22 November 2023
EMA/PRAC/497911/2023
Human Medicines Division

Pharmacovigilance Risk Assessment Committee (PRAC)

Minutes of the PRAC meeting on 25-28 September 2023

Chair: Sabine Straus – Vice-Chair: Martin Huber

Health and safety information

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

Disclaimers

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

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

Note on access to documents

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

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1. Introduction

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

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

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

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

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

The EMA Secretariat announced the names of the Committee members who delegated their vote via proxy and the Committee members who received such proxy.

1.2. Agenda of the meeting on 25-28 September 2023

The agenda was adopted with some modifications upon request from the members of the Committee and the EMA secretariat as applicable.

1.3. Minutes of the previous meeting on 28-31 August 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 28-31 August 2023 were published on the EMA website on 27 October 2023 (EMA/PRAC/452701/2023).

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

2.1. Newly triggered procedures

None

2.2. Ongoing procedures

None

2.3. Procedures for finalisation

None

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

3.1. Newly triggered procedures

None

3.2. Ongoing procedures

3.2.1. 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*[1] 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*[2] 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.

Summary of recommendation(s)/conclusions

- PRAC discussed the assessment reports issued by the Rapporteurs.
- PRAC adopted a list of outstanding issues (LoOI) to the MAHs with a revised timetable for the procedure (EMA/PRAC/194263/2023 rev.1).
- PRAC adopted a list of questions (LoQ) for an ad-hoc expert group (AHEG) meeting.
- PRAC also agreed on a LoQ inviting the study authors *Murphy et al.* to address questions related to the study that initiated the current review.

3.2.2. Pseudoephedrine (NAP); pseudoephedrine, acetylsalicylic acid (NAP); pseudoephedrine, acetylcysteine, paracetamol (NAP); pseudoephedrine, acrivastine (NAP); pseudoephedrine, ascorbic acid, paracetamol (NAP); pseudoephedrine,

[1] 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
[2] 2 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

cetirizine (NAP); pseudoephedrine, ebastine (NAP); pseudoephedrine, guaifenesin (NAP); pseudoephedrine, ibuprofen (NAP); pseudoephedrine, chlorphenamine (NAP); pseudoephedrine, chlorphenamine, codeine (NAP); pseudoephedrine, chlorphenamine, dextromethorphan (NAP); pseudoephedrine, chlorphenamine, paracetamol (NAP); pseudoephedrine, chlorphenamine, dextromethorphan, paracetamol (NAP); pseudoephedrine, dextromethorphan (NAP); pseudoephedrine, dextromethorphan, paracetamol (NAP); pseudoephedrine, dextromethorphan, ascorbic acid, paracetamol (NAP); pseudoephedrine, dextromethorphan, guaifenesin, paracetamol (NAP); pseudoephedrine, dextromethorphan, guaifenesin, triprolidine (NAP); pseudoephedrine, dextromethorphan, triprolidine (NAP); pseudoephedrine, diphenhydramine, paracetamol (NAP); pseudoephedrine, doxylamine, paracetamol (NAP); pseudoephedrine, loratadine (NAP); pseudoephedrine, paracetamol (NAP); pseudoephedrine, paracetamol, pholcodine (NAP); pseudoephedrine, triprolidine (NAP); pseudoephedrine, triprolidine, guaifenesin (NAP); pseudoephedrine, triprolidine, paracetamol (NAP); pseudoephedrine, desloratadine – AERINAZE (CAP) – EMA/H/A-31/1526

Applicant(s): various

PRAC Rapporteur: Eva Jirsová; PRAC Co-rapporteur: Maia Uusküla

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 pseudoephedrine-containing products following the assessment of the PSUR single assessment (PSUSA) procedure on ibuprofen/pseudoephedrine (PSUSA/00001711/202207) concluded in February 2023. The data submitted by the MAHs within the PSUSA procedure suggested a causal relationship between posterior reversible encephalopathy syndrome (PRES), reversible cerebral vasoconstriction syndrome (RCVS) and pseudoephedrine use, based on the compatible and suggestive time to onset, the biological plausibility and the lack of alternative aetiologies for some patients without any risk factors. Considering the seriousness of PRES and RCVS, the overall safety profile of pseudoephedrine and the indications for which the medicines are approved, the matter was referred to PRAC for further evaluation. For further background, see PRAC minutes January 2023, PRAC minutes February 2023, PRAC minutes May 2023 and PRAC minutes September 2023[3].

Summary of recommendation(s)/conclusions

- PRAC noted the feedback provided by the ad-hoc expert group (AHEG) Chair following the AHEG meeting held on 14 September 2023.
- PRAC discussed the joint assessment report issued by the Rapporteurs.
- PRAC adopted a further list of outstanding issues (LoOI) to the MAHs with a revised timetable for the procedure (EMA/PRAC/55340/2023 Rev. 3).

3.3. Procedures for finalisation

None

[3] Held 28-31 August 2023

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. Abemaciclib – VERZENIOS (CAP), Palbociclib – IBRANCE (CAP), Ribociclib – KISQALI (CAP)

Applicant(s): Eli Lilly Nederland B.V. (Verzenios), Pfizer Europe MA EEIG, Novartis Europharm Limited (Kisqali)

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Signal of erythema multiforme

EPITT 19973 – 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 erythema multiforme was identified by EMA, based on 30 cases retrieved from EudraVigilance and 1 from the literature. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by PRAC.

Discussion

Having considered the available evidence from case reports in EudraVigilance and literature, PRAC agreed that further evaluation on the signal of erythema multiforme is warranted.

PRAC appointed Marie Louise Schougaard Christiansen as Rapporteur for the signal.

Summary of recommendation(s)

- The MAHs for Kisqali (ribociclib), Ibrance (palbociclib) and Verzenios (abemaciclib) should submit to EMA, within 60 days, a cumulative review of cases of erythema multiforme, including a review of the published literature, data from spontaneous reports and reports from studies, a discussion on possible biological plausibility and mechanism of this association. The MAHs should also discuss the need for any potential

[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

amendment to the product information (PI) and/or the risk management plan (RMP) as warranted.

- A 90-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.1.2. Chlorhexidine gluconate, isopropyl alcohol (NAP); chlorhexidine digluconate, isopropyl alcohol (NAP)

Applicant: various

PRAC Rapporteur: Jo Robays

Scope: Signal of product caught fire

EPITT 19969 – New signal

Background

Solutions containing the combination of chlorhexidine (di)gluconate in isopropyl alcohol are indicated for disinfection of the skin prior to invasive medical procedures.

During routine signal detection activities, a signal of product caught fire was identified by the Spanish Medicines Agency (AEMPS), based on 6 cases retrieved from the Spanish spontaneous reporting database (FEDRA) and 4 cases retrieved from EudraVigilance. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by PRAC.

Discussion

PRAC appointed Jo Robays as Rapporteur for the signal.

Having reviewed the available evidence from EudraVigilance and taking into consideration the wording already present in nationally authorised products containing the combination chlorhexidine (di)gluconate/isopropyl alcohol, PRAC concluded that no regulatory action is deemed warranted at this stage.

Summary of recommendation(s)

- The MAHs for products containing the combination chlorhexidine (di)gluconate/isopropyl alcohol should continue to monitor these events as part of routine pharmacovigilance.

4.1.3. Glucagon-like peptide-1 (GLP-1) receptor agonists: dulaglutide – TRULICITY (CAP); exenatide – BYDUREON (CAP), BYETTA (CAP); insulin degludec, liraglutide – XULTOPHY (CAP); liraglutide – SAXENDA (CAP), VICTOZA (CAP); insulin glargine, lixisenatide – SULIQUA (CAP); lixisenatide - LYXUMIA (CAP); semaglutide – OZEMPIC (CAP), RYBELSUS (CAP), WEGOVY (CAP); tirzepatide – MOUNJARO (CAP)

Applicant: AstraZeneca AB (Bydureon, Byetta), Eli Lilly Nederland B.V. (Trulicity), Novo Nordisk A/S (Ozempic, Rybelsus, Saxenda, Victoza, Wegovy, Xultophy), Sanofi Winthrop Industrie (Lyxumia, Suliqua)

PRAC Rapporteur: Mari Thorn

Scope: Signal of aspiration and pneumonia aspiration

EPITT 19974 – 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 aspiration and pneumonia aspiration was identified by EMA based on 11 cases retrieved from EudraVigilance (4 cases for semaglutide, 2 cases for liraglutide, 2 cases for dulaglutide, 2 cases for exenatide and 1 case for tirzepatide) and on cases in the literature. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by PRAC.

Discussion

Having considered the available evidence from case reports in EudraVigilance and the literature, PRAC agreed that further evaluation on the signal of aspiration and pneumonia aspiration is warranted,

PRAC appointed Mari Thorn as Rapporteur for the signal.

Summary of recommendation(s)

- The MAHs for Ozempic, Rybelsus and Wegovy products containing semaglutide, for Victoza and Saxenda products containing liraglutide, for Xultophy (insulin degludec, liraglutide), for Byetta and Bydureon products containing exenatide, for Lyxumia (lixisenatide), for Suliqua (insulin glargine, lixisenatide), for Trulicity (dulaglutide), and for Mounjaro (tirzepatide) should submit to EMA, within 60 days, a cumulative review of cases of aspiration and pneumonia aspiration, including a review of the published literature, data from spontaneous reports and reports from studies, and a discussion on possible biological plausibility. 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 90-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.2. New signals detected from other sources

None

4.3. Signals follow-up and prioritisation

4.3.1. Azacitidine – AZACITIDINE ACCORD (CAP), AZACITIDINE BETAPHARM (CAP), AZACITIDINE MYLAN (CAP), ONUREG (CAP) - EMEA/H/C/004761/SDA/002; VIDAZA (CAP) - EMEA/H/C/003820/SDA/036

Applicant(s): Accord Healthcare S.L.U. (Azacitidine Accord), betapharm Arzneimittel GmbH (Azacitidine betapharm), Bristol-Myers Squibb Pharma EEIG (Onureg, Vidaza), Mylan Ireland Limited (Azacitidine Mylan)

PRAC Rapporteur: Menno van der Elst

Scope: Signal of cutaneous vasculitis

EPITT 19929 – follow up to May 2023

Background

For background information, see PRAC minutes May 2023.

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

Discussion

Having considered the available evidence in EudraVigilance and literature, as well as the response from the MAHs, PRAC agreed that there is sufficient evidence to establish a causal relationship between azacitidine injectable formulations and cutaneous vasculitis. Therefore, PRAC agreed to add cutaneous vasculitis as an undesirable effect to the product information with a frequency 'not known'.

Summary of recommendation(s)

- The MAHs for azacitidine-containing medicinal products (intravenous use and subcutaneous use only) should submit to EMA, within 60 days, a variation to amend[6] the product information.

For the full PRAC recommendation, see EMA/PRAC/416575/2023 published on 23 October 2023 on the EMA website.

4.3.2. Baricitinib – OLUMIANT (CAP) - EMEA/H/C/004085/SDA/017

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Signal of interstitial lung disease

EPITT 19913 – follow up to May 2023

Background

For background information, see PRAC minutes May 2023.

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

Discussion

Having considered the available evidence from clinical trials, post-marketing data including literature case reports, and the responses from the MAH, PRAC considered that the current evidence is insufficient to establish a causal relationship between treatment with baricitinib and interstitial lung disease.

Summary of recommendation(s)

- The MAH for Olumiant (baricitinib) should continue to monitor interstitial lung disease events as part of routine pharmacovigilance.

