and scientific literature, along with a discussion on the possible biological mechanism and on the need for an update of the product information, as warranted. The MAH(s) should provide a cumulative review on breastfeeding from all sources, including data from clinical trials, spontaneous reports and scientific literature and discuss the need for an update of the product information, as warranted. In addition, the MAHs for products containing mycophenolic acid should provide a cumulative review of cases concerning the risk of convulsions, including data from literature and other sources of information and discuss whether an update of the product information is warranted.

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

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

See also Annex I 16.3.

6.3.1. Ceftriaxone (NAP) - PSUSA/00000613/202305

Applicant(s): various

PRAC Lead: Zane Neikena

Scope: Evaluation of a PSUSA procedure

[40] Update of SmPC section 4.6. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion

Background

Ceftriaxone is a beta-lactam antibacterial, a third-generation cephalosporin, indicated for the treatment of various infections in adults and children, including bacterial meningitis, community or hospital acquired pneumonia, acute otitis media, intra-abdominal infections, complicated urinary tract infections, bone and joint infections, and complicated skin and soft tissue infections.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing ceftriaxone 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 ceftriaxone-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add Kounis syndrome as a warning and as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[41].
- In the next PSUR, the MAH(s) should provide a discussion on the signal of acute cholecystitis and formation of biliary sludge/biliary lithiasis following ceftriaxone administration, including a discussion on the plausible mechanism of action and discuss the need for an update of the product information, as warranted. The MAH(s) should also provide a review of cases of drug-drug interaction between ceftriaxone and theodrenaline/cafedrine causing precipitation, including data from scientific literature and post-marketing reports, and discuss a possible pharmacological mechanism.

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

6.3.2. Gadobenic acid (NAP) - PSUSA/00001500/202304

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

Gadobenic acid is a linear gadolinium-based contrast agent (GdCA) indicated for use in diagnostic magnetic resonance imaging (MRI) of the liver, only when diagnostic information is essential and not available with unenhanced MRI and when delayed phase imaging is required.

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

[41] 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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of gadobenic acid-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a warning mentioning that gadobenic acid must not be administered intrathecally. In addition, the existing wording on product information should be amended in order to reflect that data on the use of gadobenic acid in pregnant women is limited and it is unknown whether exposure to gadolinium is associated with adverse effects in the infant. Therefore, the current terms of the marketing authorisation(s) should be varied[42].
- In the next PSUR, the MAH(s) should provide a review of all available data on the use of gadolinium-based contrast agents during pregnancy, including non-clinical data, as well as an evaluation whether gadolinium is retained in the foetus after maternal exposure and whether there are any differences between active substances in this regard and discuss whether there is a need for an update of the product information. Moreover, the MAH(s) should provide a cumulative review of cases of gadolinium retention/accumulation of the infants, including outcomes of infants having been breastfed from mothers exposed to gadobenic acid, from scientific literature and post-marketing setting, and discuss whether an update of the product information is warranted. The MAH(s) should also provide an overview of the implementation of the targeted follow-up questionnaire regarding potential long-term symptoms, accompanied by an evaluation on its effectiveness to gather more detailed information on relevant cases and, based on the outcome of the evaluation, the MAH(s) should discuss the usefulness of continuation of the follow-up questionnaire or the need for any improvements, as appropriate.

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. Gadobutrol (NAP) - PSUSA/00001502/202304

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

Gadobutrol is a macrocyclic gadolinium-based contrast agent (GdCA) indicated for diagnostic magnetic resonance imaging (MRI) of the whole body, including cranial and spinal MRI, head and neck, thoracic space, breast, abdomen, pelvis, retroperitoneal space, musculoskeletal system, magnetic resonance angiography and cardiac MRI.

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

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of gadobutrol-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a warning mentioning that gadobutrol must not be administered intrathecally. In addition, the existing wording on product information should be amended in order to reflect that data on the use of gadobutrol in pregnant women is limited and it is unknown whether exposure to gadolinium is associated with adverse effects in the infant. Therefore, the current terms of the marketing authorisation(s) should be varied[43].
- In the next PSUR, the MAH(s) should provide a review of all available data on the use of gadolinium-based contrast agents during pregnancy, including non-clinical data, as well as an evaluation whether gadolinium is retained in the foetus after maternal exposure and whether there are any differences between active substances in this regard and discuss whether there is a need for an update of the product information. Moreover, the MAH(s) should provide a cumulative review of cases of gadolinium retention/accumulation of the infants, including outcomes of infants having been breastfed from mothers exposed to gadobutrol, from scientific literature and post-marketing setting, and discuss whether an update of the product information is warranted. The MAH(s) should also provide an overview of the implementation of the targeted follow-up questionnaire regarding potential long-term symptoms, accompanied by an evaluation on its effectiveness to gather more detailed information on relevant cases and, based on the outcome of the evaluation, the MAH(s) should discuss the usefulness of continuation of the follow-up questionnaire or the need for any improvements, as appropriate.

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. Gadopentetic acid (NAP) - PSUSA/00001504/202304

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

Gadopentetic acid is a linear gadolinium-contrast agent (GdCA) indicated for diagnostic magnetic resonance imaging (MRI) of the whole body, as well as cranial and spinal MRI. It is also indicated for contrast enhancement in magnetic resonance arthrography and for the demonstration and demarcation of the digestive tract from adjacent normal and pathological tissue structures in MRI, under certain conditions.

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

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing gadopentetic acid 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 gadopentetic acid-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a warning mentioning that gadopentetic acid must not be administered intrathecally. In addition, the existing wording on product information should be amended in order to reflect that data on the use of gadopentetic acid in pregnant women is limited and it is unknown whether exposure to gadolinium is associated with adverse effects in the infant. Therefore, the current terms of the marketing authorisation(s) should be varied[44].
- In the next PSUR, the MAH(s) should provide a review of all available data on the use of gadolinium-based contrast agents during pregnancy, including non-clinical data, as well as an evaluation whether gadolinium is retained in the foetus after maternal exposure and whether there are any differences between active substances in this regard and discuss whether there is a need for an update of the product information. Moreover, the MAH(s) should provide a cumulative review of cases of gadolinium retention/accumulation of the infants, including outcomes of infants having been breastfed from mothers exposed to gadopentetic acid, from scientific literature and post-marketing setting, and discuss whether an update of the product information is warranted. The MAH(s) should also provide an overview of the implementation of the targeted follow-up questionnaire regarding potential long-term symptoms, accompanied by an evaluation on its effectiveness to gather more detailed information on relevant cases and, based on the outcome of the evaluation, the MAH(s) should discuss the usefulness of continuation of the follow-up questionnaire or the need for any improvements, as appropriate.

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

6.3.5. Gadoteric acid[45] (NAP) - PSUSA/00001506/202304

Applicant(s): various

PRAC Lead: Bianca Mulder

Scope: Evaluation of a PSUSA procedure

Background

Gadoteric acid is a macrocyclic gadolinium-based contrast agent (GdCA) indicated as intravenous and intravascular formulations for intensification of the contrast in magnetic resonance imaging (MRI) for a better visualisation/delineation of lesions of the brain, spine, and surrounding tissues, lesions of the liver, kidneys, pancreas, pelvis, lungs, heart, breast,

[44] Update of SmPC sections 4.4 and 4.6. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position
[45] IV and intravascular formulations

and musculoskeletal system in adults and paediatrics. It is also indicated for a better visualisation/delineation of lesions or stenoses of the non-coronary arteries in adults.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing gadoteric acid 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 gadoteric acid-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a warning mentioning that gadoteric acid must not be administered intrathecally. In addition, the existing wording on product information should be amended in order to reflect that data on the use of gadoteric acid in pregnant women is limited and it is unknown whether exposure to gadolinium is associated with adverse effects in the infant. Therefore, the current terms of the marketing authorisation(s) should be varied[46].
- In the next PSUR, the MAH(s) should provide cumulative reviews of cases of acute generalized exanthematous pustulosis (AGEP), myalgia, neuralgia, muscle spasms and insomnia. In addition, the MAH(s) should provide a review of all available data on the use of gadolinium-based contrast agents during pregnancy, including non-clinical data, as well as an evaluation whether gadolinium is retained in the foetus after maternal exposure and whether there are any differences between active substances in this regard and discuss whether there is a need for an update of the product information. Moreover, the MAH(s) should provide a cumulative review of cases of gadolinium retention/accumulation of the infants, including outcomes of infants having been breastfed from mothers exposed to gadoteric acid, from scientific literature and post-marketing setting, and discuss whether an update of the product information is warranted. The MAH Bayer should also provide an overview of the implementation of the targeted follow-up questionnaire regarding potential long-term symptoms, accompanied by an evaluation on its effectiveness to gather more detailed information on relevant 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.

6.3.6. Gadoteridol (NAP) - PSUSA/00001507/202304

Applicant(s): various

PRAC Lead: Karin Erneholm

Scope: Evaluation of a PSUSA procedure

Background

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

Gadoteridol is a macrocyclic gadolinium-contrast agent (GdCA) indicated for diagnostic magnetic resonance imaging (MRI) of the whole body, including head, neck, liver, breast, musculoskeletal system and soft tissue pathologies, as well as cranial and spinal MRI.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing gadoteridol 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 gadoteridol-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a warning mentioning that gadoteridol must not be administered intrathecally. In addition, the existing wording on product information should be amended in order to reflect that data on the use of gadoteridol in pregnant women is limited and it is unknown whether exposure to gadolinium is associated with adverse effects in the infant. Therefore, the current terms of the marketing authorisation(s) should be varied[47].
- In the next PSUR, the MAH(s) should provide a review of all available data on the use of gadolinium-based contrast agents during pregnancy, including non-clinical data, as well as an evaluation whether gadolinium is retained in the foetus after maternal exposure and whether there are any differences between active substances in this regard and discuss whether there is a need for an update of the product information. In addition, the MAHs should provide a cumulative review of cases of gadolinium retention/accumulation of the infants, including outcomes of infants having been breastfed from mothers exposed to gadoteridol, from scientific literature and post-marketing setting, and discuss whether an update of the product information is warranted. The MAH(s) should also provide an overview of the implementation of the targeted follow-up questionnaire regarding potential long-term symptoms, accompanied by an evaluation on its effectiveness to gather more detailed information on relevant cases and, based on the outcome of the evaluation, the MAH(s) should discuss the usefulness of continuation of the follow-up questionnaire or the need for any improvements, as appropriate.

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.

6.3.7. Gadoxetic acid disodium (NAP) - PSUSA/00001509/202304

Applicant(s): various

PRAC Lead: Mari Thorn

Scope: Evaluation of a PSUSA procedure

Background

Gadoxetic acid disodium is a linear gadolinium-based contrast agent (GdCA) indicated for

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

diagnostic magnetic resonance imaging (MRI) of the liver.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing gadoxetic acid disodium 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 gadoteridol-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated in order to reflect that data on the use of gadoxetic acid disodium in pregnant women is limited and it is unknown whether exposure to gadolinium is associated with adverse effects in the infant. Therefore, the current terms of the marketing authorisation(s) should be varied[48].
- In the next PSUR, the MAH(s) should provide a review of all available data on the use of gadolinium-based contrast agents during pregnancy, including non-clinical data, as well as an evaluation whether gadolinium is retained in the foetus after maternal exposure and whether there are any differences between active substances in this regard and discuss whether there is a need for an update of the product information. Moreover, the MAHs should provide a cumulative review of cases of gadolinium retention/accumulation of the infants, including outcomes of infants having been breastfed from mothers exposed to gadoxetic acid disodium, from scientific literature and post-marketing setting, and discuss whether an update of the product information is warranted.
- The MAH(s) should submit a variation to the national competent authorities in order to update the RMP based on the results of a peri- and postnatal study and a multiple dose administration study in juvenile in juvenile mice and on of a study on juvenile non-human primates.

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.

6.3.8. Levonorgestrel[49] (NAP) - PSUSA/00010828/202305

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

Levonorgestrel is a second-generation progestin (synthetic progesterone) indicated[50] for oral contraception, heavy menstrual bleeding (hypermenorrhoea, idiopathic menorrhagia). It is also indicated for the protection from endometrial hyperplasia during oestrogen replacement therapy.

[48] Update of SmPC sections 4.4 and 4.6. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position
[49] All indications except emergency contraception
[50] All indications except emergency contraception

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing levonorgestrel[51] 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 levonorgestrel[52]-containing medicinal products in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- The MAH Bayer should submit to national competent authorities (NCAs), within 4 months, in a worksharing variation procedure, further data on cases of uterine perforation following use of levonorgestrel-intrauterine device, including a discussion on the need for update of the product information, as warranted.

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

6.3.9. Mifepristone (NAP) - PSUSA/00002060/202305

Applicant(s): various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

Background

Mifepristone is a synthetic steroid with an antiprogestational effect as a result of competition with progesterone at the progesterone receptors and is used for various gynaecological/obstetric indications.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing mifepristone 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 mifepristone-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the existing wording on 'cardiovascular accidents'. Therefore, the current terms of the marketing authorisation(s) should be varied[53].
- In the next PSUR, the MAH(s) for mifepristone-containing medicinal products should discuss any relevant follow-up information in relation to the important potential risk of

[51] All indications except emergency contraception
[52] All indications except emergency contraception
[53] Update of SmPC section 4.4. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position

'teratogenicity on ongoing pregnancies/inadvertent pregnancy exposure (risk of malformation)'.

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.

6.3.10. Mifepristone, misoprostol (NAP) - PSUSA/00010378/202305

Applicant(s): various

PRAC Lead: Bianca Mulder

Scope: Evaluation of a PSUSA procedure

Background

Mifepristone is a synthetic steroid and misoprostol is a synthetic analogue of prostaglandin E1. Their combination is indicated for medical termination of intra-uterine pregnancy of up to 63 days of amenorrhoea (intravaginal administration).

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing mifepristone/misoprostol 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 mifepristone/misoprostol-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the existing wording describing the warning regarding 'cardiovascular accidents' to reflect new information. Therefore, the current terms of the marketing authorisation(s) should be varied[54].
- The MAH Sun Pharmaceutical industries Europe B.V. should submit to national competent authorities, within 60 days, a cumulative review on cardiovascular accidents in relation to vaginal formulation of misoprostol/mifepristone via an appropriate variation procedure and discuss the need for an update of the product information.

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

6.3.11. Misoprostol[55] (NAP) - PSUSA/00010354/202305

Applicant(s): various

PRAC Lead: Marie Louise Schougaard Christiansen

Scope: Evaluation of a PSUSA procedure

Background

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

[55] Gynaecological indication - termination of pregnancy

Misoprostol is a synthetic prostaglandin E1 analogue indicated for medical termination of early pregnancy and for cervical preparation before surgical abortion during the first trimester. In addition, misoprostol has other EU-approved indications outside the scope of this PSUSA procedure, i.e. a gastrointestinal indication, an indication for labour induction, and an indication for expansion of non-pregnant uterine cervix.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing misoprostol 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 misoprostol-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the existing wording describing the adverse reactions 'cardiovascular accidents' and the warning regarding 'cardiovascular accidents' to reflect new information on on-label use. Therefore, the current terms of the marketing authorisation(s) should be varied[56].
- In the next PSUR, the MAH(s) should discuss the appropriateness of additional risk minimisation measures (aRMMs) in the form of patient guides and healthcare professional guides for those products where such aRMMs are in place, and to assess whether an update of the RMP is warranted.

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

6.3.12. Misoprostol[57] (NAP) - PSUSA/00010353/202305

Applicant(s): various

PRAC Lead: Marie Louise Schougaard Christiansen

Scope: Evaluation of a PSUSA procedure

Background

Misoprostol is a synthetic prostaglandin E1 analogue indicated for induction of labour. In addition, misoprostol has other EU-approved indications outside the scope of this PSUSA procedure, i.e. a gastrointestinal indication, an indication for medical termination of early pregnancy and cervical preparation before surgical abortion during the first trimester, and an indication for expansion of non-pregnant uterine cervix.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of misoprostol-containing medicinal products in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.

[56] 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
[57] Gynaecological indication - labour induction

- In the next PSUR, the MAH(s) should provide a cumulative review of cases of cardiovascular events associated with the use of misoprostol for labour induction, including data from spontaneous reports, literature, and discuss whether an update of the product information is warranted.

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

6.3.13. Mometasone (NAP) - PSUSA/00002085/202305

Applicant(s): various

PRAC Lead: Mari Thorn

Scope: Evaluation of a PSUSA procedure

Background

Mometasone furoate is a corticosteroid with anti-inflammatory properties and it is indicated, depending on the formulations as inhaled, oral and topical formulations. Orally inhaled formulations of mometasone are generally indicated for the prophylaxis and treatment of asthma. Mometasone furoate nasal spray is indicated in rhinitis, sinusitis, rhinosinusitis, nasal polyps and associated symptoms (congestion and loss of smell). Creams, ointments or lotions containing mometasone are indicated in the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses and in scalp lesions.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing mometasone 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 mometasone-containing medicinal products in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAH(s) of topical formulations for mometasone-containing products should provide a cumulative review of cases of topical steroid withdrawal, with special emphasis to symptoms not already described in the product information, including data from clinical trials, post-marketing setting and scientific literature, along with a causality assessment and a discussion on 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 list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC is updated accordingly.

6.3.14. Moxifloxacin[58] (NAP) - PSUSA/00009231/202305

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

Moxifloxacin is a fluoroquinolone antibiotic indicated for systemic use for treatment of bacterial infections susceptible to moxifloxacin, such as acute exacerbation of chronic bronchitis, community acquired pneumonia, except severe cases or acute bacterial sinusitis.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing moxifloxacin 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 moxifloxacin-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add drug reaction with eosinophilia and systemic symptoms (DRESS) and photosensitivity reactions as warnings and as undesirable effects with a frequency 'not known'. In addition, the product information should be updated to add fixed drug eruption as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[59].
- In the next PSUR(s), the MAH(s) should continue monitoring cases of potential interaction of moxifloxacin with angiotensin-converting enzyme inhibitors in the context of acute kidney injury, of disorders of arteries other than the aorta, of lacunar infarction, of metabolic encephalopathy and of masking of active tuberculosis by systemic moxifloxacin.

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.

6.3.15. Nalbuphine (NAP) - PSUSA/00002110/202305

Applicant(s): various

PRAC Lead: Eva Jirsová

Scope: Evaluation of a PSUSA procedure

Background

Nalbuphine is a central semi-synthetic opioid analgesic acting indicated for the treatment of moderate to severe pain of different origin.

[58] Systemic use only
[59] 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

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing nalbuphine 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 nalbuphine-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the posology and dosing recommendations to increase comprehensibility. Therefore, the current terms of the marketing authorisation(s) should be varied[60].
- In the next PSUR, the MAH(s) should provide a cumulative review of cases of respiratory depression following drug-drug interaction between nalbuphine and gabapentinoids, including data from clinical trials, post-marketing setting and scientific literature, and discuss the need for an update of the product information, as warranted.

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

6.4. Follow-up to PSUR/PSUSA procedures

See Annex I 16.4.

6.5. Variation procedure(s) resulting from PSUSA evaluation

See Annex I 16.5.

6.6. Expedited summary safety reviews[61]

None

7. Post-authorisation safety studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)[62]

See also Annex I 17.1.

7.1.1. Alemtuzumab – LEMTRADA (CAP) - EMEA/H/C/PSA/S/0110

Applicant: Sanofi Belgium

PRAC Rapporteur: Karin Erneholm

Scope: Substantial amendment to the protocol for a non-interventional PASS to investigate

[60] Update of SmPC section 4.2. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position
[61] 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
[62] In accordance with Article 107n of Directive 2001/83/EC

the risk of mortality in multiple sclerosis patients treated with alemtuzumab (LEMTRADA) relative to comparable multiple sclerosis patients using other disease modifying therapies: a cohort study

Background

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

In line with the conclusions of the referral procedures under Article 20 of Directive 2001/83/EC (EMEA/H/A-31/1483/C/3718/0028), concluded in 2019, the MAH Sanofi was required as a condition of the marketing authorisations (Annex II-D) to conduct a non-interventional post-authorisation safety study in order to investigate the risk of mortality in multiple sclerosis (MS) patients treated with LEMTRADA compared to a relevant MS patient population. The initial protocol of the study was endorsed by PRAC in July 2021. A substantial amendment to the protocol was presented for review by PRAC.

Endorsement/Refusal of the protocol

- Having considered the draft protocol version 3.0-in accordance with Article 107n of Directive 2001/83/EC, PRAC considered that that the design of the study did not fulfil the study objectives at this stage.
- PRAC considered that the MAH should discuss the new sampling approach, implement further refinements in relation to the variables included in the propensity score (PS) models in order to improve the balance between cohorts, as well as provide further details on the data analysis, including sensitivity analysis.
- The MAH should submit a revised PASS protocol within 60 days to EMA. A 60 days-assessment timetable will be followed.

7.2. Protocols of PASS non-imposed in the marketing authorisation(s)[63]

See also Annex I 17.2.

7.2.1. Gozetotide - LOCAMETZ (CAP) - EMEA/H/C/005488/MEA 003

Applicant: Novartis Europharm Limited

PRAC Rapporteur: John Joseph Borg

Scope: Protocol for a non-interventional PASS as category 3 of the RMP (CAAA517A12401): a cross-sectional knowledge and understanding survey to evaluate the effectiveness of the Locametz educational material on interpreting PET scans of patients, distributed to medical practitioners qualified to interpret PET scans

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.

[63] 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

As part of the RMP for Locametz (gozetotide), the MAH was required to conduct a PASS in order to evaluate the effectiveness of the educational material among medical practitioners qualified to interpret PET scans. The MAH submitted a protocol for a study for the evaluation of the effectiveness of the Locametz educational material on interpreting PET scans of patients, distributed to medical practitioners qualified to interpret PET scans which was assessed by the Rapporteur. PRAC was requested to provide advice to CHMP on the protocol submitted by the MAH.

Summary of advice

- Having considered the proposed protocol for a PASS assessing the effectiveness of the educational material on interpreting PET scans distributed to medical practitioners qualified to interpret PET scans to address the safety concern 'PET imaging interpretation errors', PRAC considered that the study, by design, cannot evaluate the effectiveness of the educational material since it will not allow detection of actual interpretation errors. In addition, PRAC discussed whether the risk 'PET imaging interpretation errors' for a diagnostic agent is indeed a concern related to the safety of the product and questioned the added value of the results of a non-interventional cross-sectional survey to assess HCP receipt of the material and knowledge as a way to assess the effectiveness of the educational material as compared to monitoring the potential risk of 'PET imaging interpretation errors' through routine pharmacovigilance. PRAC considered that the RMP should be updated at the next regulatory opportunity to remove the requirement for this non-imposed PASS.

7.3. Results of PASS imposed in the marketing authorisation(s)[64]

7.3.1. Chlormadinone acetate, ethinylestradiol (NAP) - EMEA/H/N/PSR/J/0042

Applicant: GEDEON RICHTER Plc (on behalf of a consoritum: acis Arzneimittel GmbH, ALIUD PHARMA GmbH, Aristo Pharma GmbH, Dermapharm GmbH, DR. KADE/BESINS Pharma GmbH, Gynial GmbH, HEATON k.s, HEXAL AG, Hormosan Pharma GmbH, ITF Farmahealth, Produtos Farmacêuticos, Lda, Jenapharm, Kwizda Pharma GmbH, Laboratorio STADA, S.L., MEDA Pharma GmbH & Co KG, Mylan Germany GmbH, PUREN Pharma GmbH, SANDOZ S.P.A,. STADApharm GmbH, Sun-Farm Sp. z.o.o.)

PRAC Rapporteur: Martin Huber

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

Background

Chlormadinone is a progestin derivative and ethinylestradiol a derivative of natural occurring oestradiol. In combination, chlormadinone acetate/ethinylestradiol is indicated for hormonal contraception (HC), for the treatment of papulopustular acne, seborrhoea oleosa, androgenic alopecia and hirsutism and in women with break-through bleedings with lower dose combined hormonal contraceptives (CHCs).

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

Further to the conclusions dated 2014 of the referral procedure under Article 31 of Directive 2001/83/EC (EMEA/H/A-31/1356) conducted by PRAC for combined hormonal contraceptives to evaluate the relative risk of thromboembolic events due to these products compared to the ones containing levonorgestrel, Gedeon Richter Plc submitted on 22 December 2022 a PASS final study report to the European Medicines Agency (EMA) for chlormadinone acetate (CMA), ethinylestradiol (EE), on behalf of a consortium. PRAC discussed the assessment of the final report of the study and adopted a PRAC recommendation based on the assessment.

Summary of recommendation(s) and conclusions

- Based on the review of the final report of the non-interventional PASS entitled 'Retrospective Cohort Study on the RIsk of Venous Thromboembolism (RIVET-RCS)', PRAC considered that the benefit-risk balance of chlormadinone/ethinylestradiol-containing products remains unchanged. However, PRAC recommended that the terms of the marketing authorisation(s) for chlormadinone/ethinylestradiol- containing products should be varied. Therefore, the product information[65] should be updated to amend the existing warning on the risk of venous thromboembolism (VTE), based on the final study results. Moreover, PRAC agreed that the RMPs of chlormadinone/ethinylestradiol-containing products should be updated to remove the category 1 PASS as an additional pharmacovigilance activity since it has been completed. Additionally, PRAC agreed with the removal of the Question and Answer document on the VTE risk as aRMM in line with HaRP[66] assessment report recommendation on dienogest/ethinylestradiol, which was also applicable for chlormadinone and ethinylestradiol. Finally, PRAC agreed on a set of key elements to support further communication at the national level on the updated VTE risk associated with chlormadinone/ethinylestradiol use, if deemed necessary by the Member States.

7.3.2. Valproate[67] (NAP) - EMEA/H/N/PSR/J/0043

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

PRAC Rapporteur: Liana Martirosyan

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

Background

Further to the conclusions dated 2018 of the referral procedure under Article 31 of Directive 2001/83/EC (EMEA/H/A-31/1454) conducted by PRAC for valproate-containing medicines, the MAHs were required as a condition to the marketing authorisation(s) (Annex IV) to conduct a retrospective observational study to investigate the association between paternal exposure to valproate and the risk of congenital anomalies and neurodevelopmental disorders, including autism, in offspring.

The MAH Sanofi-Aventis Recherche & Développement, on behalf of a consortium, submitted to EMA the final results of the study. See PRAC minutes May 2023, PRAC minutes June 2023,

[65] Update of SmPC section 4.4. The package leaflet is updated accordingly
[66] [66] Harmonisation of RMP Project Assessment Report on Dienogest/Ethinylestradiol (29 April 2020, Dienogest_Ethinylestradiol_04_2020_HaRP_AR.pdf (hma.eu))
[67] Valproic acid, sodium valproate, valproate pivoxil, valproate semisodium, valpromide, valproate bismuth, calcium valproate, valproate magnesium

PRAC minutes July 2023, PRAC minutes October 2023, PRAC minutes November 2023 and PRAC minutes December 2023.

Summary of recommendation(s) and conclusions

- Based on the review of the final study report, the MAH's responses to the requests for supplementary information (RSI), the stakeholders' and the scientific advisory group (SAG neurology enriched with psychiatry expertise) input and the Rapporteur's assessment, PRAC considered that the benefit-risk balance of valproate-containing medicinal products remains unchanged, but recommended that the terms of the marketing authorisation(s) for valproate-containing medicinal products should be varied.

  The results of the population-based, retrospective cohort study using databases from Denmark, Sweden and Norway suggested an increased risk of neurodevelopmental disorders (NDD), including autism spectrum disorders, but no difference in the risk of congenital malformations in offspring paternally exposed to valproate compared to offspring paternally exposed to lamotrigine or levetiracetam. The risk was considered by PRAC as potential (i.e. causality is not yet confirmed).

- Considering the seriousness of NDD (including ASD) and their life-long impact on children and families, PRAC concluded that the study findings, including their uncertainties, should be communicated to patients and healthcare professionals (HCP) and confirmed that current available data were sufficient to justify applying precautionary, risk proportionate, measures, also in light of the confirmed and higher risk for children following *in utero* exposure to valproate. Therefore, PRAC considered that the product information[68] should be updated.

- Regarding the aRMMs, the existing HCP guide should be updated with a dedicated section on male patients, to inform HCPs about the potential risk of NDD (including ASD) following paternal exposure to valproate and the advice to provide to male patients. Also, the currently available patient card should be updated with information for the male patients. In addition, PRAC recommended that a new, dedicated guide for male patients should be implemented to ensure the patients are well informed about the potential risk to the offspring when valproate is used around the time of conception and advised on how to minimize this risk. PRAC also recommended the distribution of a DHPC to inform HCPs about the new recommendations regarding the potential risk of valproate in male patients. In addition, PRAC recommended that the MAHs should perform a new category 1 PASS to provide the results of the additional analyses requested in the framework of the assessment of the results of study EUPAS34201, in order to further investigate the association between paternal exposure to valproate and the risk of congenital anomalies and neurodevelopmental disorders (including autism) in the offspring. The protocol of this study should be submitted for PRAC assessment within 6 months of the finalisation of the current procedure. The final study report will be submitted to PRAC within 1 year of the endorsement of the study protocol. Finally, PRAC recommended that all MAHs should submit an updated RMP, within 3 months, in line with the conclusions of the current procedure.

  Post-meeting note: Please see EMA public health communication entitled Potential risk of neurodevelopmental disorders in children born to men treated with valproate medicines: PRAC recommends precautionary measures published on EMA website on 12 January

[68] Update of SmPC sections 4.2, 4.4 and 4.6. The package leaflet is updated accordingly.

2024.

Post-meeting note: Please see the assessment report for this procedure published on EMA website on 21 February 2024. Also, the study protocol and the study results (abstract) have been published on the HMA-EMA CATALOGUES OF REAL-WORLD DATA SOURCES AND STUDIES website.

7.4. Results of PASS non-imposed in the marketing authorisation(s)[69]

See also Annex I 17.4.

7.4.1. Fentanyl - INSTANYL (CAP) - EMEA/H/C/000959/II/0082

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Tiphaine Vaillant

Scope: Submission of the final report from study Instanyl-5002 listed as a category 3 study in the RMP. This is a non-interventional PASS study with title "Assessment of the Effectiveness of Updated Educational Materials on Prescribers' Knowledge and Behavior with Respect to Risks Associated with INSTANYL Off-Label Use". The RMP version 20.0 has also been submitted

Background

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

As stated in the RMP of Instanyl (fentanyl), the MAH conducted a non-imposed non-interventional PASS (prescriber survey) to assess the effectiveness of additional risk minimisation measures (RMMs) of the product. The Rapporteur assessed the MAH's final study report.

Summary of advice

- Based on the available data and the Rapporteur's review, PRAC considered that the ongoing variation assessing the final study report could be recommended for approval.
- PRAC considered that the overall objective of this study was not met. However, the study results revealed the importance of follow up on distribution, reception and reading of the educational materials by the prescribers. No further regulatory action is deemed necessary at this stage. The final results of this study were further taken into consideration in the assessment of the PSUR procedure for fentanyl – see section 6.2.1 above.

7.4.2. Luspatercept - REBLOZYL (CAP) - EMEA/H/C/004444/II/0023, Orphan

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Jo Robays

Scope: Submission of the final report from study ACE-536-MDS-005 listed as a category 3

[69] 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

study in the RMP. This is a non-interventional PASS to evaluate the effectiveness of the additional risk minimization measure (aRMM) for Reblozyl among Healthcare Providers (HCPs) in the EU/EEA. The RMP version 3.0 has been submitted in order to reflect the completion of the study and to remove the healthcare professional (HCP) checklist as aRMM. The Annex II is updated accordingly

Background

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

As stated in the RMP of Reblozyl (luspatercept), the MAH conducted a non-imposed non-interventional PASS to assess the effectiveness of the additional risk minimization measures (aRMMs) for Reblozyl among healthcare professionals (HCPs). The Rapporteur assessed the MAH's final study report in addition to the MAH's answers to the request for supplementary information (RSI).

Summary of advice

- Based on the available data, the MAH's responses to the RSI and the Rapporteur's review, PRAC considered that the ongoing variation assessing the final study report could be recommended for approval.
- PRAC did not endorse the MAH's proposal to remove the healthcare professional (HCP) checklist as aRMM from the RMP, considering that luspatercept is the first one of its class and that the checklist remains a further reminder of the risks in pregnancy and the precautions required for women of childbearing potential (WCBP), as well as a tool to support HCPs practice and communication to patient. PRAC agreed to update the product information reminding the need to provide the patient card, however, PRAC considered that an update of the patient card is not warranted.

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

See Annex I 17.5.

7.6. Others

7.6.1. Alemtuzumab - LEMTRADA (CAP) - EMEA/H/C/003718/ANX 009.4

Applicant: Sanofi Belgium

PRAC Rapporteur: Karin Erneholm

Scope: MAH's response to ANX 009.3 [The provision of answers to questions about the feasibility report of the non-interventional PASS to investigate the risk of mortality in multiple sclerosis (MS) patients treated with alemtuzumab (Lemtrada) relative to comparable MS patients using other disease modifying treatments (DMTs)] as per request for supplementary information (RSI) adopted in September 2023

Background

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

In line with the conclusions of the referral procedures under Article 20 of Directive 2001/83/EC (EMEA/H/A-31/1483/C/3718/0028), concluded in 2019, the MAH Sanofi was required as a condition of the marketing authorisations (Annex II-D) to conduct a non-interventional post-authorisation safety study in order to investigate the risk of mortality in multiple sclerosis (MS) patients treated with LEMTRADA compared to a relevant MS patient population. The initial protocol of the study was endorsed by PRAC in July 2021. A response to the RSI adopted in September 2023 following the submission of a feasibility report for the above-mentioned study was presented for review by PRAC.