For the full PRAC recommendation, see EMA/PRAC/416575/2023 published on 23 October 2023 on the EMA website.

4.3.3. Rituximab – BLITZIMA (CAP) - EMEA/H/C/004723/SDA/005, MABTHERA (CAP) - EMEA/H/C/000165/SDA/200, RIXATHON (CAP) - EMEA/H/C/003903/SDA/006,

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

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

PRAC Rapporteur: Karin Susanne Lindenstrom Erneholm

Scope: Signal of oral lichenoid reaction

EPITT 19916 – follow up to May 2023

Background

For background information, see PRAC minutes May 2023.

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

Discussion

Having considered the available evidence from literature case reports, EudraVigilance and the responses of the MAHs, PRAC considered that the current evidence is insufficient to establish a causal relationship between treatment with rituximab and the events of oral lichenoid reaction and oral lichen planus.

Summary of recommendation(s)

- The MAHs for rituximab-containing medicinal products should continue to monitor oral lichenoid reaction and oral lichen planus events as part of routine pharmacovigilance.

For the full PRAC recommendation, see EMA/PRAC/416575/2023 published on 23 October 2023 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).

5.1.1. Concizumab - EMEA/H/C/005938

Scope: Routine prophylaxis to prevent or reduce the frequency of bleeding in patients with haemophilia A (congenital factor VIII deficiency) with FVIII inhibitors ≥ 12 years of age and haemophilia B (congenital factor IX deficiency) with FIX inhibitors of any age

5.1.2. Dopamine hydrochloride - EMEA/H/C/006044, PUMA[7]

Scope: Treatment of hypotension in neonates, infants and children

5.1.3. Epinephrine - EMEA/H/C/006139

Scope: Treatment of allergic reactions (anaphylaxis) and idiopathic or exercise induced anaphylaxis

5.1.4. Etrasimod - EMEA/H/C/006007

Scope: Treatment of patients with moderately to severely active ulcerative colitis (UC)

5.1.5. Germanium (^{68}Ge) chloride, gallium (^{68}Ga) chloride - EMEA/H/C/005165

Scope: Indicated for in vitro labelling of kits for radiopharmaceutical preparation

5.1.6. Omaveloxolone - EMEA/H/C/006084, Orphan

Applicant: Reata Ireland Limited

Scope: Treatment of Friedreich's ataxia

5.1.7. Pegcetacoplan - EMEA/H/C/005954

Scope: Treatment of geographic atrophy (GA) secondary to age-related macular degeneration (AMD)

5.1.8. Toripalimab - EMEA/H/C/006120

Scope: Combination treatment for metastatic or recurrent locally advanced nasopharyngeal carcinoma and for metastatic or recurrent oesophageal squamous cell carcinoma

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

See also Annex I 15.2.

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

Applicant: AstraZeneca AB

PRAC Rapporteur: David Olsen

Scope: Grouped application consisting of: 1) Submission of an updated RMP version 5 in order to remove the safety concern of missing information on use in pregnant and lactating women. Consequently, the MAH proposes to remove study D3250R00026 as an additional pharmacovigilance activity, and to remove the commitment to conduct additional pharmacovigilance for the use of benralizumab in pregnant and lactating women with severe eosinophilic asthma; 2) Submission of an updated RMP version 5 in order to remove the safety concern of important potential risk of serious infections

[7] Paediatric use marketing authorisation(s)

Background

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

PRAC is evaluating a type II variation procedure for Fasenra, a centrally authorised medicine containing benralizumab, to update the RMP to reflect the removal of the safety concern of missing information on use in pregnant and lactating women and consequently of the removal of study D3250R00026, as well as of the important potential risk of serious infections. PRAC is responsible for adopting an outcome based on the assessment report from the PRAC Rapporteur, to be further considered at the level of CHMP, responsible for adopting an opinion on this variation. For further background, see PRAC minutes July 2023.

Summary of advice

- The RMP version 5.1 for Fasenra (benralizumab) in the context of the variation under evaluation by PRAC and CHMP is considered acceptable.
- PRAC agreed with the removal of the category 3 PASS D3250R00026 from the RMP, however PRAC considered that 'use in pregnant and lactating women' should remain as missing information in the list of safety concerns in the RMP.

5.2.2. 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

Background

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

PRAC is evaluating a type II variation procedure for Vpriv, a centrally authorised medicine containing velaglucerase alfa, to update the RMP to reflect the removal of certain risks from the list of safety concerns. PRAC is responsible for adopting an outcome based on the assessment report from the PRAC Rapporteur, to be further considered at the level of CHMP, responsible for adopting an opinion on this variation. For further background, PRAC minutes July 2023.

S**ummary of advice**

- The RMP for Vpriv (velaglucerase alfa) in the context of the variation procedure under evaluation by PRAC and CHMP could be considered acceptable provided that an update to RMP version 12 is submitted.
- PRAC considered that the risk 'reduced efficacy due to neutralising antibodies' should be removed from the list of safety concerns in the RMP, however, the risk of antibody formation and the potential need for testing for neutralising antibodies should be reflected in the product information. Furthermore, PRAC agreed that the MAH should keep neutralising antibodies (Nab) testing services available in clinical practice, or to

provide other feasible opportunities for physicians to test for NAb in case of suspecting efficacy decrease due to antibodies. The MAH should amend the product information accordingly.

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

See also Annex I 15.3.

5.3.1. Aflibercept - EYLEA (CAP) - EMEA/H/C/002392/X/0084/G

Applicant: Bayer AG

PRAC Rapporteur: Nathalie Gault

Scope: Extension application to add a new strength of Aflibercept 114.3 mg/ml solution for injection (in a vial), to be indicated in adults for the (1) treatment of neovascular (wet) age-related macular degeneration (nAMD) and (2) visual impairment due to diabetic macular oedema (DME), grouped with a type II variation (B.II.g.2) to introduce a post-approval change management protocol to add a new presentation for Aflibercept solution 114.3 mg/ml in a single-use pre-filled syringe for intravitreal injection

Background

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

CHMP is evaluating an extension application along with a type II variation for Eylea, a centrally authorised product containing aflibercept, to add a new strength for Eylea (aflibercept) solution 114.3 mg/ml. 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 June 2023.

Summary of advice

- The RMP for Eylea (aflibercept) in the context of the variation procedure under evaluation by CHMP could be considered acceptable provided that an update to RMP version 33.2 is submitted.
- Regarding the additional pharmacovigilance activities, PRAC considered that the category 3 study as proposed by the MAH to address 'exposure with bilateral 8 mg aflibercept therapy' as missing information should be removed from the RMP. However, the MAH should consider the possibility of a further post-approval study to evaluate the safety profile of bilateral therapy with aflibercept 8 mg in case the pharmacokinetics (PK) study shows a Cmax reflecting a systemic exposure beyond what is acceptable compared to systemic aflibercept intravenous (IV) and bilateral therapy with aflibercept 2 mg. In addition, the safety concern related to the bilateral administration with the 8 mg should be monitored in the PSURs. The MAH should provide an update of the Annex II-D and RMP, taking into account that there will be a common educational material for both strengths.

5.3.2. 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

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 variation for Myozyme, a centrally authorised product containing alglucosidase, to add home infusion upon based on a cumulative search of the MAH's pharmacovigilance database and literature. 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 April 2023.

Summary of advice

- The RMP for Myozyme (alglucosidase) in the context of the variation procedure under evaluation by CHMP could be considered acceptable provided that an update to RMP version 10.1 is submitted.
- Regarding the list of safety concerns, PRAC agreed to add a new important potential risk related to medication errors in the home infusion setting. Regarding the risk minimisation measures (RMMs), PRAC agreed for a healthcare professional (HCP) guide to mitigate the risk of medication errors in the home setting and the infusion associated reactions (IARS). In addition, the MAH should add 'home infusion guide for patients and care givers' as a new additional RMM in the RMP in order to minimise the risk of medication errors in the home infusion setting and should amend the key safety messages of the educational materials in Annex II-D and RMP.

5.3.3. Vonicog alfa - VEYVONDI (CAP) - EMEA/H/C/004454/II/0030

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Mari Thorn

Scope: Extension of indication to include prophylactic treatment to prevent or reduce the frequency of bleeding episodes based on final results from study 071301 and interim results from study SHP677-304. Study 071301 is a prospective, phase 3, open-label, international multicentre study on efficacy and safety of prophylaxis with rVWF in severe von Willebrand disease; while study SHP677-304 is a phase 3B, prospective, open-label, uncontrolled, multicentre study on long term safety and efficacy of rVWF in paediatric and adult subjects with severe von Willebrand disease. As a consequence, sections 4.1, 4.2, 4.4, 5.1, 5.2, 6.2 and 6.6 of the SmPC are updated. The package leaflet is updated in accordance. Version 4.0 of the RMP has also been submitted

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 Veyvondi, a centrally authorised product containing vonicog alfa, to extend the therapeutic indication in order to include prophylactic treatment to prevent or reduce the frequency of bleeding episodes based on final results from study 071301 and interim results from study SHP677-304. 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 June 2023.

Summary of advice

- The RMP version 4.1 for Veyvondi (vonicog alfa) in the context of the procedure under evaluation by CHMP is considered acceptable.
- PRAC agreed that the protocol for the category 3 study based on the EUHASS registry proposed as additional pharmacovigilance activity in the RMP to be provided and assessed within a separate post authorisation measure procedure.

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. Apalutamide - ERLEADA (CAP) - PSUSA/00010745/202302

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Tiphaine Vaillant

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 Erleada, a centrally authorised medicine containing apalutamide 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, and taking into account the MAH position discussed in the context of the oral explanation held on the 26 September 2023, PRAC considered that the benefit-risk balance of Erleada (apalutamide) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include interstitial lung disease as a warning and as an undesirable effect with a frequency 'not known' and to add restless legs syndrome as an undesirable effect with a frequency 'uncommon'. Therefore, the current terms of the marketing authorisation(s) should be varied[8].

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

- In the next PSUR, the MAH should provide a review of cases of psoriasis/psoriatic skin lesions from all sources, including post-marketing data, clinical trials and literature and discuss any potential causal association with apalutamide. The MAH should also provide a cumulative review of cases of neutropenia from all sources. The MAH should discuss in both cases 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.

6.1.2. Ciltacabtagene autoleucel - CARVYKTI (CAP) - PSUSA/00011000/202302

Applicant: Janssen-Cilag International NV, ATMP[9]

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 Carvykti, a centrally authorised medicine containing ciltacabtagene autoleucel 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 Carvykti (ciltacabtagene autoleucel) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include information regarding a T-cell malignancy case and to include additional information on product handling issues. Therefore, the current terms of the marketing authorisation(s) should be varied[10].
- In the next PSUR, the MAH should provide a cumulative review of cases of haemophagocytic lymphohistiocytosis (HLH), as well as a cumulative review of cases of the leaked bag.

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. Etanercept - BENEPALI (CAP); ENBREL (CAP); ERELZI (CAP); NEPEXTO (CAP) - PSUSA/00010795/202302

Applicant: Samsung Bioepis NL B.V. (Benepali), Pfizer Europe MA EEIG (Enbrel), Sandoz GmbH (Erelzi), Biosimilar Collaborations Ireland Limited (Nepexto)

[9] Advanced therapy medicinal product
[10] Update of SmPC sections 4.4 and 6.6. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion.

PRAC Rapporteur: Monica Martinez Redondo

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 Benepali, Enbrel, Erelzi, Nepexto, centrally authorised medicines containing etanercept 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 Benepali, Enbrel, Erelzi, Nepexto medicinal products containing etanercept in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include glomerulonephritis as an undesirable effect with a frequency 'not known'. However, the MAHs should further provide an estimation of the frequency of this undesirable effect based on clinical trial data in a separate procedure. Therefore, the current terms of the marketing authorisation(s) should be varied[11].
- In the next PSUR, all MAHs should provide cumulative reviews of cases of deafness, panniculitis, acute ischaemic cardiovascular events and gastrointestinal events. The MAH Pfizer should provide a cumulative review of cases of neuropsychiatric disorders, including data from literature, clinical trials, post-marketing setting.

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.

6.1.4. Ivacaftor - KALYDECO (CAP) - PSUSA/00009204/202301

Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Monica Martinez Redondo

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 Kalydeco, a centrally authorised medicine containing ivacaftor and issued a recommendation on its marketing authorisation(s).

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Kalydeco (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' and to amend the existing wording regarding breastfeeding. Therefore, the current terms of the marketing authorisation(s) should be varied[12].
- In the next PSUR, the MAH should further discuss and provide more information on cases of pancreatitis, as well as on risk of seizure and of cataract/lens opacity in the infants following in utero and/or breastfeeding exposure.

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. Pregabalin - LYRICA (CAP); PREGABALIN PFIZER (CAP) - PSUSA/00002511/202301

Applicant: Upjohn EESV

PRAC Rapporteur: Liana Gross-Martirosyan

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 Lyrica, Pregabalin Pfizer, centrally authorised medicines containing pregabalin 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 Lyrica and Pregabalin Pfizer (pregabalin) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include suicidal ideation as part of the observed withdrawal symptoms. Therefore, the current terms of the marketing authorisation(s) should be varied[13].

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.

[12] 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.
[13] Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion.

6.1.6. Ribociclib - KISQALI (CAP) - PSUSA/00010633/202303

Applicant: Novartis Europharm Limited

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 Kisqali, a centrally authorised medicine containing ribociclib 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 Kisqali (ribociclib) 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 acute kidney injury, including data from clinical trials, post-marketing setting and the literature and should discuss possible biological mechanisms. In addition, the MAH should provide a cumulative review of cases of venous thromboembolic events (VTE) taking into consideration all relevant data sources (literature, spontaneous case reports, randomised clinical trials and non-interventional studies). Furthermore, the MAH should provide a review of the data from the finalised NATALEE trial in relation to VTE.

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. Rotigotine - NEUPRO (CAP) - PSUSA/00002667/202302

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Ana Sofia Diniz Martins

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 Neupro, a centrally authorised medicine containing rotigotine 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 Neupro (rotigotine) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a warning regarding the possibility for patients with Parkinson disease to experience dystonic events. Therefore, the current terms of the marketing authorisation(s) should be varied[14].

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. Submission of PSURs for products referred to in Articles 10(1), 10a, 14, 16a of Directive 2001/83/EC as amended is not required.

6.1.8. Teclistamab - TECVAYLI (CAP) - PSUSA/00011010/202302

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Jana Lukacisinova

Scope: Evaluation of a PSUSA procedure

Background

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

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Tecvayli, a centrally authorised medicine containing teclistamab 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 Tecvayli (teclistamab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the existing warning on neurological toxicities to include immune effector cell-associated neurotoxicity syndrome (ICANS) and to update section on undesirable effects to add new information and symptoms of ICANS (including Grade 3 and higher ICANS, and time to onset). Therefore, the current terms of the marketing authorisation(s) should be varied[15].
- In the next PSUR, the MAH should provide an analysis of cases of cytokine release syndrome Grade 2 and higher that occurred out of the recommended monitoring period and discuss whether the current monitoring recommendation is sufficient to minimise this risk. In addition, the MAH should provide a review of cases of agranulocytosis and cases of neutropenia Grade 4 and higher, 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.

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

6.1.9. Tezacaftor, ivacaftor - SYMKEVI (CAP) - PSUSA/00010730/202302

Applicant: Vertex Pharmaceuticals (Ireland) Limited

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 Symkevi, a centrally authorised medicine containing tezacaftor/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 Symkevi (tezacaftor/ivacaftor) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include depression as a warning and as an undesirable effect with a frequency 'not known' and amend the existing wording regarding breastfeeding. Therefore, the current terms of the marketing authorisation(s) should be varied[16].
- In the next PSUR, the MAH should provide cumulative reviews of cases of severe cutaneous adverse reactions (SCARs) and of acute pancreatitis and discuss whether any updates to the product information are warranted. In addition, the MAH should further investigate the risk of cataract in the infants following in utero and/or breastfeeding exposure, and should further monitor the risk of seizures, in particular the cases with exacerbation of seizures following tezacaftor/ivacaftor initiation treatment.

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. Upadacitinib – RINVOQ (CAP) – PSUSA/00010823/202302

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Nikica Mirošević Skvrce

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.

[16] 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.

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Rinvoq, a centrally authorised medicine containing upadacitinib 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 Rinvoq (upadacitinib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include hypoglycaemia as a warning in patients treated for diabetes. Therefore, the current terms of the marketing authorisation(s) should be varied[17].
- In the next PSUR, the MAH should further discuss available data on thrombosis, as well as provide cumulative reviews of cases of retinal thrombosis, tuberculosis, myocardial infarction and cerebrovascular accident, and discuss whether an update of the product information is warranted. In addition, the MAH should provide cumulative reviews of cases of interstitial lung disease, hearing disorders, vestibular disorders, peripheral neuropathy, rhabdomyolysis and tuberculosis.

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

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

See Annex I 16.2.

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

See also Annex I 16.3.

6.3.1. Acetylsalicylic acid, atorvastatin, ramipril (NAP) - PSUSA/00010280/202302

Applicant(s): various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

Background

Acetylsalicylic acid is a non-steroidal antiinflammatory drug (NSAID), atorvastatin is an inhibitor of 3-hydroxy 3-methylglutaryl coenzyme A (HMG-CoA) and ramipril is an angiotensin-converting enzyme (ACE) inhibitor. In combination, acetylsalicylic acid/atorvastatin/ramipril is indicated for the secondary prevention of cardiovascular accidents as substitution therapy in adult patients adequately controlled with the mono components given concomitantly at equivalent therapeutically doses.

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

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing acetyl salicylic acid/atorvastatin/ramipril 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 acetylsalicylic acid/atorvastatin/ramipril-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 MAHs should continue to closely monitor cases of drug reaction with eosinophilia and systemic symptoms (DRESS) as well as the increased risk of myopathy associated with the polymorphism in the gene encoding OATP1B1 (SLCO1B1 c.521CC) for atorvastatin.

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. Beta-alanine (NAP) - PSUSA/00010510/202301

Applicant(s): various

PRAC Lead: Željana Margan Koletić

Scope: Evaluation of a PSUSA procedure

Background

Beta-alanine is an amino acid indicated for the peripheral vasodilatation phenomena as non-hormonal inhibitor of hot flushes due to menopause.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing beta-alanine 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 beta-alanine-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add anaphylactic reaction as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[18].

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. Etoposide (NAP) - PSUSA/00001333/202302

Applicant(s): various

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

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

Etoposide is a topoisomerase inhibitor indicated for the treatment of neoplastic diseases, subject to certain conditions.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing etoposide 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 etoposide-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the existing information about the undesirable effect 'infections' in order to add 'opportunistic infections like pneumocystis jirovecii pneumonia'. In addition, the existing warning on hypersensitivity reactions should be amended to include an increased risk of hypersensitivity reactions if an in-line filter is used. Therefore, the current terms of the marketing authorisation(s) should be varied [19].
- In the next PSUR, all MAHs should provide a review concerning interaction of etoposide with CYP3A4 inducers and inhibitors, and to 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.

6.3.4. Ibuprofen; ibuprofen lysine[20]; ibuprofen, caffeine (NAP) - PSUSA/00010649/202302

Applicant(s): various

PRAC Lead: John Joseph Borg

Scope: Evaluation of a PSUSA procedure

Background

Ibuprofen and ibuprofen lysine[19] are non-steroidal anti-inflammatory drugs (NSAID) indicated as an anti-inflammatory and analgesic for a variety of indications and specifically: pain of various origin and nature (headache, toothache, neuralgia, osteoarticular and muscular pain, menstrual pain) and as an adjuvant in common cold or influenza for the symptomatic relief of pain and fever. Ibuprofen is also indicated for inflammatory forms of rheumatism: rheumatoid arthritis, ankylosing spondylitis and Still's disease.

[19] 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.
[20] All indications except ductus arteriosus

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing ibuprofen, ibuprofen lysine or ibuprofen/caffeine, 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 ibuprofen-, ibuprofen lysine- and ibuprofen/caffeine-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information (PI) of the topical formulations containing ibuprofen should be updated to include a contraindication for use during the last trimester of pregnancy, as well as to recommend avoiding usage during the first and second trimester of pregnancy unless clearly necessary, and if yes to use the lowest possible dose, and for the shortest treatment duration. Moreover, the PI for the systemic formulations should be updated to add Kounis syndrome as a warning and as an undesirable effect with a frequency 'not known'. In addition, the PI of systemic and topical formulations should be updated to amend the existing information on skin reactions by including severe cutaneous adverse reactions (SCARs). Therefore, the current terms of the marketing authorisation(s) should be varied[21].
- In the next PSUR, the MAHs should provide cumulative reviews of cases of severe hypokalaemia and renal tubular acidosis, tubulointerstitial nephritis, risk of renal toxicity, hypoglycemia, hypothermia, generalised fixed drug eruption associated with NSAIDs/fixed drug eruption. In addition, the MAHs should provide cumulative reviews of cases of frequency of immune system events, off-label use of ibuprofen in closure of patent ductus arteriosus (PDA), pancreatitis, photosensitivity, haemorrhage or bleeding (except gastro-intestinal), intestinal diaphragm-like strictures, SCARs and eosinophilic pneumonia, and discuss whether there is a need for an update of the PI. Finally, the MAHs should also provide a cumulative review on cases of complications of streptococcal infections with short-term treatment of ibuprofen for fever and/or non-rheumatologic pain, including data from spontaneous reports, literature and clinical trials and discuss the possible(s) mechanism(s) that could explain this risk, as well as the need for any potential amendments to the PI.

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. Levosalbutamol[22] (NAP); salbutamol (NAP) - PSUSA/00010330/202301

Applicant(s): various

PRAC Lead: Melinda Palfi

Scope: Evaluation of a PSUSA procedure

Background

[21] Update of SmPC sections 4.3, 4.4, 4.6 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position.
[22] No medicinal product with a valid marketing authorisation containing levosalbutamol in the European Economic Area (EEA) at the time of this assessment procedure Pharmacovigilance Risk Assessment Committee (PRAC)

Salbutamol is a sympathomimetic indicated in acting bronchodilation in reversible airways obstruction due to asthma, chronic bronchitis and emphysema. It is also indicated for the treatment of status asthmaticus and to arrest uncomplicated labour between 22 and 37 weeks of gestation in patients with no medical or obstetric contraindication to tocolytic therapy under certain conditions.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing salbutamol 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 salbutamol-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information of medicinal products containing salbutamol for inhalation use should be updated to strengthen the warning regarding the risks of short-acting beta-agonists (SABA) overuse. Therefore, the current terms of the marketing authorisation(s) should be varied[23].
- In the next PSUR, the MAHs of nebulised salbutamol should provide a cumulative review of cases of medication errors and misuse, with special attention to overdose and any harmful consequences in children.