Summary of advice

- Based on the available data, the MAH's responses to the RSI and the Rapporteur's review, PRAC considered that the MAH should provide a further response to the request for supplementary information.
- PRAC considered that the MAH should discuss the new sampling approach, implement further refinements in relation to the variables included in the propensity score (PS) models in order to improve the balance between cohorts, as well as provide further details on the data analysis, including sensitivity analysis. The methodological changes consequential to the conclusions of the extended feasibility assessment were implemented in an updated study protocol, which is assessed in parallel to this procedure in procedure EMEA/H/C/PSA/S/0110 (see section 7.1.1)
- The MAH should submit responses to the RSI within 60 days to EMA. A 60 days-assessment timetable will be followed.

7.7. New Scientific Advice

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

7.8. Ongoing Scientific Advice

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

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

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

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

8.1. Annual reassessments of the marketing authorisation

See Annex I 18.1.

8.2. Conditional renewals of the marketing authorisation

See also Annex I 18.2.

8.2.1. Volanesorsen - WAYLIVRA (CAP) - EMEA/H/C/004538/R/0026 (without RMP)

Applicant: Akcea Therapeutics Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: 5-year renewal of the marketing authorisation

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.

Waylivra, a centrally authorised product containing volanesorsen, was authorised under a conditional marketing authorisation in 2019. Based on the fulfilment of specific obligations and safety data, the MAH submitted a request for yearly renewal of the marketing authorisation for opinion by CHMP. PRAC is responsible for providing advice to CHMP on this conditional renewal with regard to safety and risk management aspects.

Summary of advice

- Based on the review of the available information on the status of the fulfilment of specific obligations and safety data submitted, PRAC considered that the conditional renewal for Waylivra could only be finalised if satisfactory responses to the request for supplementary information are provided.
- PRAC considered that all prescribers should be reminded on the need to better adhere to the instructions on platelet monitoring and dosing algorithm as set out in the product information and the guide for healthcare professionals in place in order to minimise the risk of thrombocytopenia and bleeding and that this should not be limited only to the prescribers participating in the PASS listed under Annex II-D as specific obligation. The MAH should provide a draft DHPC and communication plan to remind health care professionals on the need to better adhere to the instructions on platelet monitoring and dose algorithm for PRAC review.

8.3. Renewals of the marketing authorisation

See Annex I 18.3.

9. Product related pharmacovigilance inspections

9.1. List of planned pharmacovigilance inspections

None

9.2. Ongoing or concluded pharmacovigilance inspections

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

9.3. Others

None

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

10.1. Safety related variations of the marketing authorisation

10.1.1. Ruxolitinib - JAKAVI (CAP) - EMEA/H/C/002464/II/0068

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of sections 4.4 and 5.1 of the SmPC in order to add new warnings on 'major adverse cardiac events (MACE)', 'thrombosis' and 'second primary malignancies', following an Article 20 class referral involving JAK inhibitors approved to treat rheumatoid arthritis and to update efficacy information regarding the effects of ruxolitinib in relation to thromboembolic events based on recently published data from MAJIC-PV study (a randomised, controlled open-label study in polycythemia vera (PV))

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.

A type II variation proposing to update the product information of Jakavi (ruxolitinib) to add new warnings on 'major adverse cardiac events (MACE)', 'thrombosis' and 'second primary malignancies' following an Article 20 class referral involving JAK inhibitors is under evaluation at CHMP. Jakavi (ruxolitinib) was not included in the scope of the referral, therefore, a separate assessment had to be performed in order to determine the extent of which the outcome of the referral applies to this medicinal product. PRAC was requested to provide advice on this variation.

Summary of advice

- Based on the review of the available information, PRAC agreed, in general, with the proposed amendments to the product information. However, PRAC noted the differences between the wording previously approved for the other JAK inhibitor not part of the referral. Therefore, PRAC agreed not to include a recommendation to discontinue treatment in patients with suspected venous thromboembolism (VTE), as a causal relationship between ruxolitinib and thromboembolic events has not been established. Furthermore, thromboembolic events are one key feature of the diseases being treated with ruxolitinib, and reducing such events is an aim of the treatment. Moreover, PRAC agreed not to include the statement regarding the use ruxolitinib with caution in patients with risk factors for VTE other than malignancy and cardiovascular factors, particularly

since the conditions for which Jakavi are indicated constitute by themselves risk factors for VTE. Regarding secondary primary malignancy, as a causal relationship in general has not been established, recommending an individual benefit/risk assessment for each patient before starting treatment is not considered useful nor easily interpreted by the prescriber and patient. Finally, as a causal association between treatment with ruxolitinib and MACE, second primary malignancy, and thrombosis was not established, PRAC considered that no RMP update is warranted with regard to risks of major adverse cardiovascular events (MACE), second primary malignancy, and thrombosis.

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.0)

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

11.1. Safety related variations of the marketing authorisation

None

11.2. Other requests

None

12. Organisational, regulatory and methodological matters

12.1. Mandate and organisation of PRAC

12.1.1. PRAC membership

The Chair thanked Menno van der Elst for his contribution as PRAC member to the work of the Committee and welcomed Biana Mulder as the new alternate for The Netherlands, replacing Liana Martirosyan, who took over the role of member. The Chair also welcomed Michal Rataj as the new alternate representing Patients' Organisation nominated by the European Commission, replacing Marko Korenjak, who took over the role of member.

12.1.2. Vote by proxy

None

12.2. Coordination with EMA Scientific Committees or CMDh-v

None

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

None

12.4. Cooperation within the EU regulatory network

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

The EMA Secretariat provided PRAC with an update on the ongoing studies regarding COVID-19 vaccines and their variants as well as related to the post-COVID-19 condition, seasonal trends in COVID-19 cases, hospitalisations and mortality. An update was also provided on studies and development of updated COVID-19 vaccines, as well as a summary on severe acute respiratory infections caused by SARS-CoV-2, influenza and respiratory syncytial viruses.

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 2024

PRAC lead: Sabine Straus, Martin Huber

At the organisational, regulatory and methodological matters (ORGAM) meeting on 25 January 2024, the EMA Secretariat presented to PRAC the draft final PRAC work plan 2024, further to previous discussion and comments received. For further background, see PRAC minutes December 2023.

Post-meeting note: PRAC adopted the work plan 2024 on 26 January 2024 via written procedure. The work plan was published on the EMA website (EMA/PRAC/43499/2024) on 29 January 2024.

12.8. Planning and reporting

None

12.9. Pharmacovigilance audits and inspections

12.9.1. Pharmacovigilance systems and their quality systems

None

12.9.2. Pharmacovigilance inspections

None

12.9.3. Pharmacovigilance audits

None

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

12.10.1. Periodic safety update reports

None

12.10.2. Granularity and Periodicity Advisory Group (GPAG)

PRAC lead: Jana Lukacisinova

The EMA Secretariat provided to PRAC an update on the work of the GPAG, as well as an overview of the activities that will be included in the GPAG 2024 workplan. PRAC agreed with the proposed workplan.

Post-meeting note: Jana Lukacisinova was appointed as PRAC lead for GPAG.

12.10.3. PSURs repository

None

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

In line with the criteria for plenary presentation of updates to the EURD List adopted by PRAC in December 2021, PRAC endorsed the draft revised EURD list, version January 2024, reflecting the PRAC's comments impacting on the data lock point (DLP) and PSUR submission frequencies of the substances/combinations. PRAC endorsed the newly allocated Rapporteurs for upcoming PSUSAs in accordance with the principles previously endorsed by PRAC (see PRAC minutes April 2013).

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

PRAC was updated on the ongoing activities and the progress from the SMART working group – Processes work stream meeting held on 5 December 2023, such as discussions related to the validation of signals versus product information harmonisation and an update on the list of active substances subject to worksharing for signal management. In addition, PRAC was informed that Dennis Lex was appointed as the new Co-Chair of the Processes work stream replacing Menno van der Elst. PRAC noted the information.

12.12. Adverse drug reactions reporting and additional monitoring

12.12.1. Management and reporting of adverse reactions to medicinal products

None

12.12.2. Additional monitoring

None

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

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

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

12.13. EudraVigilance database

12.13.1. Activities related to the confirmation of full functionality

None

12.14. Risk management plans and effectiveness of risk minimisations

12.14.1. Risk management systems

None

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

None

12.15. Post-authorisation safety studies (PASS)

12.15.1. Post-authorisation Safety Studies – imposed PASS

None

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

None

12.16. Community procedures

12.16.1. Referral procedures for safety reasons

None

12.17. Renewals, conditional renewals, annual reassessments

None

12.18. Risk communication and transparency

12.18.1. Public participation in pharmacovigilance

None

12.18.2. Safety communication

None

12.19. Continuous pharmacovigilance

12.19.1. Incident management

None

12.20. Impact of pharmacovigilance activities

12.20.1. EU pharmacovigilance impact research 2016-2022: lessons learnt for PRAC regulatory decision-making – final report

PRAC lead: Liana Martirosyan

PRAC was informed about the lessons learnt exercise conducted by the PRAC Interest Group (IG) Impact which included 12 completed impact studies launched under the remit of the PRAC Impact Strategy. The main findings of this exercise and recommendations for follow up were summarised in a report which was acknowledged by PRAC following written consultation and presentation of the main findings at the SRLM in Madrid on 14-15 November 2023. The report's recommendations on methodological aspects of RMM effectiveness studies will be considered in the ongoing revision 3 of GVP Module XVI.

12.20.2. Implementation of controlled access to and distribution of medicinal products in EU Member States – draft technical specification for tender

PRAC lead: Liana Martirosyan

PRAC was consulted on the PRAC Interest Group (IG) Impact proposal for a qualitative study on the implementation of controlled access programmes/controlled distribution systems for medicinal products at national level. The draft technical specifications for tender under EMA's framework contract EMA/2020/46/TDA, including research question and study objectives was presented to PRAC. PRAC members were invited to send their comments in writing by 22 January 2024.

Post meeting note: At the organisational, regulatory and methodological matters (ORGAM) meeting held on 25 January 2024, PRAC endorsed the technical specifications and the study objectives. Liana Martirosyan was appointed as the PRAC Sponsor and the tender for the study is to be launched in February 2024.

12.21. Others

12.21.1. IRIS - update on variations, Art. 61(3) and Marketing authorisation transfers

The EMA Secretariat presented to PRAC an update on the Product Lifecycle Management (PLM) Regulatory Procedures implementation in IRIS and informed the Committee about the timelines for the 1st roll out of regulatory procedures for PLM in IRIS. The EMA Secretariat also performed a demo session. PRAC noted the information.

Post meeting note: The first roll-out of procedures in IRIS was launched on 23 January 2024.

12.21.2. Marketing authorisation applications (MAA) forecast for 2023 – planning update dated Q4 2023

At the organisational, regulatory and methodological matters (ORGAM) meeting on 25 January 2024, the EMA Secretariat presented for information to PRAC a quarterly updated report on marketing authorisation applications (MAA) planned for submission (the business 'pipeline') in 2024 highlighting the applications without appointed Rapporteur(s). For previous update, see PRAC minutes October 2023.

12.21.3. PRAC drafting group on the risks of dependence and addiction of opioids – update

PRAC lead: Liana Martirosyan

At the organisational, regulatory and methodological matters (ORGAM) meeting on 25 January 2024, the PRAC lead presented an overview of the activities performed by the drafting group since it was created in 2022, a summary of the results from consultations and interactions with various stakeholders, including with the CMDh's Multilingual Packaging Working Group, as well as proposals for next steps. For further background, see PRAC minutes June 2023 and PRAC minutes October 2023. The PRAC lead presented the various options for possibly implementing a warning in order to enhance addressing the risk of opioid use disorder (OUD), along with considerations on each one's regulatory implementation. PRAC acknowledged that OUD is an identified risk of serious nature for the patient and with wider social implications and that all tools for enhancing existing OUD-

related information in the product information have implementation challenges, a large number of products will be affected, and local situations vary. PRAC was of the view that, in order to take a decision, further discussion is needed at an upcoming PRAC plenary meeting. To prepare, PRAC members were invited, by 12 February 2024, to provide their views on which tool for enhancing existing information relating to opioid use disorder (OUD) in the product information of relevant opioid-containing medicines they would support: e.g. an outer packaging warning, a patient card inside the package, a boxed warning on the package leaflet, or any other type of tools that could reach patients, based on the information provided.

12.21.4. PRAC drafting group on multiple sclerosis and use of disease modifying drugs in women of childbearing potential: considerations on approach to labelling and risk management planning

PRAC lead: Nathalie Gault

At the organisational, regulatory and methodological matters (ORGAM) meeting on 25 January 2024, the EMA Secretariat provided to PRAC an update on the organisational matters and activities performed by the drafting group on multiple sclerosis and use of disease modifying drugs in women of childbearing potential, as well as on the identified working areas and the next steps. PRAC noted the information.

13. Any other business

None

14. Annex I – Signals assessment and prioritisation[70]

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[71].

14.1. New signals detected from EU spontaneous reporting systems

14.1.1. Clobazam (NAP)

Applicant(s): various

PRAC Rapporteur: Kimmo Jaakkola

Scope: Signal of drug rash with eosinophilia and systemic symptoms (DRESS)

EPITT 20041 – New signal

Lead Member State(s): FI

[70] 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

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

14.1.2. Dabrafenib – TAFINLAR (CAP); FINLEE (CAP); Trametinib – MEKINIST (CAP)

Applicant: Novartis Europharm Limited

PRAC Rapporteur: David Olsen

Scope: Signal of acute febrile neutrophilic dermatosis

EPITT 20022 – New signal

Lead Member State(s): NO

14.1.3. Ixazomib – NINLARO (CAP)

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of vasculitis

EPITT 20023 – New signal

Lead Member State(s): SE

14.2. New signals detected from other sources

14.2.1. Manidipine (NAP)

Applicant(s): various

PRAC Rapporteur: Amelia Cupelli

Scope: Signal of ascites

EPITT 20026 – New signal

Lead Member State(s): IT

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. Denosumab - EMEA/H/C/005964

Scope: treatment of osteoporosis

15.1.2. Denosumab - EMEA/H/C/006378

Scope: prevention of skeletal related events with advanced malignancies

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. Beclometasone dipropionate, formoterol fumarate dihydrate, glycopyrronium - RIARIFY (CAP) - EMEA/H/C/004836/WS2604/0029; TRYDONIS (CAP) - EMEA/H/C/004702/WS2604/0034

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Jan Neuhauser

Scope: C.I.11.z - To provide a new version of the RMP for Riarifly and Trydonis in order to update the post authorisation exposure data and replace the protocol of the PASS for study CLI-05993BA1-05 in Annex 3, following its approval via procedure EMEA/H/C/004257/MEA/002.3 for Trimbow (Beclometasone, formoterol, glycopyrronium bromide) concluded at PRAC in January 2023.

15.2.2. Doxorubicin - CAELYX PEGYLATED LIPOSOMAL (CAP) - EMEA/H/C/000089/II/0107

Applicant: Baxter Holding B.V.

PRAC Rapporteur: Eva Jirsová

Scope: Submission of an updated RMP version 6.1 in order to align to GVP Module V Revision 2 requirements, following a request received within the Assessment Report for procedure EMEA/H/C/PSUSA/00001172/202111

15.2.3. Risdiplam - EVRYSDI (CAP) - EMEA/H/C/005145/II/0020

Applicant: Roche Registration GmbH

PRAC Rapporteur: Jan Neuhauser

Scope: Submission of an updated RMP version 2.0 in order to remove the important potential risk of retinal toxicity with risdiplam due to the absence of evidence of retinal toxicity based on thorough ophthalmological monitoring in clinical studies to date

15.2.4. Telmisartan - KINZALMONO (CAP) - EMEA/H/C/000211/WS2577/0120; MICARDIS (CAP) - EMEA/H/C/000209/WS2577/0129; PRITOR (CAP) - EMEA/H/C/000210/WS2577/0133

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Amelia Cupelli

Scope: Submission of an updated RMP version 6.1 in order to implement an overall update regarding safety concerns based on literature and post marketing data; and to adapt the RMP to the current RMP format (Rev 2.0.1), in line with GVP Module V, Revision 2.