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. Lisdexamfetamine (NAP) - PSUSA/00010289/202302

Applicant(s): various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

Background

Lisdexamfetamine is a stimulant prodrug of dextroamphetamine, indicated as part of a comprehensive treatment programme for attention deficit/hyperactivity disorder (ADHD) in adults and in children aged 6 years and over when response to previous methylphenidate treatment is considered clinically inadequate.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing lisdexamfetamine 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 lisdexamfetamine-containing product(s) in the approved indication(s) remains unchanged.

[23] 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

- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, all MAHs should continue to closely monitor cases of long-term cardiovascular effects of lisdexamfetamine treatment and the potential risks of ischaemic cardiac and cerebrovascular conditions.

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. Lomustine (NAP) - PSUSA/00001902/202301

Applicant(s): various

PRAC Lead: Anna Mareková

Scope: Evaluation of a PSUSA procedure

Background

Lomustine is a nitrosourea agent used as an antineoplastic and it is indicated as palliative or supplementary treatment, usually in combination with radiotherapy and/or surgery as part of multiple chemotherapy regimens in brain tumours (primary or metastatic), squamous cell and small cell bronchopulmonary cancer, Hodgkin lymphoma (resistant to conventional combination chemotherapy), malignant melanoma (metastatic), as well as second-line treatment in non-Hodgkin lymphoma, myelomatosis, tumours of the gastrointestinal tract, kidney carcinoma, ovarian, cervical and breast cancer, and testicular carcinomas.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing lomustine 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 lomustine-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information (PI) of medicinal products lomustine should be updated to amend the warning regarding overdose. In addition, the PI should be updated to add thrombocytopenia as an undesirable effect with a frequency 'very common'. Therefore, the current terms of the marketing authorisation(s) should be varied[24].
- In the next PSUR, all MAHs should provide a cumulative review of cases of multiple organ dysfunction syndrome both with and without lomustine overdose, including data from clinical trials, spontaneous reports and literature. Moreover, all MAHs should closely monitor cases of interaction between glucocorticoids and lomustine.

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 sections 4.2, 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.

6.3.8. Omega-3-acid ethyl esters (NAP) - PSUSA/00010312/202301

Applicant(s): various

PRAC Lead: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

Background

Omega-3-acid ethyl esters are ethyl esters of polyunsaturated fatty acids (PUFAs) with eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) as major components of the active ingredient and are indicated for the reduction of raised triglyceride levels (hypertriglyceridemia) when the response to diet and other nonpharmacological measures alone has proved inadequate.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing omega-3-acid ethyl esters 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 omega-3-acid ethyl esters-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add atrial fibrillation as a warning and as an undesirable effect with a frequency 'common'. Therefore, the current terms of the marketing authorisation(s) should be varied[25].
- In the next PSURs, all MAHs should include 'atrial fibrillation' as important identified risk in the list of safety concerns and monitor any new evidence about this risk from any source, as well as discuss the need to implement further risk minimisation measures (RMMs) as appropriate. In addition, all MAHs should monitor cases of 'blood creatine phosphokinase increased' and discuss on possible contributory role of omega-3-acid ethyl esters administration.

PRAC agreed on the distribution of a direct professional communication (DHPC) together with a communication plan.

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

6.4. Follow-up to PSUR/PSUSA procedures

See Annex I 16.4.

[25] 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.

6.5. Variation procedure(s) resulting from PSUSA evaluation

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

Applicant: Mylan Ire Healthcare Limited

PRAC Rapporteur: Mari Thorn

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

Background

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

Following the evaluation of the most recently submitted PSUR(s) for the above-mentioned medicine(s), PRAC requested the MAH to submit a variation to update the adverse drug reaction (ADR) table from section 4.8 of the product information, following the assessment of the PSUSA procedure (PSUSA/00001467/202112) concluded in July 2022. PRAC is responsible for adopting an outcome based on the assessment report from the PRAC Rapporteur, to be further considered at the level of CHMP, responsible for adopting an opinion on this variation. For further background, see PRAC minutes April 2023 and PRAC minutes July 2023.

Summary of recommendation(s)

- Based on the available data and the Rapporteur's assessment and the responses submitted by the MAH, PRAC agreed to amend[26] the product information accordingly.

6.6. Expedited summary safety reviews[27]

None

7. Post-authorisation safety studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)[28]

See Annex I 17.1.

7.2. Protocols of PASS non-imposed in the marketing authorisation(s)[29]

See Annex I 17.2.

[26] Update of SmPC section 4.8. The package leaflet is updated accordingly.
[27] 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
[28] In accordance with Article 107n of Directive 2001/83/EC
[29] 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

7.3. Results of PASS imposed in the marketing authorisation(s)[30]

7.3.1. Oral retinoids (acitretin, alitretinoin, isotretinoin) (NAP) - EMEA/H/N/PSR/J/0040

Applicant (s): F.Hoffmann-La Roche Ltd. (on behalf of a consortium) (2CARE4GENERICS, ALFASIGMA ESPAÑA, ALLIANCE PHARMACEUTICALS, ALMIRALL, ARISTO PHARMA, AUROBINDO, BAILLEUL, BAUSCHHEALTH, DERMAPHARM, ENNOGEN HEALTHCARE, ESPECIALIDADES FARMACÉUTICAS CENTRUM, EXPANSCIENCE, FIDIA, GALENPHARMA, GAP, GSK, HEXAL, IASIS PHARMA, INDUSTRIAL FARMACÉUTICA CANTABRIA, ISDIN, MEDINFAR, MORNINGSIDE HEALTHCARE, MYLAN, ORIFARM, PELPHARMA, PHARMATHEN, PIERRE FABRE, ROCHE, SANOSWISS, LABORATOIRES SMB S.A., STADA, SUN PHARMA, TARGET, and TEVA)

PRAC Rapporteur: Ana Sofia Diniz Martins

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

Background

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

In line with the conclusions reached in February 2018 of the referral procedure under Article 31 of Directive 2001/83/EC (EMEA/H/A-31/1446) conducted by PRAC for retinoid-containing medicinal products, the MAHs of oral retinoids acitretin, alitretinoin and isotretinoin were required as a condition to the marketing authorisations (Annex IV) to conduct a drug utilisation study to assess the effectiveness of the updated RMMs in women of childbearing potential resulting from this referral procedure. The final study report was submitted to EMA by the MAH Roche. PRAC discussed the final study results in addition to the MAH's responses to the request for supplementary information (RSI). For further background, see PRAC minutes March 2023.

Summary of recommendation(s) and conclusions

- Based on the review of the final report of the non-interventional PASS entitled 'Evaluation of the effectiveness of pregnancy prevention programme (PPP) for oral retinoids (acitretin, alitretinoin, and isotretinoin): a European before-after drug utilisation study (DUS) using secondary data', PRAC considered that the benefit-risk balance of medicinal products containing acitretin, alitretinoin or isotretinoin remains unchanged.
- Nevertheless, PRAC recommended that the terms of the marketing authorisation(s) for medicinal products containing acitretin, alitretinoin or isotretinoin should be varied to remove the PASS as an obligation from Annex II-D on 'conditions or restrictions with regard to the safe and effective use of the medicinal product' and to remove the respective medicinal products from list of medicines under additional monitoring. In addition, PRAC agreed that a qualitative study is necessary to investigate barriers and

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

reasons why certain measures part of the PPP are not always followed in clinical practice. The full protocol of the qualitative study should be submitted in a separate procedure.

7.3.2. Prasterone – INTRAROSA (CAP) - EMEA/H/C/PSR/S/0044

Applicant: Endoceutics S.A.

PRAC Rapporteur: Menno van der Elst

Scope: Final study report for a drug utilisation study (DUS) to describe the baseline characteristics and utilisation patterns of EU postmenopausal women initiating treatment with Intrarosa and to assess whether EU prescribers abide by the contraindications stated in the EU SmPC

Background

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

As a condition to the marketing authorisation(s) (Annex II-D), the MAH was required to conduct a DUS to describe the baseline characteristics and utilisation patterns of EU postmenopausal women initiating treatment with Intrarosa.

The final study report was submitted to EMA by the MAH on 26 April 2023. PRAC discussed the final study results.

Summary of recommendation(s) and conclusions

- Based on the review of the final report of the non-interventional PASS entitled 'Drug utilisation of Intrarosa (6.5 mg prasterone pessary) in European Countries', PRAC considered that the benefit-risk balance of Intrarosa (prasterone) remains unchanged. PRAC recommended that the terms of the marketing authorisation(s) for Intrarosa (prasterone) should be varied to remove the PASS as an obligation from the Annex II-D on 'conditions or restrictions with regard to the safe and effective use of the medicinal product', as well as to remove Intrarosa (prasterone) from the list of products under additional monitoring.

7.3.3. Valproate[31] (NAP) - EMEA/H/N/PSR/J/0043

Applicant: Sanofi-Aventis Recherche & Développement

PRAC Rapporteur: Liana Gross-Martirosyan

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

Background

Further to the conclusions dated 2018 of the referral procedure under Article 31 of Directive 2001/83/EC (EMEA/H/A-31/1454) conducted by PRAC for valproate-containing medicines, the MAHs were required as a condition to the marketing authorisation(s) (Annex IV) to

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

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 and PRAC minutes July 2023.

Following the revised list of questions (LoQ) adopted in July 2023, the MAH Sanofi-Aventis Recherche & Développement submitted to EMA the first set of responses on the study results on behalf of a consortium.

Summary of recommendation(s) and conclusions

- Based on the review of the final report of the registry study, the MAH's responses to the request for supplementary information (RSI) and the Rapporteur's assessment, PRAC agreed that there is a need for stakeholder's and expert input in order to further conclude on the results of the PASS, as well as on the most appropriate risk minimisation measures (routine and additional) before a final recommendation can be issued.
- PRAC adopted a revised LoQ and an updated timetable for this procedure.

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

See also Annex I 17.4.

7.4.1. Lenalidomide - REVLIMID (CAP) - EMEA/H/C/000717/II/0126

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Tiphaine Vaillant

Scope: Submission of the final report from study CC-5013-MDS-010 listed as an obligation in the Annex II of the product information. This is a prospective non-interventional PASS, designed as a disease registry of patients with transfusion dependent International Prognostic Scoring System (IPSS) low or intermediate-1-risk myelodysplastic syndromes (MDS) and isolated del(5q). Section D of the Annex II and the RMP (version 39) are 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 Revlimid (lenalidomide) the MAH conducted a PASS listed as an obligation in the Annex II of the product information (PI) of Revlimid (category 1 study) to gather safety data on the use of lenalidomide in MDS patients and monitor off-label use. The Rapporteur assessed the MAH's final study report in addition to the MAH's answers to the request for supplementary information (RSI). For further background, see PRAC minutes June 2023.

Summary of advice

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

- 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 agreed to remove the study as an obligation from the Annex II-D on 'conditions or restrictions with regard to the safe and effective use of the medicinal product' and from the RMP. In addition, PRAC considered that the PI should be amended to add 'anaemia' as an undesirable effect reported in clinical trials in patients with myelodysplastic syndromes treated with lenalidomide, using the highest frequency reported in the pivotal trials.

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

See Annex I 17.6.

7.7. New Scientific Advice

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

7.8. Ongoing Scientific Advice

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

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

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

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

8.1. Annual reassessments of the marketing authorisation

See Annex I 18.1.

8.2. Conditional renewals of the marketing authorisation

See Annex I 18.2.

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

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

None

10.3. Other requests

None

10.4. Scientific Advice

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

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

11.1. Safety related variations of the marketing authorisation

11.1.1. Oral retinoids (acitretin, alitretinoin, isotretinoin) (NAP) - DE/H/xxxx/WS/1115

Applicant(s): GAP AE (GAP SA) Beiname: G.A. Pharmaceuticals S.A. (on behalf of a consortium) (2CARE4GENERICS, ALFASIGMA ESPAÑA, ALLIANCE PHARMACEUTICALS, ALMIRALL, ARISTO PHARMA, AUROBINDO, BAILLEUL, BAUSCHHEALTH, DERMAPHARM, ENNOGEN HEALTHCARE, ESPECIALIDADES FARMACÉUTICAS CENTRUM, EXPANSCIENCE, FIDIA, GALENPHARMA, GAP, GSK, HEXAL, IASIS PHARMA, INDUSTRIAL FARMACÉUTICA CANTABRIA, ISDIN, MEDINFAR, MORNINGSIDE HEALTHCARE, MYLAN, ORIFARM, PELPHARMA, PHARMATHEN, PIERRE FABRE, ROCHE, SANOSWISS, LABORATOIRES SMB S.A., STADA, SUN PHARMA, TARGET, and TEVA)

PRAC Lead: Martin Huber

Scope: PRAC consultation on a worksharing variation (WS) procedure regarding the final study report of the category 3 PASS to assess the effectiveness of the Pregnancy Prevention Programme (PPP) for the oral retinoids acitretin, alitretinoin and isotretinoin, following an Article 31 referral on retinoid-containing medicinal products (EMEA/H/A-31/1446), on request of Germany

Background

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

In the context of the evaluation of a worksharing variation procedure on the final study report of the category 3 PASS to assess the effectiveness of the PPP for the oral retinoids acitretin, alitretinoin and isotretinoin, following an Article 31 referral on retinoid-containing medicinal products (EMEA/H/A-31/1446), Germany requested PRAC advice on its assessment.

Summary of advice

- PRAC discussed the proposal for a direct healthcare professional communication (DHPC) in the context of procedure EMEA/H/N/PSR/J/0040 and agreed that, at this point, based on the review of the available information, an aligned, centralised DHPC would not address the lack of adherence observed in the survey and in the drug utilisation study (DUS) that is being assessed in parallel. A DHPC would have been useful to reinforce awareness; however, the outcome of the studies suggests that health care professionals and patients have sufficient information and knowledge to take an informed decision. PRAC concurred that a national decision on the need for a DHPC would be preferable and that the Member States should decide whether a DHPC would be suitable depending on the national circumstances and tailor the messages accordingly. PRAC suggested that the Member States may also consider at the national level whether other measures could be implemented, such as communication through learned societies. Finally, PRAC highlighted that the outcome of the proposed qualitative study will further inform whether any further measures are needed, of which the results should be awaited first.

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 welcomed Karin Ernholm, as the new alternate for Denmark.

12.1.2. Vote by proxy

Annalisa Capuano gave a proxy to Amelia Cupelli to vote on her behalf during the entire meeting.

12.2. Coordination with EMA Scientific Committees or CMDh-v

None

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

None

12.4. Cooperation within the EU regulatory network

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

The topic was postponed for the next plenary meeting.

12.5. Cooperation with International Regulators

None

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

None

12.7. PRAC work plan

None

12.8. Planning and reporting

12.8.1. Marketing authorisation applications (MAA) forecast for 2023 – planning update dated Q3 2023

At the organisational, regulatory and methodological matters (ORGAM) meeting on 12 October 2023, the EMA Secretariat presented for information to PRAC a quarterly updated report on marketing authorisation applications (MAA) planned for submission (the business 'pipeline'). For previous update, see PRAC minutes July 2023.

12.9. Pharmacovigilance audits and inspections

12.9.1. Pharmacovigilance systems and their quality systems

None

12.9.2. Pharmacovigilance inspections

None

12.9.3. Pharmacovigilance audits

None

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

12.10.1. Periodic safety update reports

None

12.10.2. Granularity and Periodicity Advisory Group (GPAG)

None

12.10.3. PSURs repository

None

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

In line with the criteria for plenary presentation of updates to the EURD List adopted by PRAC in December 2021, PRAC endorsed the draft revised EURD list, version September 2023, reflecting the PRAC's comments impacting on the data lock point (DLP) and PSUR submission frequencies of the substances/combinations. PRAC endorsed the newly allocated Rapporteurs for upcoming PSUSAs in accordance with the principles previously endorsed by PRAC (see PRAC minutes April 2013).

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

12.11. Signal management

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

None

12.12. Adverse drug reactions reporting and additional monitoring

12.12.1. Management and reporting of adverse reactions to medicinal products

None

12.12.2. Additional monitoring

None

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

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

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

12.13. EudraVigilance database

12.13.1. Activities related to the confirmation of full functionality

None

12.14. Risk management plans and effectiveness of risk minimisations

12.14.1. Risk management systems

None

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

None

12.15. Post-authorisation safety studies (PASS)

12.15.1. Post-authorisation Safety Studies – imposed PASS

None

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

None

12.16. 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

None

12.21. Others

12.21.1. Patient Experience Data – priority activities and actions

At the organisational, regulatory and methodological matters (ORGAM) meeting on 12 October 2023, the EMA Secretariat presented to PRAC the context and relevance of patient expert data for pharmacovigilance and risk minimisation, as well as the progress made on the actions agreed following the patient experience data (PED) workshop in 2022 and described the key deliverables for next year. PRAC noted the presentation on the PED project. PRAC members were invited to express their interest to participate to the development of the reflection paper on the EU approach aiming to provide advice on the best EU approach to generate and collect PED .

12.21.2. International data standards: ISO planned update to the ICSR standard - opportunity to create new standard for electronic PSURs and RMPs

The EMA Secretariat presented to PRAC a summary of the domains identified to organise the recommendations for the development and adoption of new data standards and which are further detailed in the European Medicines Regulatory Network Data Standardisation Strategy. The presentation focused on the safety & risk management domain of the strategy, which covers individual case safety reports (ICSR), product safety update reports (PSUR), environmental risk assessment and risk management plans (RMP). An explanation of the activities that would need to be performed in order to fulfil the recommendations detailed in the EMRN Data Standardisation Strategy was provided. PRAC was informed that the Member States would need to identify experts to take this work forward. PRAC acknowledged the importance of such project and agreed that further consultation with other stakeholders is needed before the work on the development of the electronic PSUR (ePSUR) and the electronic RMP (eRMP) can be initiated with the support of the EU network. The EMA Secretariat will follow-up on the matter with PRAC to see if experts in the regulatory network have been identified and if this work will be taken forward.

12.21.3. EMA-funded study - Association between COVID-19 vaccines and paediatric safety outcomes in children and adolescents in the Nordic countries – study results

Invited speaker(s): Anders Peter Hviid (Statens Serum Institut), Jesper Kjær (Danish Medicines Agency)

The invited speakers presented to PRAC the results of an EMA-funded study on the association between COVID-19 vaccines and paediatric safety outcomes in children and adolescents in the Nordic countries. The presentation focused on the association between Comirnaty (COVID-19 vaccine) and myocarditis, pericarditis and thromboembolic events, as well as a large series of immune-mediated diseases. PRAC noted the conclusions presented by the study author(s). The study report(s) are published on the EU PAS Register: EMA_ROC09_Study Report_II_14042023_EMA comments (encepp.eu) and 103720 (encepp.eu)

12.21.4. PRAC drafting group on the risks of dependence and addiction of opioids - update

PRAC lead: Liana Gross-Martirosyan

At the organisational, regulatory and methodological matters (ORGAM) meeting on 12 October 2023, the PRAC lead presented to PRAC the summary of the consultation with stakeholders, the working group on Quality Review of Documents (QRD) working group (WG), as well as the feedback received from the Member States on the warning on the addiction/dependence potential of opioid-containing medicines. For further background, see PRAC minutes June 2023. Overall, the outcome of the consultations and the feedback received were in favour of warning patients of the addiction risk, in addition to having a warning in the package leaflet only. Potential alternative ways for warning patients on the opioid use disorder (OUD) risk, apart from the warning printed on the outer packaging, such as a patient card attached outside or inserted inside the outer packaging box, were brought to PRAC's attention. PRAC concluded that further consultation with CMDh's Multilingual Packaging Working Group is needed in order to conclude on the most appropriate risk minimisation measures to address the risk of OUD.

12.21.5. Multi-stakeholder workshop on registries

PRAC lead: Patricia McGettigan

At the organisational, regulatory and methodological matters (ORGAM) meeting on 12 October 2023, the EMA Secretariat informed PRAC about the upcoming multi-stakeholder workshop on patient registries scheduled to take place on 12 and 13 February 2024 by presenting also the key topics that will be discussed. PRAC noted the information.

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

At the organisational, regulatory and methodological matters (ORGAM) meeting on 12 October 2023, 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.

13. Any other business

None

14. Annex I – Signals assessment and prioritisation[33]

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[34].

14.1. New signals detected from EU spontaneous reporting systems

14.1.1. Chlorhexidine (NAP)[35] and other relevant fixed-dose combinations[36]

Applicant: various

PRAC Rapporteur: Lina Seibokiene

Scope: Signal of persistent corneal injury and significant visual impairment

14.1.2. Teriparatide – FORSTEO (CAP), MOVYMIA (CAP), TERROSA (CAP), LIVOGIVA (CAP), SONDELBAY (CAP), KAULIV (CAP), TERIPARATIDE SUN (CAP); NAP

Applicant: Accord Healthcare S.L.U. (Sondelbay), Eli Lilly Nederland B.V. (Forsteo), Gedeon Richter Plc. (Terrosa), STADA Arzneimittel AG (Movymia), Strides Pharma (Cyprus) Limited (Kauliv), Sun Pharmaceutical Industries Europe B.V. (Teriparatide SUN), Theramex Ireland Limited (Livogiva)

PRAC Rapporteur: Tiphaine Vaillant

Scope: Signal of alopecias

14.2. New signals detected from other sources

None

[33] 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

[34] 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

[35] For cutaneous use only

[36] Chlorhexidine, chlorocresol, hexamidine; chlorhexidine gluconate, chlorocresol, hexamidine; chlorocresol, hexamidine, chlorhexidine digluconate; benzalkonium chloride, chlorhexidine gluconate; chlorhexidine gluconate, benzoxonium chloride, retinol; benzalkonium chloride, chlorhexidine gluconate, benzyl alcohol; chlorhexidine gluconate; chlorhexidine gluconate, cetrimonium; chlorhexidine gluconate, chlorocresol, hexamidine; chlorhexidine gluconate, dexpanthenol; chlorhexidine gluconate, hydrocortisone; chlorhexidine gluconate, hydrogen peroxide, isopropyl alcohol; chlorhexidine gluconate, isopropyl alcohol; chlorhexidine gluconate, ethanol; chlorhexidine gluconate, phenol; benzalkonium chloride, chlorhexidine gluconate; benzalkonium chloride, chlorhexidine digluconate; chlorhexidine digluconate; chlorhexidine digluconate, ethanol; chlorhexidine digluconate, isopropyl alcohol; chlorhexidine dihydrochloride; benzalkonium chloride, chlorhexidine dihydrochloride, isopropyl myristate, liquid paraffin; chlorhexidine dihydrochloride, dexpanthenol; chlorhexidine dihydrochloride, nystatin; chlorhexidine dihydrochloride, nystatin, dexamethasone; chlorhexidine dihydrochloride, nystatin, hydrocortisone; chlorhexidine dihydrochloride, zinc oxide, pramocaine hydrochloride;, triamcinolone acetonide; chlorhexidine dihydrochloride, dexpanthenol, alphatocopherol acetate, vitamin A; chlorhexidine gluconate; cetrimide, chlorhexidine digluconate; chlorhexidine acetate; cetrimide, chlorhexidine acetate; retinol palmitate, chlorhexidine acetate; retinol palmitate, benzocaine, retinol, chlorhexidine acetate; bacitracin zinc, chlorhexidine acetate; nystatin, hydrocortisone, chlorhexidine acetate.