15.2.5. Telmisartan, hydrochlorothiazide - KINZALKOMB (CAP) - EMEA/H/C/000415/WS2611/0123; MICARDISPLUS (CAP) -

EMEA/H/C/000413/WS2611/0130; PRITORPLUS (CAP) - EMEA/H/C/000414/WS2611/0133

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Amelia Cupelli

Scope: Submission of an updated RMP version 9.1 for MicardisPlus, PritorPlus and Kinzalkomb in order to remove all important identified and potential risks from the list of safety concerns and to adapt the RMP to the current RMP format (Rev 2.0.1), in line with GVP Module V, Revision 2

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

Applicant: Takeda Pharmaceuticals International AG Ireland Branch

PRAC Rapporteur: Martin Huber

Scope: Submission of an updated RMP version 12.0 in order to remove certain risks from the list of safety concerns

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

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

15.3.1. Amivantamab - RYBREVANT (CAP) - EMEA/H/C/005454/II/0010

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Gabriele Maurer

Scope: Extension of indication to include amivantamab in combination with carboplatin and pemetrexed for the first-line treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with activating epidermal-growth factor receptor (EGFR) Exon 20 insertion mutations for RYBREVANT, based on the final results from study 61186372NSC3001 listed as a Specific Obligation in the Annex II of the product information; this is a global, open-label, randomised Phase 3 study of ACP compared to CP alone in participants with newly diagnosed, locally advanced or metastatic NSCLC characterized by EGFR exon 20ins. The primary objective of the PAPILLON study is to compare efficacy, as demonstrated by PFS, in participants treated with ACP versus CP alone. As a consequence, sections 4.1, 4.2, 4.8, 4.9, 5.1, 5.2 and 6.6 of the SmPC are updated. The package leaflet is updated in accordance. Version 3.1 of the RMP has also been submitted. In addition, the MAH took the opportunity to update Annex II and Annex IV of the product information. Consequently, the MAH proposes a switch from marketing authorisation under exceptional circumstances to full marketing authorisation given the fulfilment of the SOB. As part of the application, the MAH also requests an extension of the market protection by one additional year

15.3.2. Aripiprazole - ABILIFY MAINTENA (CAP) - EMEA/H/C/002755/X/0045

Applicant: Otsuka Pharmaceutical Netherlands B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension application to introduce a new pharmaceutical form associated with two new strengths (720 and 960 mg Prolonged-release suspension for injection). The RMP (version 12.1) is updated in accordance

15.3.3. Bimekizumab - BIMZELX (CAP) - EMEA/H/C/005316/II/0020

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Liana Martirosyan

Scope: Extension of indication to include treatment of moderate to severe hidradenitis suppurativa (HS) in adults, based on final results from study HS0003 (BE HEARD I) and study HS0004 (BE HEARD II). These are phase 3, randomised, double blind, placebo controlled, multicentre, pivotal studies evaluating the efficacy and safety of bimekizumab in study participants with moderate to severe HS. Further supportive data are based on the results of phase 2 study HS0001 and phase 3 currently ongoing open-label extension study HS0005. As a consequence, sections 4.1, 4.2, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet is updated in accordance. Version 1.10 of the RMP has also been submitted. Furthermore, the product information is brought in line with the latest QRD template version 10.3

15.3.4. Bimekizumab - BIMZELX (CAP) - EMEA/H/C/005316/X/0021

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Liana Martirosyan

Scope: Extension application to add a new strength of 320 mg (160 mg/ml) for bimekizumab solution for injection in pre-filled syringe or pre-filled pen, for subcutaneous (SC) administration. Version 1.11 of the RMP has also been submitted

15.3.5. Budesonide - KINPEYGO (CAP) - EMEA/H/C/005653/II/0008, Orphan

Applicant: STADA Arzneimittel AG

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Extension of indication to slow kidney function decline in adults with primary immunoglobulin A (IgA) nephropathy (IgAN) for KINPEYGO, based on Part B of study NefIgArd (NEF-301), listed as the final specific obligation in the Annex II; this is a Phase 3, randomised, double-blind, placebo-controlled, multicentre study to evaluate the efficacy, safety, and tolerability of oral Nefecon[72] compared to matching placebo in patients with primary IgAN on a background of optimised renin-angiotensin system (RAS) inhibitor therapy. 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 1.1 of the RMP has also been submitted

15.3.6. Coronavirus (COVID-19) vaccine (recombinant protein receptor binding domain fusion heterodimer) - BIMERVAX (CAP) - EMEA/H/C/006058/II/0010

Applicant: Hipra Human Health S.L.

PRAC Rapporteur: Zane Neikena

[72] Kinpeygo is referred to as "Nefecon" in clinical studies

Scope: Submission of the final report from study HIPRA-HH-5, a phase III, open label, single arm, multi-centre, trial to assess the safety and immunogenicity of a booster vaccination with a recombinant protein RBD fusion heterodimer candidate (PHH-1V) against SARS-COV-2, in adults vaccinated against COVID-19. The RMP version 1.3 has also been submitted

15.3.7. Dolutegravir, abacavir, lamivudine - TRIUMEQ (CAP) - EMEA/H/C/002754/II/0116

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Martin Huber

Scope: Extension of indication to include treatment of paediatric patients from 6 kg to less than 25 kg for Triumeq dispersible tablets, based on PK, safety, and efficacy data observed in the final results of study 205860 (IMPAACT 2019), further supported by extrapolation to data generated in adults and additional data in paediatric patients with the single entities. IMPAACT 2019 is a Phase 1/2 open-label, multicentre, multiple dose study of dolutegravir/lamivudine/abacavir fixed dose combination tablets in treatment-experienced and treatment-naïve HIV-1-infected children less than 12 years of age. As a consequence, sections 4.1, 4.2, 4.5, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated. The package leaflet is updated in accordance. Version 22.0 of the RMP has also been submitted. In addition, the marketing authorisation holder (MAH) took the opportunity to introduce minor editorial changes to the product information

15.3.8. Dupilumab - DUPIXENT (CAP) - EMEA/H/C/004390/II/0079

Applicant: Sanofi Winthrop Industrie

PRAC Rapporteur: Kimmo Jaakkola

Scope: Extension of indication for DUPIXENT to include treatment of adults as add-on maintenance treatment for uncontrolled chronic obstructive pulmonary disease (COPD) with type 2 inflammation on triple therapy or double therapy if inhaled corticosteroids (ICS) are contraindicated, based on final results from study EFC15804 (BOREAS); this is a phase 3, randomised, double blind, placebo-controlled, multi-centre, parallel group, 52-week study to assess the efficacy, safety and tolerability of dupilumab in patients with moderate-to-severe COPD with type 2 inflammation. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet is updated in accordance. Version 10.0 of the RMP has also been submitted

15.3.9. Durvalumab - IMFINZI (CAP) - EMEA/H/C/004771/WS2463/0063; Olaparib - LYNPARZA (CAP) - EMEA/H/C/003726/WS2463/0066

Applicant: AstraZeneca AB

PRAC Rapporteur: Amelia Cupelli

Scope: Extension of indication for Lynparza in combination with Imfinzi for the maintenance treatment of adult patients with newly diagnosed advanced or recurrent endometrial cancer following treatment with Imfinzi and platinum-based chemotherapy, based on results from pivotal phase III study, D9311C00001 (DUO-E). This was a phase III, randomised, double-blind, placebo-controlled, multicentre study evaluating the efficacy and safety of durvalumab in combination with platinum-based chemotherapy (paclitaxel + carboplatin)

followed by maintenance durvalumab with or without olaparib for patients with newly diagnosed advanced or recurrent endometrial cancer. 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 30 of the RMP has also been submitted

15.3.10. Efgartigimod alfa - VYVGART (CAP) - EMEA/H/C/005849/II/0014, Orphan

Applicant: Argenx

PRAC Rapporteur: Rhea Fitzgerald

Scope: Update of section 4.4 of the SmPC in order to amend an existing warning on infusion reactions and hypersensitivity reactions, and update of section 5.1 of the SmPC to update the mechanism of action of efgartigimod in relation to albumin; based on final results from study ARGX-113-1705 listed a category 3 study in the RMP. This is a long-term, single-arm, open-label, multicentre, phase 3 follow-on study of ARGX-113-1704 to evaluate the safety and tolerability of ARGX-113 in patients with myasthenia gravis having generalised muscle weakness. The RMP version 2.2 has also been submitted

15.3.11. Encorafenib - BRAFTOVI (CAP) - EMEA/H/C/004580/WS2538/0034; Binimetinib - MEKTOVI (CAP) - EMEA/H/C/004579/WS2538/0030

Applicant: Pierre Fabre Medicament

PRAC Rapporteur: Rugile Pilviniene

Scope: Extension of indication to include binimetinib in combination with encorafenib for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with a BRAF V600 mutation for MEKTOVI and BRAFTOVI based on results from study PHAROS (study ARRAY-818-202) at the primary completion date; this is a phase II, open-label, multicentre, non-comparative study (interventional). As a consequence, sections 4.1, 4.4, 4.8, 5.1, 5.2, 9 and 10 of the SmPC are updated. The package leaflet is updated in accordance. Version 2.1 of the RMP has also been submitted. As part of the application, the MAH is requesting a 1-year extension of the market protection for MEKTOVI

15.3.12. Esketamine - SPRAVATO (CAP) - EMEA/H/C/004535/II/0020

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Kirsti Villikka

Scope: Update of sections 4.4 and 4.8 of the SmPC in order to amend an existing warning on severe hepatic impairment and to include the long-term safety information based on final results from study 54135419TRD3008:an open-label long-term extension safety study of esketamine nasal spray in treatment-resistant depression (TRD), listed as a category 3 study in the RMP; this was a multicentre, open-label, long-term extension safety study to evaluate safety, tolerability, and efficacy of esketamine in participants with TRD. The RMP version 5.1 has also been submitted. In addition, the MAH took the opportunity to introduce editorial changes to the product information

15.3.13. Florbetapir (^{18}F) - AMYVID (CAP) - EMEA/H/C/002422/II/0046

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Martin Huber

Scope: Extension of indication to include monitoring response to therapy for AMYVID, based on supporting literature. As a consequence, sections 4.1 and 4.4 of the SmPC are updated. The package leaflet is updated in accordance. Version 5.1 of the RMP has also been submitted. In addition, the marketing authorisation holder (MAH) took the opportunity to update section 4.8 of the SmPC to reflect the current clinical trial exposures to align it with the updated RMP

15.3.14. Ibandronic acid - BONDRONAT (CAP) - EMEA/H/C/000101/WS2451/0090; BONVIVA (CAP) - EMEA/H/C/000501/WS2451/0075

Applicant: Atnahs Pharma Netherlands B.V.

PRAC Rapporteur: Karin Erneholm

Scope: Update of sections 4.2, 4.4 and 4.8 of the SmPC in order to add information regarding the risk of 'atypical fractures of long bones other than femour' based on literature. The package leaflet is updated accordingly. The RMP version 3.1 has also been submitted. In addition, the MAH took the opportunity to bring the product information in line with the latest QRD template version 10.3

15.3.15. Idecabtagene vicleucel - ABECMA (CAP) - EMEA/H/C/004662/II/0031, Orphan

Applicant: Bristol-Myers Squibb Pharma EEIG, ATMP

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension of indication to include treatment of adult patients with relapsed and refractory multiple myeloma (RRMM) who have received at least two prior therapies, including an immunomodulatory agent, a proteasome inhibitor and an anti-CD-38 antibody and have demonstrated disease progression on the last therapy for Abecma (idecabtagene vicleucel, ide-cel), based on results from study BB2121-MM-003 (MM-003, KarMMa-3). This is a Phase 3, multicentre, randomised, open-label study to compare the efficacy and safety of ide-cel versus standard regimens in subjects with RRMM. As a consequence, sections 2.1, 2.2, 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2, 6.3, 6.4 and 6.6 of the SmPC are updated. The package leaflet and labelling are updated in accordance. Version 3.0 of the RMP has also been submitted. Furthermore, the product information is brought in line with the Guideline on core SmPC, labelling and package leaflet for advanced therapy medicinal products (ATMPs) containing genetically modified cells

15.3.16. Isavuconazole - CRESEMBA (CAP) - EMEA/H/C/002734/X/0042/G, Orphan

Applicant: Basilea Pharmaceutica Deutschland GmbH

PRAC Rapporteur: Adam Przybylkowski

Scope: Extension application to add a new strength of 40 mg hard capsule to be used in paediatric patients 6 years and older grouped with a type II variation (C.I.6.a) in order to extend the indication to include treatment of paediatric patients aged 1 year and older for CRESEMBA 200 mg powder, based on final results from studies 9766-CL-0107 and 9766-CL-0046. Study 9766-CL-0046 is a phase 1, open-label, multicentre study to evaluate the PK, safety and tolerability of intravenous and oral isavuconazonium sulfate in paediatric

patients. This study was conducted in two sequential parts: Part 1 with three intravenous dosing cohorts, and Part 2 with two oral dosing cohorts. Study 9766-CL-0107 is a phase 2, open-label, non-comparative, multicentre study to evaluate the safety and tolerability, efficacy, and PK of isavuconazole for the treatment of invasive aspergillosis or mucormycosis in paediatric patients aged 1 to < 18 years. As a consequence, sections 4.1, 4.2, 4.5, 4.8, 5.1, 5.2, and 6.6 of the SmPC are updated. The package leaflet is updated in accordance. Version 9.1 of the RMP has also been submitted

15.3.17. Meningococcal Group A, C, W and Y conjugate vaccine - MENQUADFI (CAP) - EMEA/H/C/005084/II/0027

Applicant: Sanofi Pasteur

PRAC Rapporteur: Jean-Michel Dogné

Scope: Submission of the final report from study MET52, listed as a category 3 study in the RMP. This was a phase III, open-label, randomised, parallel-group, active-controlled, multi-centre study to evaluate the immunogenicity and describe the safety of MenACYW conjugate vaccine when administered concomitantly with a Meningococcal Group B vaccine and other routine paediatric vaccines as part of the national immunization schedule in healthy infants and toddlers in the United Kingdom. The RMP version 1.3 has also been submitted

15.3.18. Nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/II/0137

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Martin Huber

Scope: Extension of indication to include in combination with cisplatin-based chemotherapy the first-line treatment of adult patients with unresectable or metastatic urothelial carcinoma for OPDIVO, based on interim results from study CA209901 (CheckMate901); this is a Phase 3, open-label, randomised study of nivolumab combined with ipilimumab, or with standard of care chemotherapy, versus standard of care chemotherapy in participants with previously untreated unresectable or metastatic urothelial cancer. 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 35.0 of the RMP has also been submitted

15.3.19. Ocrelizumab - OCREVUS (CAP) - EMEA/H/C/004043/X/0039

Applicant: Roche Registration GmbH

PRAC Rapporteur: Gabriele Maurer

Scope: Extension application to introduce a new pharmaceutical form (solution for injection) associated with a new strength (920 mg) and new route of administration (subcutaneous use). The RMP (version 9.0) is updated in accordance

15.3.20. Ozanimod - ZEPOSIA (CAP) - EMEA/H/C/004835/II/0023

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Update of sections 4.4 and 5.1 of the SmPC in order to update efficacy and safety information based on the final results from study RPC01-3001, listed as a category 3 study in the RMP. This is a multi-site, open label extension trial of RPC1063 in relapsing multiple sclerosis. The study's main objectives were to characterise the long-term safety and tolerability, and the long-term efficacy of ozanimod in patients with relapsing multiple sclerosis. The RMP version 7.0 has also been submitted

15.3.21. Pembrolizumab - KEYTRUDA (CAP) - EMEA/H/C/003820/II/0145

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Bianca Mulder

Scope: Extension of indication to include in combination with chemoradiotherapy (external beam radiation therapy followed by brachytherapy) the treatment of high-risk locally advanced cervical cancer in adults who have not received prior definitive therapy [stage IB2-IIB (with node-positive disease) or stage III-IVA based on FIGO 2014] for Keytruda, based on KEYNOTE-A18: a randomised, phase 3, double-blind study of chemoradiotherapy with or without pembrolizumab for the treatment of high-risk, locally advanced cervical cancer. As a consequence, sections 4.1 and 5.1 of the SmPC are updated. The package leaflet is updated in accordance. Version 44.1 of the RMP has also been submitted

15.3.22. Risankizumab - SKYRIZI (CAP) - EMEA/H/C/004759/X/0043/G

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Liana Martirosyan

Scope: Extension application to a new strength of 180 mg of risankizumab (solution for injection in cartridge) grouped with a type II variation extension of indication (C.I.6.a) to include treatment of adult patients with moderately to severely active ulcerative colitis, for SKYRIZI, based on final results from studies M16-067 sub-study 2: a phase 2b/3 multicentre, randomised, double-blind, placebo-controlled induction study to evaluate the efficacy and safety of risankizumab in subjects with moderately to severely active ulcerative colitis, and M16-066 sub-study 1: a multicentre, randomised, double-blind, placebo controlled 52-week maintenance and an open-label extension study of the efficacy and safety of risankizumab in subjects with ulcerative colitis, as well as drug-drug interaction (DDI) study M19-974. As a consequence, sections 4.1, 4.2, 4.8, 5.1, 5.2, 5.3 and 6.6 of the SmPC for the Skyrizi 600 mg concentrate for solution for infusion, and sections 1, 2, 4.1, 4.2, 4.8, 5.1, 5.2, 5.3, 6.5 and 6.6 of the SmPC for the Skyrizi 360 mg solution for injection in cartridge are updated. The Annex II, Labelling and package leaflets are updated in accordance. Version 5.0 of the RMP has also been submitted

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

Applicant: BioMarin International Limited

PRAC Rapporteur: Eamon O'Murchu

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

15.3.24. Selexipag - UPTRAVI (CAP) - EMEA/H/C/003774/X/0038

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Nathalie Gault

Scope: Extension application to add a new strength of 100 µg film-coated tablets in HDPE bottle. The RMP (version 10.1) is updated in accordance

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

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Bianca Mulder

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

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

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Bianca Mulder

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

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

Applicant: Eurocept International B.V.