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).

15.2. 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. Dapagliflozin - EDISTRIDE (CAP) - EMEA/H/C/004161/WS2517/0063; FORXIGA (CAP) - EMEA/H/C/002322/WS2517/0084

Applicant: AstraZeneca AB

PRAC Rapporteur: Mari Thorn

Scope: Submission of an updated RMP version 30 in order to remove the potential important risk for lower limb amputation

15.2.2. Deferasirox - EXJADE (CAP) - EMEA/H/C/000670/II/0085

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Tiphaine Vaillant

Scope: Submission of an updated RMP version 21.0 in order to include the physician survey CICL670A2429 as a PASS category 3, based on the submission of a draft version of the protocol for the physician survey CICL670A2429. The Annex IID is updated to remove one sentence related to 'surveillance programme' and to introduce a minor correction

15.2.3. 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

15.2.4. Rilpivirine - REKAMBYS (CAP) - EMEA/H/C/005060/II/0019

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Submission of an updated RMP version 4.1 in order to update the risk

characterisation information for the missing information 'use in pregnancy' based on interim data of the Antiretroviral Pregnancy Register (APR), listed as a category 3 study in the RMP; and to align the milestones and due dates of this study following the outcome of procedure EMEA/H/C/PSUSA/00010901/202209. In addition, the MAH took the opportunity to update the status and the interim report milestones for the studies DUS and COMBINE-2

15.2.5. Tecovirimat - TECOVIRIMAT SIGA (CAP) - EMEA/H/C/005248/II/0006

Applicant: SIGA Technologies Netherlands B.V.

PRAC Rapporteur: Martin Huber

Scope: Submission of substantial updates to the protocol of study SIGA-246-021 listed as a specific obligation in the Annex II of the product information in order to reflect the transfer of sponsorship from SIGA Technologies, Inc. to the NIH Division of Microbiology and Infection Disease protocol. This is a phase 4, observational field study to evaluate safety and clinical benefit in tecovirimat-treated patients following exposure to variola virus and clinical diagnosis of smallpox disease. The Annex II and the RMP submitted version 1.2 are updated accordingly

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

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

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

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Kimmo Jaakkola

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

15.3.2. Adalimumab - AMGEVITA (CAP) - EMEA/H/C/004212/X/0036/G

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Mari Thorn

Scope: Extension application to introduce a new strength, 80 mg [0.8 ml (100 mg/ml)] solution for injection, grouped with various quality variations:

- B.II.a.5 (type II) - To introduce a high-concentration formulation (100 mg/ml) to the already existing concentration (50 mg/ml) where the amount of AS per unit dose (i.e. the

strength, 20 mg, 40 mg) remains the same. The new pack-size of 1 in pre-filled syringe (glass) in 20 mg /0.2ml solution for injection is consequently introduced.

- B.II.e.5.a.1 (type IAIN) - To introduce the new pack-size of 1 pre-filled syringe (glass) in 40mg /0.4ml Solution for injection.
- B.II.e.5.a.1 (type IAIN) - To introduce the new pack-size of 2 pre-filled syringe (glass) in 40mg /0.4ml Solution for injection.
- B.II.e.5.a.1 (type IAIN) - To introduce the new pack-size of 6 (3 x 2) in pre-filled syringe (glass) (multipack) in 40mg /0.4ml Solution for injection.
- B.II.e.5.a.1 (type IAIN) - To introduce the new pack-size of 1 pre-filled syringe (glass) in pre-filled pen (SureClick) in 40mg /0.4ml Solution for injection.
- B.II.e.5.a.1 (type IAIN) - To introduce the new pack-size of 2 pre-filled syringe (glass) in pre-filled pen (SureClick) in 40mg /0.4ml Solution for injection.
- B.II.e.5.a.1 (type IAIN) - To introduce the new pack-size of 6 (3 x 2) pre-filled syringe (glass) (multipack) in pre-filled pen (SureClick) in 40mg /0.4ml Solution for injection.
- B.II.f.1.b.5 (type IB) - To extend the shelf-life of the 50 mg/ml finished product, in accordance with the approved stability protocol, from 24 months to 36 months. The shelf-life is aligned with the proposed shelf life for the 100 mg/ml finished product.
- B.I.a.2.a (type IB) - Minor changes in the manufacturing process of the active substance formulation (applies to both 50 mg/ml and 100 mg/ml) Additionally, editorial changes are introduced to update method number updates. The RMP (version 6.0) is updated in accordance

15.3.3. Bezlotoxumab - ZINPLAVA (CAP) - EMEA/H/C/004136/II/0037

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Extension of indication to include treatment of the paediatric population (1 to 18 years of age) for ZINPLAVA, based on final results from study MK-6072-001 (MODIFY III) listed as a category 3 study in the RMP; this is a phase 3, randomised, placebo-controlled, parallel-group, multi-site, double-blind trial evaluating the safety, tolerability, pharmacokinetics (PK) and efficacy of a single infusion of bezlotoxumab in paediatric participants from 1 to <18 years of age receiving antibacterial drug treatment for Clostridioides difficile infection (CDI). As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet is updated in accordance. Version 2.3 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the product information

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

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Liana Gross-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

15.3.5. Brentuximab vedotin - ADCETRIS (CAP) - EMEA/H/C/002455/II/0109, Orphan

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication to include in combination with cyclophosphamide, doxorubicin, and prednisone (CHP) treatment of adult patients with previously untreated CD30+ peripheral T-cell lymphoma not otherwise specified (PTCL-NOS) for ADCETRIS based on the final overall survival results of Echelon-2 (SGN035-014): a randomised, double-blind, placebo-controlled, phase 3 study of brentuximab vedotin and CHP (A+CHP) versus CHOP in the frontline treatment of patients with CD30-positive mature T-cell lymphomas. As a consequence, sections 4.1, 4.2 and 5.1 of the SmPC are updated. The package leaflet is updated in accordance. Version 19.0 of the RMP has also been submitted. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet

15.3.6. Cerliponase alfa - BRINEURA (CAP) - EMEA/H/C/004065/II/0039, Orphan

Applicant: BioMarin International Limited

PRAC Rapporteur: Mari Thorn

Scope: Update of sections 4.2, 4.4, 4.8, 5.1, 5.2, 6.5 and 9 of the SmPC in order to state that clinical data are available for patients aged 1 year and older and to include updates to the frequency of adverse reactions, immunogenicity, pharmacokinetic, and paediatric population sections based on the final results from studies 190-203, listed as a specific obligation and 190-202 (submitted in P46/013). Study 190-203 was a phase 2, open-label, multicentre study in paediatric patients < 18 years of age with CLN2 disease, confirmed by deficiency of TPP1 enzyme activity and mutation of the CLN2 gene. The package leaflet, Annex II and Annex IV are updated accordingly. The RMP version 4.0 has also been submitted

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

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Tiphaine Vaillant

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

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

Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Extension of indication to include in combination with platinum-containing chemotherapy the treatment of adult patients with mismatch repair deficient (dMMR)/ microsatellite instability-high (MSI-H) primary advanced or recurrent endometrial cancer (EC) and who are candidates for systemic therapy, based on results from study 213361 (RUBY) Part 1, listed as a Specific Obligation in the Annex II; this is a phase 3, randomised, double-blind, multicentre study of dostarlimab (TSR-042) plus carboplatin-paclitaxel versus placebo plus carboplatin-paclitaxel in patients with recurrent or primary advanced endometrial cancer. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Annex II and package leaflet are updated in accordance. Version 3.0 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the product information. As part of the application, the MAH is requesting a 1-year extension of the market protection

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

Applicant: Daiichi Sankyo Europe GmbH

PRAC Rapporteur: Nathalie Gault

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

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

Applicant: Argenx

PRAC Rapporteur: Rhea Fitzgerald

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

15.3.11. Florbetapir (^{18}F) - AMYVID (CAP) - EMEA/H/C/002422/II/0044

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Martin Huber

Scope: Update of section 4.4 of the SmPC in order to remove the limitation regarding monitoring response to therapy based on available information in the scientific literature. The RMP version 4.1 has also been submitted. In addition, the MAH took the opportunity to update section 4.8 to the SmPC to align the clinical trial exposures with the RMP

15.3.12. Gilteritinib - XOSPATA (CAP) - EMEA/H/C/004752/II/0013, Orphan

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Martin Huber

Scope: Update of sections 4.2 and 5.2 in order to update the information on renal impairment based on final results from study 2215-CL-0114, listed as a category 3 study in the RMP. Study 2215-CL-0114 is a phase 1, single-dose, open-label study to investigate the effect of renal impairment on gilteritinib pharmacokinetics, safety and tolerability in 9 participants with severe renal impairment compared to 8 participants with normal renal function. The RMP version 4.0 has also been submitted. In addition, the MAH took the opportunity to introduce editorial changes

15.3.13. 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: Marie Louise Schougaard Christiansen

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

15.3.14. Inotersen - TEGSEDI (CAP) - EMEA/H/C/004782/II/0038, Orphan

Applicant: Akcea Therapeutics Ireland Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Update of sections 4.4 and 4.8 of the SmPC in order to modify the warning on liver monitoring and drug-induced liver injury and to add 'drug-induced liver injury' to the list of adverse drug reactions (ADRs) with frequency 'not known', following the request in the assessment report for PAM procedure EMEA/H/C/004782/LEG/008. The Annex II and package leaflet are updated accordingly. The RMP version 4.0 has also been submitted. In addition, the MAH took the opportunity to introduce minor updates to the product information

15.3.15. Irinotecan hydrochloride trihydrate - ONIVYDE PEGYLATED LIPOSOMAL (CAP) - EMEA/H/C/004125/II/0034, Orphan

Applicant: Les Laboratoires Servier

PRAC Rapporteur: David Olsen

Scope: Extension of indication to include first-line treatment of adult patients with metastatic adenocarcinoma of the pancreas for Onivyde in combination with oxaliplatin, 5 fluorouracil (5 FU) and leucovorin (LV) based on final results from phase 3 study NAPOLI 3 (D-US-60010-001): an interventional study with a primary objective to evaluate the efficacy of the regimen of irinotecan liposome injection + oxaliplatin + 5-fluorouracil (5-FU)/leucovorin (LV) versus nab-paclitaxel + gemcitabine in improving overall survival (OS) in subjects who have not previously received chemotherapy for metastatic adenocarcinoma of the pancreas. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated. The package leaflet is updated in accordance. The updated RMP version 4.1 is also submitted

15.3.16. Luspatercept - REBLOZYL (CAP) - EMEA/H/C/004444/II/0021, Orphan

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Jo Robays

Scope: Extension of indication to include treatment of adult patients with anaemia due to very low, low and intermediate-risk myelodysplastic syndromes (MDS), who may require RBC transfusions for Reblozyl, based on results from study ACE-536-MDS-002 (COMMANDS), an active-controlled, open-label, randomised phase 3 study comparing the efficacy and safety of luspatercept vs epoetin alfa in adult subjects with anaemia due to IPSS-R very low, low or intermediate risk MDS, who are ESA naïve and require RBC transfusions, and studies ACE-536-MDS-001(MEDALIST), ACE-536-MDS-004 , A536-03, A536-05 and ACE-536-LTFU-001. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet is updated in accordance. Version 2.0 of the RMP has also been submitted

15.3.17. Meningococcal group A, C, W135 and Y conjugate vaccine - MENVEO (CAP) - EMEA/H/C/001095/X/0119

Applicant: GSK Vaccines S.r.l

PRAC Rapporteur: Menno van der Elst

Scope: Extension application to introduce a new pharmaceutical form (solution for injection). The RMP (version 11.0) is updated in accordance.