PRAC Rapporteur: Eamon O'Murchu

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

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

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Update of sections 4.2 and 5.2 of the SmPC in order to update recommendations for patients with moderate to severe hepatic impairment following final results from study 20200362 listed as a category 3 PASS in the EU RMP; this is a phase I clinical study to evaluate the pharmacokinetics (PK) of a single oral dose of sotorasib administered in subjects with moderate or severe hepatic impairment compared with subjects who have normal hepatic function. The EU RMP version 1.0 has also been submitted. In addition, the MAH took the opportunity to bring the product information in line with the latest QRD template version 10.3

15.3.29. Tenofovir alafenamide - VEMLIDY (CAP) - EMEA/H/C/004169/II/0043/G

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Valentina Di Giovanni

Scope: Grouped application consisting of 1) submission of the final report from study GS-US-320-0108 listed as category 3 study in the RMP: a phase 3, randomised, double-blind study to evaluate the safety and efficacy of tenofovir alafenamide (TAF) 25 mg QD versus tenofovir disoproxil fumarate (TDF) 300 mg QD for the treatment of HBeAg-negative, chronic hepatitis B. The RMP version 10.1 has also been submitted; 2) submission of the final report from study GS-US-320-0110 listed as category 3 studies in the RMP: a phase 3, randomised, double-blind study to evaluate the safety and efficacy of TAF 25 mg QD versus TDF 300 mg QD for the treatment of HBeAg-positive, chronic hepatitis B. The RMP version 10.1 has also been submitted

15.3.30. Thiotepa - TEPADINA (CAP) - EMEA/H/C/001046/X/0049

Applicant: ADIENNE S.r.l. S.U.

PRAC Rapporteur: Tiphaine Vaillant

Scope: Extension application to add a new strength (200 mg powder and solvent for solution for infusion). The RMP (version 015) is updated in accordance

15.3.31. Trastuzumab deruxtecan - ENHERTU (CAP) - EMEA/H/C/005124/II/0040

Applicant: Daiichi Sankyo Europe GmbH

PRAC Rapporteur: Carla Torre

Scope: Update of sections 4.2 and 5.2 of the SmPC based on final results from studies DS8201-A-J101, DS8201-A-J102, DS8201-A-A103, DS8201-A-A104, DS8201-A-U201, DS8201-A-J202, DS8201-A-J203, DS8201-A-U204, DS8201-A-U205, DS8201-A-U206, DS8201-A-U207, DS8201-A-U301, DS8201-A-U302, and DS8201-A-U303, listed as category 3 activity in the RMP. The updated RMP version 7.1 has also been submitted. In addition, the MAH took this opportunity to introduce editorial changes to the SmPC and Annex II.D

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. Afamelanotide - SCENESSE (CAP) - PSUSA/00010314/202306

Applicant: Clinuvel Europe Limited

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.2. Alpelisib - PIQRAY (CAP) - PSUSA/00010871/202305

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Bianca Mulder

Scope: Evaluation of a PSUSA procedure

16.1.3. Amivantamab - RYBREVANT (CAP) - PSUSA/00010977/202305

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Gabriele Maurer

Scope: Evaluation of a PSUSA procedure

16.1.4. Artesunate - ARTESUNATE AMIVAS (CAP) - PSUSA/00010958/202306

Applicant: Amivas Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.5. Bromfenac - YELLOX (CAP) - PSUSA/00000436/202305

Applicant: Bausch + Lomb Ireland Limited

PRAC Rapporteur: Karin Erneholm

Scope: Evaluation of a PSUSA procedure

16.1.6. Budesonide[73] - KINPEYGO (CAP) - PSUSA/00011007/202306

Applicant: STADA Arzneimittel AG

[73] For centrally authorised products indicated for primary immunoglobulin A nephropathy only

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Evaluation of a PSUSA procedure

16.1.7. Buprenorphine[74] - SIXMO (CAP) - PSUSA/00010778/202305

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

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.8. Cannabidiol[75] - EPIDYOLEX (CAP) - PSUSA/00010798/202306

Applicant: Jazz Pharmaceuticals Ireland Limited

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.1.9. Cholera vaccine, oral, live - VAXCHORA (CAP) - PSUSA/00010862/202306

Applicant: Bavarian Nordic A/S

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

16.1.10. Coronavirus (COVID-19) vaccine (recombinant, adjuvanted) - NUVAXOVID (CAP) - PSUSA/00010972/202306

Applicant: Novavax CZ, a.s.

PRAC Rapporteur: Gabriele Maurer

Scope: Evaluation of a PSUSA procedure

16.1.11. Darunavir, cobicistat - REZOLSTA (CAP) - PSUSA/00010315/202305

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Valentina Di Giovanni

Scope: Evaluation of a PSUSA procedure

16.1.12. Decitabine - DACOGEN (CAP) - PSUSA/00009118/202305

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

[74] Implant
[75] For centrally authorised product(s) only

16.1.13. Delafloxacin - QUOFENIX (CAP) - PSUSA/00010822/202306

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

PRAC Rapporteur: Petar Mas

Scope: Evaluation of a PSUSA procedure

16.1.14. Efgartigimod alfa - VYVGART (CAP) - PSUSA/00011014/202306

Applicant: Argenx

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

16.1.15. Efmoroctocog alfa - ELOCTA (CAP) - PSUSA/00010451/202306

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Sonja Hrabcik

Scope: Evaluation of a PSUSA procedure

16.1.16. Eladocagene exuparvovec - UPSTAZA (CAP) - PSUSA/00011004/202306

Applicant: PTC Therapeutics International Limited, ATMP

PRAC Rapporteur: Gabriele Maurer

Scope: Evaluation of a PSUSA procedure

16.1.17. Emedastine - EMADINE (CAP) - PSUSA/00001207/202305

Applicant: Immedica Pharma AB

PRAC Rapporteur: Nathalie Gault

Scope: Evaluation of a PSUSA procedure

16.1.18. Enfortumab vedotin - PADCEV (CAP) - PSUSA/00010989/202306

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Eva Jirsová

Scope: Evaluation of a PSUSA procedure

16.1.19. Entrectinib - ROZLYTREK (CAP) - PSUSA/00010874/202306

Applicant: Roche Registration GmbH

PRAC Rapporteur: Bianca Mulder

Scope: Evaluation of a PSUSA procedure

16.1.20. Etranacogene dezaparvovec - HEMGENIX (CAP) - PSUSA/00011037/202305

Applicant: CSL Behring GmbH, ATMP

PRAC Rapporteur: Bianca Mulder

Scope: Evaluation of a PSUSA procedure

16.1.21. Fidaxomicin - DIFICLIR (CAP) - PSUSA/00001390/202305

Applicant: Tillotts Pharma GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedurP

16.1.22. Formoterol fumarate dihydrate, glycopyrronium bromide, budesonide - RILTRAVA AEROSPHERE (CAP); TRIXEO AEROSPHERE (CAP) - PSUSA/00010908/202306

Applicant: AstraZeneca AB

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.1.23. Gemtuzumab ozogamicin - MYLOTARG (CAP) - PSUSA/00010688/202305

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Carla Torre

Scope: Evaluation of a PSUSA procedure

16.1.24. Givosiran - GIVLAARI (CAP) - PSUSA/00010839/202305

Applicant: Alnylam Netherlands B.V.

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.25. Human fibrinogen, human thrombin - EVICEL (CAP); TACHOSIL (CAP); VERASEAL (CAP) - PSUSA/00010297/202306

Applicant: Omrix Biopharmaceuticals N. V. (Evicel), Corza Medical GmbH (TachoSil), Instituto Grifols, S.A. (VeraSeal)

PRAC Rapporteur: Gabriele Maurer

Scope: Evaluation of a PSUSA procedure

16.1.26. Imiglucerase - CEREZYME (CAP) - PSUSA/00001727/202305

Applicant: Sanofi B.V.

PRAC Rapporteur: Liana Martirosyan

Scope: Evaluation of a PSUSA procedure

16.1.27. Indacaterol, mometasone furoate - ATECTURA BREEZHALER (CAP); BEMRIST BREEZHALER (CAP) - PSUSA/00010850/202305

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.1.28. Inebilizumab - UPLIZNA (CAP) - PSUSA/00010996/202306

Applicant: Horizon Therapeutics Ireland DAC

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.1.29. Larotrectinib - VITRAKVI (CAP) - PSUSA/00010799/202305

Applicant: Bayer AG

PRAC Rapporteur: Rugile Pilviniene

Scope: Evaluation of a PSUSA procedure

16.1.30. Latanoprost, netarsudil - ROCLANDA (CAP) - PSUSA/00010905/202306

Applicant: Santen Oy

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.31. Levodopa - INBRIJA (CAP) - PSUSA/00107800/202306

Applicant: Acorda Therapeutics Ireland Limited

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Evaluation of a PSUSA procedure

16.1.32. Lonafarnib - ZOKINVY (CAP) - PSUSA/00011005/202305

Applicant: EigerBio Europe Limited

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.33. Luspatercept - REBLOZYL (CAP) - PSUSA/00010860/202306

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Jo Robays

Scope: Evaluation of a PSUSA procedure

16.1.34. Maribavir - LIVTENCITY (CAP) - PSUSA/00011024/202305

Applicant: Takeda Pharmaceuticals International AG Ireland Branch

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.35. Methylthioninium chloride - LUMEBLUE (CAP); METHYLTHIONINIUM CHLORIDE PROVEBLUE (CAP) - PSUSA/00002029/202305

Applicant: Alfasigma S.p.A. (Lumeblue), Provepharm SAS (Methylthioninium chloride Proveblue)

PRAC Rapporteur: Mari Thorn

Scope: Evaluation of a PSUSA procedure

16.1.36. Netarsudil - RHOKIINSA (CAP) - PSUSA/00107812/202306

Applicant: Santen Oy

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

16.1.37. Nonacog beta pegol - REFIXIA (CAP) - PSUSA/00010608/202305

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Gabriele Maurer

Scope: Evaluation of a PSUSA procedure

16.1.38. Nusinersen - SPINRAZA (CAP) - PSUSA/00010595/202305

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.39. Obeticholic acid - OCALIVA (CAP) - PSUSA/00010555/202305

Applicant: Advanz Pharma Limited

PRAC Rapporteur: Liana Martirosyan

Scope: Evaluation of a PSUSA procedure

16.1.40. Octreotide[76] - MYCAPSSA (CAP) - PSUSA/00011036/202306

Applicant: Amryt Pharmaceuticals DAC

PRAC Rapporteur: Eamon O'Murchu

[76] For centrally authorised product(s) only

Scope: Evaluation of a PSUSA procedure

16.1.41. Pandemic influenza vaccine (H5N1) (live attenuated, nasal) - PANDEMIC INFLUENZA VACCINE H5N1 ASTRAZENECA (CAP) - PSUSA/00010501/202305

Applicant: AstraZeneca AB

PRAC Rapporteur: Sonja Hrabcik

Scope: Evaluation of a PSUSA procedure

16.1.42. Pertuzumab, trastuzumab - PHESGO (CAP) - PSUSA/00010906/202306

Applicant: Roche Registration GmbH

PRAC Rapporteur: Gabriele Maurer

Scope: Evaluation of a PSUSA procedure

16.1.43. Pneumococcal polysaccharide conjugate vaccine (20-valent, adsorbed) - APEXXNAR (CAP) - PSUSA/00010981/202306

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

16.1.44. Polatuzumab vedotin - POLIVY (CAP) - PSUSA/00010817/202306

Applicant: Roche Registration GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.45. Relugolix, estradiol, norethisterone acetate - RYEQO (CAP) - PSUSA/00010942/202305

Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.46. Roxadustat - EVRENZO (CAP) - PSUSA/00010955/202306

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Anna Mareková

Scope: Evaluation of a PSUSA procedure

16.1.47. Satralizumab - ENSPRYNG (CAP) - PSUSA/00010944/202305

Applicant: Roche Registration GmbH

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.1.48. Setmelanotide - IMCIVREE (CAP) - PSUSA/00010941/202305

Applicant: Rhythm Pharmaceuticals Netherlands B.V.,

PRAC Rapporteur: Anna Mareková

Scope: Evaluation of a PSUSA procedure

16.1.49. Sonidegib - ODOMZO (CAP) - PSUSA/00010408/202306

Applicant: Sun Pharmaceutical Industries Europe B.V.

PRAC Rapporteur: Petar Mas

Scope: Evaluation of a PSUSA procedure

16.1.50. Sotorasib - LUMYKRAS (CAP) - PSUSA/00010970/202305

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Evaluation of a PSUSA procedure

16.1.51. Tabelecleucel - EBVALLO (CAP) - PSUSA/00011028/202306

Applicant: Pierre Fabre Medicament, ATMP

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.1.52. Tezepelumab - TEZSPIRE (CAP) - PSUSA/00011015/202306

Applicant: AstraZeneca AB

PRAC Rapporteur: Eva Jirsová

Scope: Evaluation of a PSUSA procedure

16.1.53. Tilmanocept - LYMPHOSEEK (CAP) - PSUSA/00010313/202305

Applicant: Navidea Biopharmaceuticals Europe Ltd.

PRAC Rapporteur: Rugile Pilviniene

Scope: Evaluation of a PSUSA procedure

16.1.54. Tirbanibulin - KLISYRI (CAP) - PSUSA/00010943/202306

Applicant: Almirall, S.A.

PRAC Rapporteur: Anna Mareková

Scope: Evaluation of a PSUSA procedure

16.1.55. Tozinameran (COMIRNATY), tozinameran, riltozinameran (COMIRNATY Original/Omicron BA.1), tozinameran, famtozinameran (COMIRNATY Original/Omicron BA.4-5), raxtozinameran (COMIRNATY Omicron XBB.1.5) - COMIRNATY (CAP) - PSUSA/00010898/202306

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Liana Martirosyan

Scope: Evaluation of a PSUSA procedure

16.1.56. Tralokinumab - ADTRALZA (CAP) - PSUSA/00010937/202306

Applicant: LEO Pharma A/S

PRAC Rapporteur: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

16.1.57. Trastuzumab deruxtecan - ENHERTU (CAP) - PSUSA/00010894/202306

Applicant: Daiichi Sankyo Europe GmbH

PRAC Rapporteur: Carla Torre

Scope: Evaluation of a PSUSA procedure

16.1.58. Treosulfan[77] - TRECONDI (CAP) - PSUSA/00010777/202306

Applicant: medac Gesellschaft fur klinische Spezialpraparate mbH

PRAC Rapporteur: Julia Pallos

Scope: Evaluation of a PSUSA procedure

16.1.59. Turoctocog alfa pegol - ESPEROCT (CAP) - PSUSA/00010782/202306

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Gabriele Maurer

Scope: Evaluation of a PSUSA procedure

16.1.60. Vadadustat - VAFSEO (CAP) - PSUSA/00011050/202306

Applicant: AKEBIA EUROPE Limited

PRAC Rapporteur: Eva Jirsová

Scope: Evaluation of a PSUSA procedure

16.1.61. Varenicline - CHAMPIX (CAP) - PSUSA/00003099/202305

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Karin Erneholm

[77] For centrally authorised product

Scope: Evaluation of a PSUSA procedure

16.1.62. Vutrisiran - AMVUTTRA (CAP) - PSUSA/00011021/202306

Applicant: Alnylam Netherlands B.V.