15.3.18. Meropenem, vaborbactam - VABOREM (CAP) - EMEA/H/C/004669/II/0020

Applicant: Menarini International Operations Luxembourg S.A.

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Submission of the final reports from Global Microbiology Surveillance Study and Molecular Surveillance Report, listed as a category 3 study in the RMP. The RMP version 2.0 has also been submitted

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

Applicant: AstraZeneca AB

PRAC Rapporteur: Kimmo Jaakkola

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

15.3.20. Osimertinib - TAGRISSO (CAP) - EMEA/H/C/004124/II/0052

Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: Update of section 5.1 of the SmPC in order to update efficacy information (final OS data) based on final results from study D5164C00001 (ADAURA) listed as a post-authorisation efficacy study (PAES) in the Annex II: a phase III, double-blind, randomised, placebo-controlled study, designed to assess the efficacy and safety of osimertinib versus placebo in patients with stage IB-IIIA epidermal growth factor receptor mutation positive (EGFRm) non-small cell lung cancer (NSCLC) who have undergone complete tumour resection, with or without postoperative adjuvant chemotherapy. The RMP version 15 has also been submitted. In addition, the MAH took the opportunity to update Annex II section D of the product information and to implement editorial changes to the SmPC

15.3.21. Patisiran - ONPATTRO (CAP) - EMEA/H/C/004699/II/0034, Orphan

Applicant: Alnylam Netherlands B.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: Submission of the final report from study ALN-TTR02-006 (study 006), listed a category 3 study in the RMP. This is a multicentre, open-label, extension study to evaluate the long-term safety and efficacy of patisiran in patients with familial amyloidotic polyneuropathy who have completed a prior clinical study with patisiran. The RMP version 2.2 has also been submitted

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

Applicant: BioMarin International Limited

PRAC Rapporteur: Rhea Fitzgerald

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

15.3.23. Talazoparib - TALZENNA (CAP) - EMEA/H/C/004674/X/0015/G

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Grouped application consisting of: 1) addition of a new strength of 0.1 mg hard capsules; 2) extension of indication to add talazoparibin combination with enzalutamide for the treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC), based on final results from study C3441021 (TALAPRO-2) as well as supplemental data from study C3441006 (TALAPRO-1). Study C3441021 (TALAPRO-2) is a randomised, double-blind, placebo-controlled, phase 3 study of talazoparib in combination with enzalutamide in mCRPC, while study C3441006 (TALAPRO-1) is a phase 2, open-label, response rate study of talazoparib in men with DNA repair defects and mCRPC who previously received taxane-based chemotherapy and progressed on at least one novel hormonal agent. As a consequence, sections 1, 2, 3, 4.1, 4.2, 4.5, 4.7, 4.8, 5.1, 5.2, 6.1, 6.5, 8 of the SmPC are updated. The package leaflet and labelling are updated in accordance. Version 1.1 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the product information

15.3.24. 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 studies 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

15.3.25. Zanubrutinib - BRUKINSA (CAP) - EMEA/H/C/004978/II/0014

Applicant: BeiGene Ireland Ltd

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication to include zanubrutinib in combination with obinutuzumab treatment of adult patients with relapsed or refractory follicular lymphoma who have received at least two prior systemic treatments for BRUKINSA, based on results from studies BGB-3111-212 and BGB-3111-GA101-001. BGB-3111-212 is an ongoing international, Phase 2, open-label, randomised (2:1), active control study of zanubrutinib plus obinutuzumab (Arm A) versus obinutuzumab monotherapy (Arm B) in patients with R/R FL. The primary efficacy endpoint is overall response rate (ORR); while BGB-3111-GA101-001 is a Phase 1b Study to Assess Safety, Tolerability and Antitumor Activity of the Combination of BGB-3111 with Obinutuzumab in Subjects with B-Cell Lymphoid Malignanciesa. As a consequence, sections 4.1, 4.4, 4.8 and 5.1 of the SmPC are updated. The package leaflet is updated in accordance. Version 3.1 of the RMP has also been

submitted. In addition, the MAH took the opportunity to implement editorial changes to the SmPC

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. Abrocitinib - CIBINQO (CAP) - PSUSA/00010976/202303

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Evaluation of a PSUSA procedure

16.1.2. Baloxavir marboxil - XOFLUZA (CAP) - PSUSA/00010895/202302

Applicant: Roche Registration GmbH

PRAC Rapporteur: Sonja Hrabcik

Scope: Evaluation of a PSUSA procedure

16.1.3. Baricitinib - OLUMIANT (CAP) - PSUSA/00010578/202302

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.4. Bedaquiline - SIRTURO (CAP) - PSUSA/00010074/202303

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.5. Bempedoic acid - NILEMDO (CAP); bempedoic acid, ezetimibe - NUSTENDI (CAP) - PSUSA/00010841/202302

Applicant: Daiichi Sankyo Europe GmbH

PRAC Rapporteur: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

16.1.6. Bimekizumab - BIMZELX (CAP) - PSUSA/00010953/202302

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

16.1.7. Burosumab - CRYSVITA (CAP) - PSUSA/00010669/202302

Applicant: Kyowa Kirin Holdings B.V.

PRAC Rapporteur: Gabriele Maurer

Scope: Evaluation of a PSUSA procedure

16.1.8. Ceftazidime, avibactam - ZAVICEFTA (CAP) - PSUSA/00010513/202302

Applicant: Pfizer Ireland Pharmaceuticals

PRAC Rapporteur: Rugile Pilviniene

Scope: Evaluation of a PSUSA procedure

16.1.9. Colistimethate sodium[37] - COLOBREATHE (CAP) - PSUSA/00009112/202302

Applicant: Teva B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.10. Coronavirus (COVID-19) vaccine (Ad26.COV2-S, recombinant) - JCOVDEN (CAP) - PSUSA/00010916/202302

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.11. Coronavirus (COVID-19) vaccine (inactivated, adjuvanted, adsorbed) - COVID-19 VACCINE (INACTIVATED, ADJUVANTED) VALNEVA (CAP) - PSUSA/00011001/202302

Applicant: Valneva Austria GmbH

[37] Dry inhalation powder only

PRAC Rapporteur: Gabriele Maurer

Scope: Evaluation of a PSUSA procedure

16.1.12. Dengue tetravalent vaccine (live, attenuated) - DENGUE TETRAVALENT VACCINE (Art 58[38]) - EMEA/H/W/005362/PSUV/0004

Applicant: Takeda GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUR procedure

16.1.13. Dengue tetravalent vaccine[39] (live, attenuated) - QDENGA (CAP) - PSUSA/00011034/202302

Applicant: Takeda GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.14. Difelikefalin - KAPRUVIA (CAP) - PSUSA/00010995/202302

Applicant: Vifor Fresenius Medical Care Renal Pharma France

PRAC Rapporteur: Mari Thorn

Scope: Evaluation of a PSUSA procedure

16.1.15. Diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA), poliomyelitis (inactivated), haemophilus type b conjugate vaccine (adsorbed) - VAXELIS (CAP) - PSUSA/00010469/202302

Applicant: MCM Vaccine B.V.

PRAC Rapporteur: Gabriele Maurer

Scope: Evaluation of a PSUSA procedure

16.1.16. Emtricitabine, rilpivirine, tenofovir alafenamide - ODEFSEY (CAP) - PSUSA/00010514/202302

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

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

[39] Dengue virus, serotype 2, expressing Dengue virus, serotype 1, surface proteins, live, attenuated, Dengue virus, serotype 2, expressing Dengue virus, serotype 3, surface proteins, live, attenuated, Dengue virus, serotype 2, expressing Dengue virus, serotype 4, surface proteins, live, attenuated, Dengue virus, serotype 2, live, attenuated

16.1.17. Epoetin beta - NEORECORMON (CAP) - PSUSA/00001239/202302

Applicant: Roche Registration GmbH

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.18. Eptinezumab - VYEPTI (CAP) - PSUSA/00010966/202302

Applicant: H. Lundbeck A/S

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

16.1.19. Esketamine[40] - SPRAVATO (CAP) - PSUSA/00010825/202303

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

16.1.20. Evinacumab - EVKEEZA (CAP) - PSUSA/00010945/202302

Applicant: Ultragenyx Germany GmbH

PRAC Rapporteur: Mari Thorn

Scope: Evaluation of a PSUSA procedure

16.1.21. Ex vivo expanded autologous human corneal epithelial cells containing stem cells - HOLOCLAR (CAP) - PSUSA/00010352/202302

Applicant: Holostem Terapie Avanzate s.r.l., ATMP[41]

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

16.1.22. Fampridine - FAMPYRA (CAP) - PSUSA/00001352/202301

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

16.1.23. Fedratinib - INREBIC (CAP) - PSUSA/00010909/202302

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Sonja Hrabcik

[40] Centrally authorised product(s) only
[41] Advanced therapy medicinal product

Scope: Evaluation of a PSUSA procedure

16.1.24. Ferric maltol - FERACCRU (CAP) - PSUSA/00010476/202302

Applicant: Norgine B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.25. Florbetaben (^{18}F) - NEURACEQ (CAP) - PSUSA/00010094/202302

Applicant: Life Radiopharma Berlin GmbH

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.26. Fosdenopterin - NULIBRY (CAP) - PSUSA/00011017/202302

Applicant: TMC Pharma (EU) Limited

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.27. Imlifidase - IDEFIRIX (CAP) - PSUSA/00010870/202302

Applicant: Hansa Biopharma AB

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.28. Influenza vaccine (surface antigen, inactivated, adjuvanted) - FLUAD TETRA (CAP) - PSUSA/00010300/202303

Applicant: Seqirus Netherlands B.V.

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.1.29. Influenza vaccine (surface antigen, inactivated, prepared in cell cultures) - FLUCELVAX TETRA (CAP) - PSUSA/00010737/202303

Applicant: Seqirus Netherlands B.V.