PRAC Rapporteur: Liana Martirosyan

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

16.2.1. Treprostinil - TREPULMIX (CAP); NAP - PSUSA/00003013/202305

Applicant: SciPharm Sarl (Trepulmix), various

PRAC Rapporteur: Zane Neikena

Scope: Evaluation of a PSUSA procedure

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

16.3.1. Aciclovir (NAP) - PSUSA/00000048/202306

Applicant(s): various

PRAC Lead: Marie Louise Schougaard Christiansen

Scope: Evaluation of a PSUSA procedure

16.3.2. Azithromycin[78] (NAP) - PSUSA/00010491/202304

Applicant(s): various

PRAC Lead: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

16.3.3. Azithromycin[79] (NAP) - PSUSA/00010492/202304

Applicant(s): various

PRAC Lead: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

16.3.4. Chlorpromazine (NAP) - PSUSA/00000715/202305

Applicant(s): various

PRAC Lead: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

[78] Systemic use formulation(s) only
[79] Ocular use formulation(s) only

16.3.5. Cyproterone, ethinylestradiol (NAP) - PSUSA/00000906/202305

Applicant(s): various

PRAC Lead: Bianca Mulder

Scope: Evaluation of a PSUSA procedure

16.3.6. Ebastine (NAP) - PSUSA/00001191/202305

Applicant(s): various

PRAC Lead: Marie Louise Schougaard Christiansen

Scope: Evaluation of a PSUSA procedure

16.3.7. Fluorescein[80] (NAP) - PSUSA/00009153/202304

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.3.8. Irinotecan[81] (NAP) - PSUSA/00001783/202305

Applicant(s): various

PRAC Lead: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

16.3.9. Lanreotide (NAP) - PSUSA/00001826/202305

Applicant(s): various

PRAC Lead: Zane Neikena

Scope: Evaluation of a PSUSA procedure

16.3.10. Latanoprost[82] (NAP) - PSUSA/00001834/202304

Applicant(s): various

PRAC Lead: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.3.11. Norfloxacin (NAP) - PSUSA/00002190/202306

Applicant(s): various

PRAC Lead: Maria del Pilar Rayon

[80] Systemic use only
[81] Except for liposomal formulation(s)
[82] Products with paediatric indication only

Scope: Evaluation of a PSUSA procedure

16.3.12. Patent blue V sodium (NAP) - PSUSA/00002320/202304

Applicant(s): various

PRAC Lead: Melinda Palfi

Scope: Evaluation of a PSUSA procedure

16.3.13. Pelargonium sidoides DC and/or pelargonium reniforme Curt., radix (NAP) - PSUSA/00002329/202306

Applicant(s): various

PRAC Lead: Melinda Palfi

Scope: Evaluation of a PSUSA procedure

16.3.14. Thiamphenicol (NAP) - PSUSA/00002925/202305

Applicant(s): various

PRAC Lead: Valentina Di Giovanni

Scope: Evaluation of a PSUSA procedure

16.3.15. Xylometazoline (NAP) - PSUSA/00003134/202305

Applicant(s): various

PRAC Lead: Zane Neikena

Scope: Evaluation of a PSUSA procedure

16.3.16. Zuclopenthixol (NAP) - PSUSA/00003155/202305

Applicant(s): various

PRAC Lead: Jean-Michel Dogné

16.4. Follow-up to PSUR/PSUSA procedures

16.4.1. Tisagenlecleucel - KYMRIAH (CAP) - EMEA/H/C/004090/LEG 021.1

Applicant: Novartis Europharm Limited, ATMP

PRAC Rapporteur: Gabriele Maurer

Scope: MAH's response to LEG 021 [Submission of further data on cases of secondary malignancies, as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00010702/202208) adopted in March 2023] as per request for supplementary information (RSI) adopted in September 2023

16.5. Variation procedure(s) resulting from PSUSA evaluation

16.5.1. Alglucosidase alfa - MYOZYME (CAP) - EMEA/H/C/000636/II/0094

Applicant: Sanofi B.V.

PRAC Rapporteur: Nathalie Gault

Scope: Update of section 4.2 of the SmPC in order to add home infusion upon request by PRAC following the assessment of PSUSA/00000086/202109 based on a cumulative search of the MAH Global Pharmacovigilance database and literature. The package leaflet and Annex II are updated accordingly. The RMP version 10.0 has also been submitted

16.5.2. Amlodipine, valsartan - COPALIA (CAP) - EMEA/H/C/000774/WS2610/0132; DAFIRO (CAP) - EMEA/H/C/000776/WS2610/0136; EXFORGE (CAP) - EMEA/H/C/000716/WS2610/0131

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Karin Erneholm

Scope: To add interaction with tacrolimus to section 4.5 of the SmPC following the outcome of the amlodipine/ramipril PSUSA (PSUSA/00000181/201503). The package leaflet was updated accordingly. In addition the MAH is removing the Adverse Events in section 4.8 of SmPC where "Hypokalaemia, Anorexia, Hypercalcaemia, Hyperlipidaemia and Hyperuricaemia" that had been added in error. The MAH is also including a QRD update to package leaflet section 5 on the expiry of the product

16.5.3. Amlodipine, valsartan, hydrochlorothiazide - COPALIA HCT (CAP) - EMEA/H/C/001159/WS2609/0110; DAFIRO HCT (CAP) - EMEA/H/C/001160/WS2609/0112; EXFORGE HCT (CAP) - EMEA/H/C/001068/WS2609/0109

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Karin Erneholm

Scope: To add interaction with tacrolimus to section 4.5 of the SmPC following the outcome of the amlodipine/ramipril PSUSA (PSUSA/00000181/201503). The package leaflet was updated accordingly

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

Applicant: Sanofi B.V.

PRAC Rapporteur: Nathalie Gault

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

16.6. Expedited summary safety reviews[83]

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)[84]

17.1.1. Axicabtagene ciloleucel – YESCARTA (CAP) - EMEA/H/C/PSA/S/0102.3

Applicant: Kite Pharma EU B.V., ATMP

PRAC Rapporteur: Karin Erneholm

Scope: MAH's response to S/0102.2 on the substantial amendment to a protocol for a long-term, non-interventional study of recipients of Yescarta for treatment of relapsed or refractory diffuse large B-cell lymphoma and primary mediastinal B-cell lymphoma

17.2. Protocols of PASS non-imposed in the marketing authorisation(s)[85]

17.2.1. Abaloparatide - ELADYNOS (CAP) - EMEA/H/C/005928/MEA 001.1

Applicant: Theramex Ireland Limited

PRAC Rapporteur: Karin Erneholm

Scope: MAH's response to MEA 001 [Submission of a protocol for an European non-interventional PASS to assess serious cardiovascular events of MI, stroke, all-cause and cardiovascular mortality, and arrhythmias for abaloparatide] as per the request for supplementary information (RSI) adopted in June 2023

17.2.2. Cabotegravir - APRETUDE (CAP) - EMEA/H/C/005756/MEA 002

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Martin Huber

Scope: Submission of a protocol for a non-interventional PASS as category 3 of the RMP: Antiretroviral Pregnancy Registry (APR) to monitor CAB LA PrEP use in Pregnancy. The APR is an international registry that monitors prenatal exposures to antiretroviral (ARV) drugs to detect a potential increase in the risk of birth defects through a prospective exposure registration cohort. The registry's primary objective is to monitor for birth defects among ARV exposed pregnancies. The registry has been monitoring pregnancies with prenatal

[83] 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
[84] In accordance with Article 107n of Directive 2001/83/EC
[85] 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

exposure to ARVs used for PrEP since the approval of ARVs used in oral PrEP. The APR is a MAH-sponsored study involving the collaborative effort of multiple companies. Data from the APR will assess maternal (pregnancy outcomes, abortions, still births) and foetal outcomes (premature births and low birth weight) following CAB LA PrEP use during pregnancy. Exposure to CAB LA PrEP relative to gestation period and conception will be captured in the registry, thus enabling assessment of pre-conception exposures along with first, second and third trimester exposures

17.2.3. Cabotegravir - VOCABRIA (CAP) - EMEA/H/C/004976/MEA 006.4

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Martin Huber

Scope: Submission of an amended protocol for a category 3 study (Study No 215325) included in the RMP: Pregnancy and Neonatal Outcomes following Prenatal Exposure to Cabotegravir: Data from The Antiretroviral Pregnancy Registry (APR)

17.2.4. Coronavirus (COVID-19) vaccine (recombinant, adjuvanted) - NUVAXOVID (CAP) - EMEA/H/C/005808/MEA 005.2

Applicant: Novavax CZ, a.s.

PRAC Rapporteur: Gabriele Maurer

Scope: Amended protocol (v.3.0) for study 2019nCoV-405: Global Safety Surveillance Study of Pregnancy and Infant Outcomes Study Using C-VIPER. A registry-based observational cohort safety surveillance study to characterise the population of pregnant women who are vaccinated with Nuvaxovid, estimate the frequency of selected adverse pregnancy outcomes in women and selected adverse foetal/neonatal/infant outcomes at birth and up to the first 12 months of life of infants from pregnancies in women who received Nuvaxovid during pregnancy

17.2.5. Efgartigimod alfa - VYVGART (CAP) - EMEA/H/C/005849/MEA 007

Applicant: Argenx

PRAC Rapporteur: Rhea Fitzgerald

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

17.2.6. Fentanyl - INSTANYL (CAP) - EMEA/H/C/000959/MEA 029.5

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Tiphaine Vaillant

Scope: MAH's response to MEA 029.4 [Updated protocol for study Instanyl-5002 (listed as a category 3 study in the RMP): a non-interventional study to assess the effectiveness of updated educational materials on prescribers' knowledge and behaviour with respect to risks associated with Instanyl (fentanyl) off-label use together with an interim report and

the statistical analysis plan (SAP)] as per request for supplementary information (RSI) adopted in September 2023

17.2.7. Ipilimumab - YERVOY (CAP) - EMEA/H/C/002213/MEA 036.6

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Bianca Mulder

Scope: Protocol Amendment (v. 3.0/Study no.: CA184557): 'long-term follow-up of nivolumab and ipilimumab (as monotherapy and as combination therapy)-treated paediatric patients enrolled in the Dutch melanoma treatment registry (DMTR)'

17.2.8. Niraparib, abiraterone acetate - AKEEGA (CAP) - EMEA/H/C/005932/MEA 001.1

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Jan Neuhauser

Scope: Protocol for a non-interventional PASS (PCSONCA0485, RMP Cat. 3): PASS to characterise the risk of second primary malignancies (SPM) including MDS/AML among metastatic prostate cancer patients exposed to AKEEGA

17.2.9. Nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/MEA 057

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Martin Huber

Scope: PASS Protocol Amendment (v. 3.0 / Study no.: CA184557): long-term follow-up of nivolumab and ipilimumab (as monotherapy and as combination therapy)-treated paediatric patients enrolled in the Dutch melanoma treatment registry (DMTR)

17.2.10. Ponesimod – PONVORY (CAP) - EMEA/H/C/005163/MEA/004.4

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Karin Erneholm

Scope: Revised Protocol for study number: PCSNSP003693: Survey among healthcare professionals (neurologists treating patients with MS along with MS specialist nurses) in selected European countries to evaluate knowledge and behaviors required for the safe use of ponesimod. Due date: 1 year after the end of data collection [cat.3]

17.2.11. Risankizumab - SKYRIZI (CAP) - EMEA/H/C/004759/MEA 010.2

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Liana Martirosyan

Scope: Revised PASS Protocol (v2.1 / Study no.: P23-654): long-term comparative cohort study in patients with Crohn's disease in a real world setting. Additional long-term data from the real-world experience of patients with Crohn's disease treated with risankizumab to assess product potential risks. A comparative cohort study will be conducted to estimate rates of malignancy (malignancy excluding NMSC, NMSC), serious infections, serious

hypersensitivity reactions, and MACE in risankizumab treated patients with Crohn's disease, relative to alternative systemic therapies (e.g., biologics)

17.2.12. Romosozumab - EVENITY (CAP) - EMEA/H/C/004465/MEA 001.9

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Tiphaine Vaillant

Scope: Protocol amendment for study OP0005: European non-interventional PASS to study the adherence to the risk minimisation measures (RMMs) in the product information by estimating the compliance with contraindications and target indication(s) amongst incident romosozumab users, and analysing the utilisation pattern using the EU-adverse drug reactions (EU-ADR) Alliance as per request for supplementary information (RSI) adopted in July 2023 (MEA 001.6)

17.2.13. Romosozumab - EVENITY (CAP) - EMEA/H/C/004465/MEA 002.9

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Tiphaine Vaillant

Scope: Protocol amendment for study OP0004: European non-interventional PASS to evaluate potential differences in terms of serious cardiovascular adverse events between romosozumab and currently available therapies used in comparable patients in real-world conditions using the EU-adverse drug reactions (EU-ADR) Alliance as per request of supplementary information (RSI) adopted in July 2023 (MEA 002.6)

17.2.14. Romosozumab - EVENITY (CAP) - EMEA/H/C/004465/MEA 003.7

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Tiphaine Vaillant

Scope:Protocol amendment for study OP0006: evaluate potential differences in terms of serious infection between romosozumab and currently available therapies used in comparable patients in real-world conditions using the EU-adverse drug reactions (EU-ADR) Alliance as per request of supplementary information (RSI) adopted in July 2023 (MEA 003.4)

17.2.15. Ruxolitinib - OPZELURA (CAP) - EMEA/H/C/005843/MEA 001

Applicant: Incyte Biosciences Distribution B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Protocol for study INCB88888-037 (PASS) (non-interventional, RMP Category 3) to evaluate the safety of long-term ruxolitinib cream use with respect to incidence of non-melanoma skin cancers

17.2.16. Tezepelumab - TEZSPIRE (CAP) - EMEA/H/C/005588/MEA 001.2

Applicant: AstraZeneca AB

PRAC Rapporteur: Eva Jirsová

Scope: MAH's response to MEA 001.1 [PROTOCOL D5180R00010:: A Non-Interventional Multi-Database Post-Authorisation Study to Assess Pregnancy-Related Safety Data from Women with Severe Asthma Exposed to Tezepelumab] as per RSI adopted in October 2023

17.2.17. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/MEA 011.7

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Martirosyan

Scope: Protocol amendment for study A3921317 (listed as a category 3 study in the RMP): a prospective non-interventional comparative active surveillance PASS of serious infection, malignancy, cardiovascular and other safety events of interest among patients treated with Xeljanz (tofacitinib) for moderately to severely active rheumatoid arthritis (RA) within the German registry Rheumatoide Arthritis: Beobachtung der Biologika-Therapie (RABBIT) following on the recommendation of the signal on major adverse cardiovascular events (MACE) and malignancies excluding non-melanoma skin cancer (NMSC) (EPITT 19382) finalised in June 2021

17.2.18. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/MEA 025.2

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Martirosyan

Scope: MAH's response to MEA 025.1 and revised protocol for PASS Study No921403 (RMP Cat. 3): a PASS of the Utilisation and Prescribing Patterns of Xeljanz (tofacitinib) Using an Administrative Healthcare Database in France: a descriptive drug utilisation study using real-world data collected from routine clinical care in France. The overall goal is to determine if there is evidence that prescribers in France are compliant with the recommendations and limitations for use described in the tofacitinib additional risk minimisation measures (aRMM) materials as per the request for supplementary information (RSI) adopted in September 2023

17.2.19. Ublituximab - BRIUMVI (CAP) - EMEA/H/C/005914/MEA 001.1

Applicant: Neuraxpharm Pharmaceuticals S.L.

PRAC Rapporteur: Liana Martirosyan

Scope: MAH's response to MEA 001 [Protocol for PASS Study TG1101-RMS402 (cat. 3): a long-term observational study of the safety and effectiveness of ublituximab in patients with relapsing multiple sclerosis, to assess the incidence of serious infections and malignancies in relapsing multiple sclerosis (MS) participants treated with ublituximab compared with other disease-modifying treatments (DMTs) observed longitudinally, to evaluate the long-term safety of ublituximab compared to other DMTs in patients with relapsing forms of MS in a real world setting and to assess long-term effectiveness of ublituximab compared with other DMTs in participants with relapsing forms of MS] as per request for supplementary information (RSI) adopted in October 2023 (25-28 September 2023)

17.2.20. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/MEA 048.4

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: MAH's response to MEA 048.3 [Revised protocol for an observational PASS to describe the safety of ustekinumab and other ulcerative colitis treatments in a cohort of patients with ulcerative colitis using SNDS PCSIMM002659 together with the first progress report] as per request for supplementary information (RSI) adopted in December 2021

17.2.21. Vosoritide - VOXZOGO (CAP) - EMEA/H/C/005475/MEA 005.3

Applicant: BioMarin International Limited

PRAC Rapporteur: Zane Neikena

Scope: MAH's response to MEA 005.2 [Protocol Amendment (v.6., PASS 111-603): a multicentre, non-interventional study to evaluate long-term safety in patients with achondroplasia treated with Voxzogo (vosoritide)] as per request for supplementary information (RSI) adopted in December 2022

17.3. Results of PASS imposed in the marketing authorisation(s)[86]

None

17.4. Results of PASS non-imposed in the marketing authorisation(s)[87]

17.4.1. Adalimumab - HEFIYA (CAP) - EMEA/H/C/004865/WS2591/0050/G; HYRIMOZ (CAP) - EMEA/H/C/004320/WS2591/0049/G

Applicant: Sandoz GmbH

PRAC Rapporteur: Mari Thorn

Scope: C.I.13: Submission of the final report from study RABBIT. This is a German registry for the long-term observation of therapy with biologics in adult patients with rheumatoid arthritis. C.I.13: Submission of the final report from the British Association of Dermatologists Biologics and Immunomodulators Register (BADBIR). This is a registry to investigate the long-term safety outcomes of psoriasis patients treated with biologic therapy. C.I.13: Submission of the final report from the Inflammatory Bowel Disease Registry (UK-IBD). This registry was used to identify adverse reactions to Hyrimoz in a cohort of inflammatory bowel disease patients managed in a real-world setting

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

Applicant: Takeda Pharmaceuticals International AG Ireland Branch

PRAC Rapporteur: Liana Martirosyan

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

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

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

Applicant: Sanofi B.V.

PRAC Rapporteur: Nathalie Gault

Scope: Submission of the final non-interventional Pompe Registry Report 2022 (MEA024 and MEA025)

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

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Mari Thorn

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

17.4.5. Filgrastim - NIVESTIM (CAP) - EMEA/H/C/001142/II/0074/G

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Kirsti Villikka

Scope: Grouped application consisting of:
C.I.13: Submission of the final report from non-interventional PASS study ZOB-NIV-1513/C1121008 listed as a category 3 study in the RMP. This is a multinational, multi-centre, prospective, non-interventional, PASS in Healthy Donors (HDs) exposed to nivestim (biosimilar filgrastim) for Haematopoietic Stem Cell (HSC) Mobilisation (NEST). The RMP version 12 has also been submitted.
C.I.11 for RMP: Submission of an updated RMP version 12.0 in order to align it with the reference product, Neupogen, RMP v. 6.3 dated June 2022

17.4.6. Isatuximab - SARCLISA (CAP) - EMEA/H/C/004977/II/0024

Applicant: Sanofi Winthrop Industrie

PRAC Rapporteur: Monica Martinez Redondo

Scope: Submission of the final report from study SARSAC09715, listed as a category 3 study in the RMP. This is a non-interventional survey to evaluate the effectiveness of the isatuximab educational materials to minimize the risk of interference for blood typing (minor antigen) (positive indirect Coombs test). The RMP version 1.3 has also been submitted

17.4.7. Naltrexone hydrochloride, bupropion hydrochloride - MYSIMBA (CAP) - EMEA/H/C/003687/II/0066

Applicant: Orexigen Therapeutics Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: Submission of final report from study NB-453 study, listed as a category 3 study in the RMP. This is a non-interventional qualitative research using online focus groups to assess understanding, attitude and behaviour for usage of the Mysimba Physician Prescribing Checklist (PPC) among physicians in the European Union (EU), following a previous cross-sectional survey that aimed at evaluating the effectiveness of the same PPC (Study NB-452). The RMP version 12.10 has also been submitted

17.4.8. Piperaquine tetraphosphate, artenimol - EURARTESIM (CAP) - EMEA/H/C/001199/II/0040/G

Applicant: Alfasigma S.p.A.

PRAC Rapporteur: Martin Huber

Scope: C.I.13: Submission of the final report from the effectiveness evaluation survey for Eurartesim (protocol no. 3366) listed as a category 3 study in the RMP. This is a European multi-centre online survey to assess physician understanding of the revised edition of the educational material. Consequential changes to RMP version 16.1 have been implemented. C.I.11.b: Submission of an updated RMP version 16.1 in order to delete "Severe Malaria" from the Missing Information

17.4.9. Plasmodium falciparum and hepatitis B vaccine (recombinant, adjuvanted) - MOSQUIRIX (Art 58) - EMEA/H/W/002300/II/0077

Applicant: GlaxoSmithkline Biologicals SA

PRAC Rapporteur: Jean-Michel Dogné

Scope: Submission of the final report from study EPI-MALALARIA-002 VS AME (115055). This is a non-interventional study, designed to estimate the incidence of diseases specified as adverse events of special interest, of other adverse events leading to hospitalisation or death, and of meningitis in infants and young children in sub-Saharan Africa

17.4.10. Trastuzumab deruxtecan - ENHERTU (CAP) - EMEA/H/C/005124/II/0036

Applicant: Daiichi Sankyo Europe GmbH

PRAC Rapporteur: Carla Torre

Scope: Submission of the final report from study 'EU survey of relevant healthcare professionals on understanding of key risk minimisations measures pertaining to ILD/pneumonitis' listed as a category 3 study in the RMP. This is a non-imposed non-interventional PASS

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

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Rhea Fitzgerald

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

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

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: Submission of the final report from study RRA-20745 listed as a category 3 study in the RMP. This is an observational PASS to describe the safety of ustekinumab and other Crohn's disease treatments in a cohort of patients with Crohn's disease. The RMP version 27.2 has also been submitted

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

17.5.1. Botulinum toxin type A - NUCEIVA (CAP) - EMEA/H/C/004587/MEA 002.4

Applicant: Evolus Pharma B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Annual update for the Non-Interventional PASS of NUCEIVA for the Treatment of Moderate-to-Severe Glabellar Lines

17.5.2. Ciltacabtagene autoleucel - CARVYKTI (CAP) - EMEA/H/C/005095/ANX 003.1

Applicant: Janssen-Cilag International NV, ATMP

PRAC Rapporteur: Jo Robays

Scope: First interim report for study: An Observational PASS to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel

17.5.3. Coronavirus (COVID-19) vaccine (recombinant, adjuvanted) - NUVAXOVID (CAP) - EMEA/H/C/005808/MEA 006.3

Applicant: Novavax CZ, a.s.

PRAC Rapporteur: Gabriele Maurer

Scope: Interim report for study 2019nCoV-404: US PASS to evaluate the pooled of risk of selected AESI within specified time periods after vaccination with Nuvaxovid using a claim and/or EHR database

17.5.4. Damoctocog alfa pegol - JIVI (CAP) - EMEA/H/C/004054/ANX 001.2

Applicant: Bayer AG

PRAC Rapporteur: Bianca Mulder

Scope: Second ínterim report for an observational study evaluating long-term safety of real-world treatment with damoctocog alfa pegol in previously treated patients with hemophilia A' (HA-SAFE). The HA-SAFE study is a post-authorisation measure defined in Annex II.D of the Jivi EU product information. The study protocol was agreed with EMA/PRAC in Nov 2019 (outcome letter); the date of FPFV was 14 May 2021 (impacted by the Covid-19 pandemic). As Annex to the first interim report also the statistical analysis

plan is submitted

17.5.5. Difelikefalin - KAPRUVIA (CAP) - EMEA/H/C/005612/MEA 002.1

Applicant: Vifor Fresenius Medical Care Renal Pharma France

PRAC Rapporteur: Mari Thorn

Scope: Interim report DSUR version 10.0 for study CR845- 310301 (listed as category 3 study in the RMP): a Multicenter, Randomised, Double-blind, Placebo-controlled 12-Week Study to Evaluate the Safety and Efficacy of Oral Difelikefalin in Advanced Chronic Kidney Disease Subjects With Moderate-to-Severe Pruritus and Not on Dialysis With an up to 52-Week Long-term Extension

17.5.6. Difelikefalin - KAPRUVIA (CAP) - EMEA/H/C/005612/MEA 003.1

Applicant: Vifor Fresenius Medical Care Renal Pharma France

PRAC Rapporteur: Mari Thorn

Scope: Interim report DSUR version 10.0 for study CR845- 310302 (listed as category 3 study in the RMP): a Multicenter, Randomised, Double-blind, Placebo-controlled 12-Week Study to Evaluate the Safety and Efficacy of Oral Difelikefalin in Advanced Chronic Kidney Disease Subjects With Moderate-to-Severe Pruritus and Not on Dialysis With an up to 52-Week Long-term Extension

17.5.7. Difelikefalin - KAPRUVIA (CAP) - EMEA/H/C/005612/MEA 004.1

Applicant: Vifor Fresenius Medical Care Renal Pharma France

PRAC Rapporteur: Mari Thorn

Scope: Interim report DSUR version 10.0 for study CR845- 310501 (listed as category 3 study in the RMP): a Two-part, Multicenter, Randomised, Double-blind Study to Evaluate the Efficacy and Safety of Oral Difelikefalin as Adjunct Therapy to a Topical Corticosteroid for Moderate-to-Severe Pruritus in Adult Subjects With Atopic Dermatitis

17.5.8. Elasomeran - SPIKEVAX (CAP) - EMEA/H/C/005791/MEA 066.3

Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Second Interim Report for study mRNA-1273-P911 Long-term outcomes of myocarditis following administration of Spikevax (COVID-19 vaccine mRNA) and MAH's responses to MEA 066.2

17.5.9. Hydroxycarbamide - SIKLOS (CAP) - EMEA/H/C/000689/MEA 035.1

Applicant: Theravia

PRAC Rapporteur: Jo Robays

Scope: Third interim report for ESCORT-HU Extension: European Sickle Cell Disease Cohort – Hydroxyurea

17.5.10. Idecabtagene vicleucel - ABECMA (CAP) - EMEA/H/C/004662/MEA 007

Applicant: Bristol-Myers Squibb Pharma EEIG, ATMP

PRAC Rapporteur: Ulla Wändel Liminga

Scope: First interim report for long-term follow-up study (GC-LTFU-001) to assess the risk of delayed AEs following exposure to GM T cells, to monitor for long-term persistence of GM T cells, including analysis of vector integration sites, as appropriate and to monitor for generation of replication competent retroviruses

17.5.11. Ketoconazole - KETOCONAZOLE HRA (CAP) - EMEA/H/C/003906/ANX 002.11

Applicant: HRA Pharma Rare Diseases

PRAC Rapporteur: Petar Mas

Scope: Sixth ínterim anual report for PASS EUPAS21731: Prospective, multi-country, observational registry to collect clinical information on patients with endogenous Cushing's syndrome exposed to Ketoconazole (using the existing European Registry on Cushing's Syndrome (ERCUSYN)), to assess drug utilization pattern and to document the safety (e.g. hepatotoxicity, QT prolongation) and effectiveness of Ketoconazole

17.5.12. Lisocabtagene maraleucel, lisocabtagene maraleucel - BREYANZI (CAP) - EMEA/H/C/004731/MEA 007

Applicant: Bristol-Myers Squibb Pharma EEIG, ATMP

PRAC Rapporteur: Gabriele Maurer

Scope: Interim report for LTFU study (GC LTFU 001): Long-term follow-up of safety and efficacy for all paediatric and adult subjects exposed do a GM T cell therapy in Bristol-Myers Squibb sponsored, or Bristol Myers Squibb alliance partner sponsored, clinical trials in accordance with Health Authorities' guidance for long-term (up to 15 years) follow-up of subjects treated with gene therapy products

17.5.13. Natalizumab - TYSABRI (CAP) - EMEA/H/C/000603/MEA 064.4

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Gabriele Maurer

Scope: Seventh annual interim report for an observational study utilising data from the US Tysabri TOUCH programme and select EU MS Registries to estimate the risk of progressive multifocal leukoencephalopathy (PML) and other serious opportunistic infections among patients who were exposed to an MS disease modifying treatment prior to treatment with Tysabri. Objectives: to estimate the risk of PML among patients on Tysabri switching from the newer DMTs (including fingolimod,dimethyl fumarate, teriflunomide) and from established DMTs (interferon beta and glatimer acetate). Safety concerns addressed: PML risk in patients switching from DHMTs with immunosuppressant effect

17.5.14. Natalizumab - TYSABRI (CAP) - EMEA/H/C/000603/MEA 066.5

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Gabriele Maurer

Scope: Annual report of a retrospective analysis of extended interval dosing (EID) versus standard interval dosing (SID) to further investigate the efficacy and safety in terms of progressive multifocal leukoencephalopathy (PML) risk reduction with EID relative to SID (TOUCH database)

17.5.15. Patisiran - ONPATTRO (CAP) - EMEA/H/C/004699/MEA 003.6

Applicant: Alnylam Netherlands B.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: Third interim study report for Patisiran-LNP Pregnancy Surveillance Program. To collect primary data on pregnant women from the US, the United Kingdom (UK), France, Spain, Italy, Portugal and Germany, and other potential countries, who have been exposed to patisiran during the exposure window, defined as 12 weeks prior to their last menstrual period (LMP), or at any time during pregnancy. Establish a worldwide Pregnancy Surveillance Program (PSP) to collect and analyze information pertaining to pregnancy complications and birth outcomes in women exposed to patisiran during pregnancy. The collection and analysis of data should continue for a minimum of 10 years

17.5.16. Pitolisant - WAKIX (CAP) - EMEA/H/C/002616/ANX 001.6

Applicant: Bioprojet Pharma

PRAC Rapporteur: Kirsti Villikka

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

17.5.17. Ponesimod - PONVORY (CAP) - EMEA/H/C/005163/MEA 001.4

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Karin Erneholm

Scope: MAH’s response to MEA 001.3 [First annual progress report for study POEM: PASS: Ponesimod Pregnancy Outcomes Program Utilizing Enhanced Pharmacovigilance Monitoring] as per the RSI adopted in September 2023

17.5.18. Risankizumab - SKYRIZI (CAP) - EMEA/H/C/004759/MEA 001.7

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Liana Martirosyan

Scope:Progress report for PASS Study P19-633 (NI/NI, RMP): A post-marketing registry-based prospective cohort study of long term safety of risankizumab in Denmark and Sweden. Long-Term Prospective Cohort Study in Real World Setting

17.5.19. Selexipag - UPTRAVI (CAP) - EMEA/H/C/003774/MEA 003.5

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Nathalie Gault

Scope: Progress report for PASS to evaluate risk minimisation measures for mEDication errors with Uptravi during the titration phase in patients with pulmonary arterial hypertension (PAH) in Clinical prAcTicE (EDUCATE)

17.5.20. Semaglutide - OZEMPIC (CAP) - EMEA/H/C/004174/MEA 002.6

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Mari Thorn

Scope: Fourth progress report for PASS Study No. NN9535-4447: Epidemiological assessment of the risk for pancreatic cancer associated with the use of semaglutide in patients with type 2 diabetes – A cohort study based on Nordic registry data

17.5.21. Semaglutide - RYBELSUS (CAP) - EMEA/H/C/004953/MEA 002.4

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Mari Thorn

Scope: Fourth progress report for PASS Study No. NN9535-4447: Epidemiological assessment of the risk for pancreatic cancer associated with the use of semaglutide in patients with type 2 diabetes – A cohort study based on Nordic registry data

17.5.22. Tozinameran - COMIRNATY (CAP) - EMEA/H/C/005735/MEA 017.8

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Liana Martirosyan

Scope: Statistical analysis plan amendment and interim report for study C4591021 (former ACCESS/VAC4EU: Assessment of occurrence of safety events of interest, including severe or atypical COVID 19 in real-world use of COVID-19 mRNA vaccine (ACCESS/VAC4EU). Post Conditional approval active surveillance study among individuals in Europe receiving the Pfizer BioNTech Coronavirus Disease 2019 (COVID-19) vaccine. (Non-Interv.)

17.5.23. Tozinameran - COMIRNATY (CAP) - EMEA/H/C/005735/MEA 047.4

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Liana Martirosyan

Scope: MAH’s response to MEA 047 [Protocol for study C4591038 (listed as a category 3 study in the RMP): a post conditional approval active surveillance study among individuals in Europe receiving the Pfizer BioNTech coronavirus disease 2019 (COVID-19) vaccine to investigate natural history of post-vaccination myocarditis and pericarditis] as per RSI adopted in May 2022

17.5.24. Turoctocog alfa pegol - ESPEROCT (CAP) - EMEA/H/C/004883/ANX 001.3

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Gabriele Maurer

Scope: Third progress report for study ID: NN7088-4029: PASS: In order to investigate the potential effects of PEG accumulation in the choroid plexus of the brain and other tissues/organs, the MAH should conduct and submit the results of a PASS according to an agreed protocol. Study ID: NN7088-4029 A multinational, prospective, open labelled, non-controlled, non-interventional post-authorisation study of turoctocog alfa pegol (N8-GP) during long-term routine prophylaxis and treatment of bleeding episodes in patients with haemophilia A.MAH also includes the interim results of the study with the data cut-off date 23-Apr-2023

17.5.25. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/MEA 047.4

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: Interim report for an Observational PASS to Describe The Safety of Ustekinumab and Other Biologic Treatments in a Cohort of Patients With Ulcerative Colitis or Crohn's Disease Using Compulsory Swedish Nationwide Healthcare Registers and the Independent Swedish National Quality Register for Inflammatory Bowel Disease

17.6. Others

None

17.7. New Scientific Advice

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

17.8. Ongoing Scientific Advice

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

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

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

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

Based on the review of the available pharmacovigilance data for the medicine(s) listed below and the CHMP Rapporteur's assessment report, PRAC considered that either the renewal of the marketing authorisation procedure could be concluded - and supported the renewal of their marketing authorisations for an unlimited or additional period, as applicable - or no

amendments to the specific obligations of the marketing authorisation under exceptional circumstances for the medicines listed below were recommended. As per the agreed criteria, the procedures were finalised at the PRAC level without further plenary discussion.

18.1. Annual reassessments of the marketing authorisation

18.1.1. Lonafarnib - ZOKINVY (CAP) - EMEA/H/C/005271/S/0008 (without RMP)

Applicant: EigerBio Europe Limited

PRAC Rapporteur: Adam Przybylkowski

Scope: Annual reassessment of the marketing authorisation

18.1.2. Metreleptin - MYALEPTA (CAP) - EMEA/H/C/004218/S/0035 (without RMP)

Applicant: Amryt Pharmaceuticals DAC

PRAC Rapporteur: Adam Przybylkowski

Scope: Annual reassessment of the marketing authorisation

18.1.3. Odevixibat - BYLVAY (CAP) - EMEA/H/C/004691/S/0016 (without RMP)

Applicant: Albireo

PRAC Rapporteur: Adam Przybylkowski

Scope: Annual reassessment of the marketing authorisation

18.2. Conditional renewals of the marketing authorisation

18.2.1. Andexanet alfa - ONDEXXYA (CAP) - EMEA/H/C/004108/R/0041 (without RMP)

Applicant: AstraZeneca AB

PRAC Rapporteur: Bianca Mulder

Scope: Conditional renewal of the marketing authorisation

18.2.2. Ciltacabtagene autoleucel - CARVYKTI (CAP) - EMEA/H/C/005095/R/0025 (without RMP)

Applicant: Janssen-Cilag International NV, ATMP

PRAC Rapporteur: Jo Robays

Scope: Conditional renewal of the marketing authorisation

18.2.3. Lorlatinib - LORVIQUA (CAP) - EMEA/H/C/004646/R/0031 (with RMP)

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Conditional renewal of the marketing authorisation

18.3. Renewals of the marketing authorisation

18.3.1. Ambrisentan - AMBRISENTAN MYLAN (CAP) - EMEA/H/C/004985/R/0009 (without RMP)

Applicant: Mylan Pharmaceuticals Limited

PRAC Rapporteur: Maria del Pilar Rayon

Scope: 5-year renewal of the marketing authorisation

PRAC advice adopted via written procedure on 16 January 2024.

18.3.2. Angiotensin II - GIAPREZA (CAP) - EMEA/H/C/004930/R/0027 (without RMP)

Applicant: Paion Deutschland GmbH

PRAC Rapporteur: Bianca Mulder

Scope: 5-year renewal of the marketing authorisation

18.3.3. Buprenorphine - SIXMO (CAP) - EMEA/H/C/004743/R/0017 (with RMP)

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

PRAC Rapporteur: Adam Przybylkowski

Scope: 5-year renewal of the marketing authorisation

18.3.4. Dolutegravir, lamivudine - DOVATO (CAP) - EMEA/H/C/004909/R/0045 (without RMP)

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: David Olsen

Scope: 5-year renewal of the marketing authorisation

18.3.5. Hydroxycarbamide - XROMI (CAP) - EMEA/H/C/004837/R/0023 (without RMP)

Applicant: Nova Laboratories Ireland Limited

PRAC Rapporteur: Jo Robays

Scope: 5-year renewal of the marketing authorisation

18.3.6. Ioflupane (^{123}I) - STRIASCAN (CAP) - EMEA/H/C/004745/R/0012 (with RMP)

Applicant: CIS BIO International

PRAC Rapporteur: Tiphaine Vaillant

Scope: 5-year renewal of the marketing authorisation

18.3.7. L-lysine hydrochloride, l-arginine hydrochloride - LYSAKARE (CAP) - EMEA/H/C/004541/R/0016 (without RMP)

Applicant: Advanced Accelerator Applications

PRAC Rapporteur: Adam Przybylkowski

Scope: 5-year renewal of the marketing authorisation

18.3.8. Ravulizumab - ULTOMIRIS (CAP) - EMEA/H/C/004954/R/0040 (without RMP)

Applicant: Alexion Europe SAS

PRAC Rapporteur: Kimmo Jaakkola

Scope: 5-year renewal of the marketing authorisation

18.3.9. Talazoparib - TALZENNA (CAP) - EMEA/H/C/004674/R/0017 (without RMP)

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Carla Torre

Scope: 5-year renewal of the marketing authorisation

18.3.10. Trientine - CUFENCE (CAP) - EMEA/H/C/004111/R/0016 (without RMP)

Applicant: Univar Solutions BV

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: 5-year renewal of the marketing authorisation

19. Annex II – List of participants

including any restrictions with respect to involvement of members/alternates/experts following evaluation of declared interests for the 8 January 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
Sabine Straus [a,b]	Chair	The Netherlands	No interests declared	
Jan Neuhauser [a,b]	Member	Austria	No interests declared	
Sonja Hrabcik [a]	Alternate	Austria	No interests declared	
Jean-Michel Dogné [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	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Nikica Mirošević Skvrce [a]	Member	Croatia	No interests declared	
Petar Mas [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	Czech Republic	No interests declared	
Jana Lukacisinova [a,b]	Alternate	Czech Republic	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]	Member	Estonia	No interests declared	
Kirsti Villikka [a,b]	Member	Finland	No interests declared	
Kimmo Jaakkola [a,b]	Alternate	Finland	No interests declared	
Tiphaine Vaillant [a,b]	Member	France	No interests declared	
Nathalie Gault [a,b]	Alternate	France	No interests declared	
Martin Huber [a,b]	Member	Germany	No interests declared	
Gabriele Maurer [a,b]	Alternate	Germany	No participation in final deliberations and voting on:	15.3.18. Nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/II/0137 17.2.9. Nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/MEA 057
Sofia Trantza [a,b]	Member	Greece	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Georgia Gkegka [a,b]	Alternate	Greece	No interests declared	
Julia Pallos [a,b]	Member	Hungary	No participation in final deliberations and voting on:	4.1.2. Axicabtagene ciloleucel – YESCARTA (CAP); idecabtagene vicleucel – ABECMA (CAP); lisocabtagene maraleucel – BREYANZI (CAP); ciltabtagene autoleucel – CARVYKTI (CAP); tisagenlecleucel – KYMRIAH (CAP); brexucabtagene autoleucel – TECARTUS (CAP) 6.1.12. Ozanimod - ZEPOSIA (CAP) - PSUSA/00010852/202305 7.4.2. Luspatercept - REBLOZYL (CAP) - EMEA/H/C/004444/II/0023 , Orphan 15.3.15. Idecabtagene vicleucel - ABECMA (CAP) - EMEA/H/C/004662/II/0031, Orphan 15.3.18. Nivolumab - OPDIVO (CAP) -

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				EMEA/H/C/003985/II/0137 15.3.20. Ozanimod - ZEPOSIA (CAP) - EMEA/H/C/004835/II/0023 16.1.33. Luspatercept - REBLOZYL (CAP) - PSUSA/00010860/202306 17.2.7. Ipilimumab - YERVO Y (CAP) - EMEA/H/C/002213/MEA 036.6 17.2.9. Nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/MEA 057 17.5.10. Idecabtagene vicleucel - ABECMA (CAP) - EMEA/H/C/004662/MEA 007 17.5.12. Lisocabtagene maraleucel, lisocabtagene maraleucel - BREYANZI (CAP) - EMEA/H/C/004731/MEA 007
Guðrún Stefánsdóttir [b]	Member	Iceland	No participation in final deliberations and voting on:	5.3.1. Denosumab - PROLIA (CAP) - EMEA/H/C/001120/II/0099 15.3.28. Sotorasib -

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				LUMYKRAS (CAP) - EMEA/H/C/005522/II/0007 16.1.50. Sotorasib - LUMYKRAS (CAP) - PSUSA/00010970/202305 17.4.4. Denosumab - PROLIA (CAP) - EMEA/H/C/001120/II/0100
Gudrun Þengilsdóttir [a]	Alternate	Iceland	No restrictions applicable to this meeting	
Rhea Fitzgerald [a,b]	Member	Ireland	No interests declared	
Eamon O Murchu [a,b]	Alternate	Ireland	No interests declared	
Amelia Cupelli [a,b]	Member	Italy	No interests declared	
Valentina Di Giovanni [a]	Alternate	Italy	No interests declared	
Zane Neikena [a,b]	Member	Latvia	No interests declared	
Rugile Pilviniene [a]	Member	Lithuania	No interests declared	
Lina Seibokiene [a,b]	Alternate	Lithuania	No restrictions applicable to this meeting	
Nadine Petitpain [a,b]	Member	Luxembourg	No restrictions applicable to this meeting	
Benjamin Micallef [a,b]	Alternate	Malta	No interests declared	
Liana Martirosyan [a,b]	Member	Netherlands	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Bianca Mulder [a],[b]	Alternate	Netherlands	No interests declared	
David Olsen [a],[b]	Member	Norway	No participation in final deliberations and voting on:	3.2.1 Hydroxyprogest[SPM1] erone (NAP) - EMEA/H/A-31/1528 4.1.1. Aflibercept – EYLEA (CAP), YESAFILI (CAP); ranibizumab – LUCENTIS (CAP) 6.3.3. Gadobutrol (NAP) - PSUSA/00001502/202304 6.3.4. Gadopentetic acid (NAP) - PSUSA/00001504/202304 6.3.5. Gadoteric acid (NAP) - PSUSA/00001506/202304 6.3.7. Gadoxetic acid disodium (NAP) - PSUSA/00001509/202304 6.3.8. Levonorgestrel (NAP) - PSUSA/00010828/202305 6.3.12. Mometasone (NAP) - PSUSA/00002085/202305

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				6.3.13. Moxifloxacin (NAP) - PSUSA/00009231/202305 16.1.29. Larotrectinib - VITRAKVI (CAP) - PSUSA/00010799/202305 16.3.5. Cyproterone, ethinylestradiol (NAP) - PSUSA/00000906/202305 17.5.4. Damoctocog alfa pegol - JIVI (CAP) - EMEA/H/C/004054/ANX 001.2
Pernille Harg [a,b]	Alternate	Norway	No interests declared	
Adam Przybylkowski [a]	Member	Poland	No interests declared	
Katarzyna Ziolkowska [a,b]	Alternate	Poland	No interests declared	
Ana Sofia Diniz Martins [a,b]	Member	Portugal	No interests declared	
Carla Torre [a]	Alternate	Portugal	No interests declared	
Roxana Dondera [a,b]	Member	Romania	No interests declared	
Irina Sandu [a,b]	Alternate	Romania	No interests declared	
Anna Mareková [a,b]	Member	Slovakia	No interests declared	
Miroslava Gocova [a,b]	Alternate	Slovakia	No interests declared	
Polona Golmajer [a,b]	Member	Slovenia	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Maria del Pilar Rayon [a,b]	Member	Spain	No interests declared	
Monica Martinez Redondo [a]	Alternate	Spain	No interests declared	
Ulla Wändel Liminga [a,b]	Member	Sweden	No interests declared	
Mari Thorn [a,b]	Alternate	Sweden	No restrictions applicable to this meeting	
Annalisa Capuano [a]	Member	Independent scientific expert	No interests declared	
Milou Daniel Drici [a,b]	Member	Independent scientific expert	No interests declared	
Maria Teresa Herdeiro [a]	Member	Independent scientific expert	No interests declared	
Patricia McGettigan [a]	Member	Independent scientific expert	No interests declared	
Tania Schink [a]	Member	Independent scientific expert	No participation in final deliberations and voting on:	17.2.12. Romosozumab - EVENITY (CAP) - EMEA/H/C/004465/MEA 001.9 17.2.13. Romosozumab - EVENITY (CAP) - EMEA/H/C/004465/MEA 002.9 17.2.14. Romosozumab - EVENITY (CAP) - EMEA/H/C/004465/MEA 003.7
Hedvig Nordeng [a]	Member	Independent scientific expert	No interests declared	
Roberto Frontini [a,b]	Member	Healthcare Professionals' Representative	No restrictions applicable to this meeting	
Salvatore Messana [a]	Alternate	Healthcare Professionals' Representative	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Marko Korenjak [a]	Member	Patients' Organisation Representative	No interests declared	
Michal Rataj [a]	Alternate	Patients' Organisation Representative	No interests declared	
Marianne Lunzer [a]	Expert	Austria	No interests declared	
Ilona G. Reischl [a]	Expert	Austria	No interests declared	
Laurence De Fays [b]	Expert	Belgium	No interests declared	
Olga Kholmanskikh Van Criekingen [a]	Expert	Belgium	No interests declared	
Gabriela Burianová [a]	Expert	Czech Republic	No interests declared	
Lucie Skálová [a]	Expert	Czech Republic	No interests declared	
Marian Hjortlund Allon [a]	Expert	Denmark	No interests declared	
Alexander Braathen [a]	Expert	Denmark	No interests declared	
Annette Cleveland Nielsen [a]	Expert	Denmark	No restrictions applicable to this meeting	
Boje Kvorning Pires Ehmsen [a]	Expert	Denmark	No interests declared	
Mona El-Sayed Hervig [a]	Expert	Denmark	No interests declared	
Nicklas Hasselblad Lundstrøm [a]	Expert	Denmark	No interests declared	
Kirsten Egebjerg Juul [a]	Expert	Denmark	No interests declared	
Irene Mandrup Krüger [a]	Expert	Denmark	No interests declared	
Kristina Laursen [a]	Expert	Denmark	No interests declared	
Moritz Sander [a]	Expert	Denmark	No interests declared	
Per Sindahl [a]	Expert	Denmark	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Ditte Søgaard [a]	Expert	Denmark	No interests declared	
Helene Stenbæk Hansen [a,b]	Expert	Denmark	No restrictions applicable to this meeting	
Karima Adamo [a]	Expert	France	No restrictions applicable to this meeting	
Benjamin Burrus [a]	Expert	France	No interests declared	
Camille De-Kervasdoue [a]	Expert	France	No interests declared	
Vincent Gazin [a]	Expert	France	No interests declared	
Dina Habib-Hanawy [a]	Expert	France	No interests declared	
Ludivine Martin [a]	Expert	France	No interests declared	
Philipp Berg [a]	Expert	Germany	No interests declared	
Dennis Lex [a,b]	Expert	Germany	No interests declared	
Susanne Müller [a]	Expert	Germany	No interests declared	
Jan Müller-Berghaus [a]	Expert	Germany	No interests declared	
Gabriele Ruppert-Seipp [a]	Expert	Germany	No interests declared	
Clare Foley [a]	Expert	Ireland	No interests declared	
Diāna Litenboka [a]	Expert	Latvia	No interests declared	
Gunta Paukšena [a]	Expert	Latvia	No interests declared	
Thijs Ambagts [a]	Expert	Netherlands	No interests declared	
Helen Gatling [a]	Expert	Netherlands	No interests declared	
Lisa Heltzel [a]	Expert	Netherlands	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Evelyn Mulder-Olthof [a]	Expert	Netherlands	No interests declared	
Anne Taams [a]	Expert	Netherlands	No interests declared	
Inge Zomerdijk [a]	Expert	Netherlands	No interests declared	
Rune Kjeken [a]	Expert	Norway	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	
Elin Blom [a]	Expert	Sweden	No interests declared	
Kristina Magnusson-Lundqvist [a]	Expert	Sweden	No interests declared	
Karin Nylén [a]	Expert	Sweden	No interests declared	
Daiana Vasilcanu [a]	Expert	Sweden	No interests declared	
A representative from the European Commission attended the meeting				
Observers from Health Canada (Canada), FDA (USA) and PMDA (Japan) 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:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000150.jsp&mid=WC0b01ac05800240d0

Signals assessment and prioritisation

(Item 4 of the PRAC minutes)

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

Risk Management Plans (RMPs)

(Item 5 of the PRAC minutes)

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

Assessment of Periodic Safety Update Reports (PSURs)

(Item 6 of the PRAC minutes)

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

Post-authorisation Safety Studies (PASS)

(Item 7 of the PRAC minutes)

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

Product related pharmacovigilance inspections

(Item 9 of the PRAC minutes)

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

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