PRAC Rapporteur: Gabriele Maurer

Scope: Evaluation of a PSUSA procedure

16.1.30. Isatuximab - SARCLISA (CAP) - PSUSA/00010851/202303

Applicant: Sanofi Winthrop Industrie

PRAC Rapporteur: Monica Martinez Redondo

Scope: Evaluation of a PSUSA procedure

16.1.31. Lenacapavir - SUNLENCA (CAP) - PSUSA/00011012/202302

Applicant: Gilead Sciences Ireland Unlimited Company

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.1.32. Lonapegsomatropin - SKYTROFA (CAP) - PSUSA/00010969/202302

Applicant: Ascendis Pharma Endocrinology Division A/S

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.33. Mitapivat - PYRUKYND (CAP) - PSUSA/00011025/202302

Applicant: Agios Netherlands B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.34. Plasmodium falciparum and hepatitis B vaccine (recombinant, adjuvanted) - MOSQUIRIX (Art 58[42]) - EMEA/H/W/002300/PSUV/0071

Applicant: GlaxoSmithkline Biologicals SA

PRAC Rapporteur: Jean-Michel Dogné; PRAC Co-rapporteur: Gabriele Maurer

Scope: Evaluation of a PSUR procedure

16.1.35. Pralsetinib - GAVRETO (CAP) - PSUSA/00010961/202303

Applicant: Roche Registration GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.36. Pretomanid - DOVPRELA (CAP) - PSUSA/00010863/202302

Applicant: Mylan IRE Healthcare Limited

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

16.1.37. Rasburicase - FASTURTEC (CAP) - PSUSA/00002613/202302

Applicant: Sanofi Winthrop Industrie

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

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.38. Rimegepant - VYDURA (CAP) - PSUSA/00010997/202302

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Evaluation of a PSUSA procedure

16.1.39. Risperidone[43] - OKEDI (CAP) - PSUSA/00010985/202302

Applicant: Laboratorios Farmaceuticos Rovi S.A.

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.40. Ropeginterferon alfa-2b - BESREMI (CAP) - PSUSA/00010756/202302

Applicant: AOP Orphan Pharmaceuticals GmbH

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.1.41. Ruxolitinib - JAKAVI (CAP) - PSUSA/00010015/202302

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.42. Safinamide - XADAGO (CAP) - PSUSA/00010356/202302

Applicant: Zambon S.p.A.

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

16.1.43. Silodosin - SILODYX (CAP); UROREC (CAP) - PSUSA/00002701/202301

Applicant: Recordati Ireland Ltd

PRAC Rapporteur: Valentina Di Giovanni

Scope: Evaluation of a PSUSA procedure

16.1.44. Simoctocog alfa - NUWIQ (CAP); VIHUMA (CAP) - PSUSA/00010276/202301

Applicant: Octapharma AB

[43] Centrally authorised product(s) only

PRAC Rapporteur: Mari Thorn

Scope: Evaluation of a PSUSA procedure

16.1.45. Somapacitan - SOGROYA (CAP) - PSUSA/00010920/202302

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.46. Sotrovimab (Xevudy) - XEVUDY (CAP) - PSUSA/00010973/202302

Applicant: Glaxosmithkline Trading Services Limited

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

16.1.47. Spesolimab - SPEVIGO (CAP) - PSUSA/00011033/202303

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Nathalie Gault

Scope: Evaluation of a PSUSA procedure

16.1.48. Telotristat - XERMELO (CAP) - PSUSA/00010639/202302

Applicant: SERB S.A.S.

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.49. Ulipristal acetate[44] - ESMYA (CAP) - PSUSA/00009325/202302

Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.50. Valoctocogene roxaparvovec - ROCTAVIAN (CAP) - PSUSA/00011009/202302

Applicant: BioMarin International Limited, ATMP[45]

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.51. Vosoritide - VOXZOGO (CAP) - PSUSA/00010952/202302

Applicant: BioMarin International Limited

[44] Indication(s) for the treatment of moderate to severe symptoms of uterine fibroids only
[45] Advanced therapy medicinal product

PRAC Rapporteur: Zane Neikena

Scope: Evaluation of a PSUSA procedure

16.1.52. Voxelotor - OXBRYTA (CAP) - PSUSA/00010983/202302

Applicant: Pfizer Europe Ma EEIG

PRAC Rapporteur: Jo Robays

Scope: Evaluation of a PSUSA procedure

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

16.2.1. Dexrazoxane - SAVENE (CAP); NAP - PSUSA/00001001/202302

Applicant: Clinigen Healthcare B.V. (Savene), various

PRAC Rapporteur: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

16.2.2. Imiquimod - ALDARA (CAP); ZYCLARA (CAP); NAP - PSUSA/00001729/202301

Applicant: Viatris Healthcare Limited (Aldara, Zyclara), various

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

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

16.3.1. Ciprofloxacin[46] (NAP) - PSUSA/00000776/202301

Applicant(s): various

PRAC Lead: Karen Pernille Harg

Scope: Evaluation of a PSUSA procedure

16.3.2. Dacarbazine (NAP) - PSUSA/00000919/202302

Applicant(s): various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.3.3. Fenoterol, ipratropium (NAP) - PSUSA/00001367/202302

Applicant(s): various

[46] For topical use only

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.3.4. Haemophilus type B and meningococcal group C conjugate vaccine (NAP) - PSUSA/00001583/202302

Applicant(s): various

PRAC Lead: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

16.3.5. Haemophilus type B conjugate vaccines (NAP) - PSUSA/00001584/202302

Applicant(s): various

PRAC Lead: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

16.3.6. Hydrochlorothiazide, losartan (NAP) - PSUSA/00001655/202302

Applicant(s): various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.3.7. Hydroxyethyl starch (NAP) - PSUSA/00001694/202303

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.3.8. Influenza vaccine (split virion, inactivated)[47] (NAP) - PSUSA/00010298/202303

Applicant(s): various

PRAC Lead: Gabriele Maurer

Scope: Evaluation of a PSUSA procedure

16.3.9. Influenza vaccine (surface antigen, inactivated) (NAP) - PSUSA/00001744/202303

Applicant(s): various

PRAC Lead: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

[47] Non-centrally authorised product(s) only

16.3.10. Ipratropium (NAP) - PSUSA/00001780/202301

Applicant(s): various

PRAC Lead: Melinda Palfi

Scope: Evaluation of a PSUSA procedure

16.3.11. Ipratropium, salbutamol (NAP) - PSUSA/00001781/202301

Applicant(s): various

PRAC Lead: Željana Margan Koletić

Scope: Evaluation of a PSUSA procedure

16.3.12. Landiolol (NAP) - PSUSA/00010570/202302

Applicant(s): various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.3.13. Mefloquine (NAP) - PSUSA/00001955/202302

Applicant(s): various

PRAC Lead: Karen Pernille Harg

Scope: Evaluation of a PSUSA procedure

16.3.14. Saccharomyces boulardii (NAP) - PSUSA/00009284/202302

Applicant(s): various

PRAC Lead: Eva Jirsová

Scope: Evaluation of a PSUSA procedure

16.3.15. Sodium citrate[48] (NAP) - PSUSA/00010986/202301

Applicant(s): various

PRAC Lead: Polona Golmajer

Scope: Evaluation of a PSUSA procedure

16.3.16. Tick-borne encephalitis vaccine (inactivated) (NAP) - PSUSA/00002951/202301

Applicant(s): various

PRAC Lead: Gabriele Maurer

Scope: Evaluation of a PSUSA procedure

[48] For extracorporeal use only

16.3.17. Tauroselcholic [^{75}Se] acid (NAP) - PSUSA/00010486/202301

Applicant(s): various

PRAC Lead: Melinda Palfi

Scope: Evaluation of a PSUSA procedure

16.4. Follow-up to PSUR/PSUSA procedures

16.4.1. Piperaquine tetraphosphate, artenimol - EURARTESIM (CAP) - EMEA/H/C/001199/LEG 018

Applicant: Alfasigma S.p.A.

PRAC Rapporteur: Martin Huber

Scope: Submission of a cumulative review including a causality assessment regarding cases of haemolytic anaemia, as well as a cumulative analysis of all cases of delayed haemolytic anaemia with the use of oral artemisinin combination therapy from all available worldwide sources, since the last review until now, including a causality assessment

16.5. Variation procedure(s) resulting from PSUSA evaluation

None

16.6. Expedited summary safety reviews[49]

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)[50]

17.1.1. Chenodeoxycholic acid – CHENODEOXYCHOLIC ACID LEADIANT (CAP) - EMEA/H/C/PSA/S/0103.1

Applicant: Leadiant GmbH

PRAC Rapporteur: Adam Przybylkowski

Scope: MAH's response to PSA/S/0103: substantial amendment to a Cerebrotendinous Xanthomatosis Registry: long term non-interventional follow-up of safety and effectiveness of Chenodeoxycholic Acid Leadiant

[49] 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

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

17.1.2. Lisocabtagene maraleucel – BREYANZI (CAP) - EMEA/H/C/PSA/S/0105

Applicant: Bristol-Myers Squibb Pharma EEIG, ATMP[51]

PRAC Rapporteur: Gabriele Maurer

Scope: Substantial amendment to a protocol for a non-interventional PASS of patients treated with commercially available liso-cel (lisocabtagene maraleucel) for relapsed/refractory diffuse large B-cell lymphoma, primary mediastinal B-cell lymphoma, and follicular lymphoma Grade 3B after 2 or more lines of systemic therapy in the post-marketing setting to characterise the incidence and severity of selected adverse drug reactions (ADRs), as outlined in the SmPC, and to monitor for potential clinically important adverse events (AEs) that have not yet been identified as part of the liso-cel safety profile

17.1.3. Pomalidomide – IMNOVID (CAP) - EMEA/H/C/PSA/S/0106

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Monica Martinez Redondo

Scope: Substantial amendment to a non-interventional post authorisation registry of patients treated with pomalidomide for relapsed and refractory multiple myeloma who have received at least two prior treatment regimens, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy

17.1.4. Tabelecleucel – EBVALLO (CAP) - EMEA/H/C/PSP/S/0104.1

Applicant: Pierre Fabre Medicament, ATMP[52]

PRAC Rapporteur: Amelia Cupelli

Scope: MAH's response to PSP/0104 [An observational, PASS to describe the safety and effectiveness of tabelecleucel in patients with Epstein-Barr Virus positive (EBV+) Post-Transplant Lymphoproliferative Disease (PTLD) in a real-world setting in Europe] as per the request to supplementary information (RSI) adopted in May 2023

17.2. Protocols of PASS non-imposed in the marketing authorisation(s)[53]

17.2.1. Abrocitinib - CIBINQO (CAP) - EMEA/H/C/005452/MEA 003.3

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: MAH’s response to MEA 003.2 [protocol for study B7451085: a drug utilisation study to evaluate the effectiveness of risk minimisation measures (RMMs) for abrocitinib in the EU using electronic healthcare data. The study objectives will be to evaluate indicators of HCP’s adherence to the risk minimisation measures in accordance with the abrocitinib SmPC and prescriber brochure] as per the request to supplementary information (RSI) adopted in June 2023

[51] Advanced therapy medicinal product
[52] Advanced therapy medicinal product
[53] 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

17.2.2. Acalabrutinib - CALQUENCE (CAP) - EMEA/H/C/005299/MEA 002.8

Applicant: AstraZeneca AB

PRAC Rapporteur: Željana Margan Koletić

Scope: MAH's response to MEA 002.7 [protocol amendment to Study D8220C00008: phase 3b, multicentre, open-label, single-arm in subjects with chronic lymphocytic leukaemia (ASSURE) to address missing information around moderate to severe cardiac impaired patients in subjects treated with Calquence (acalabrutinib)] as per the request for supplementary information (RSI) adopted in June 2023

17.2.3. Alemtuzumab - LEMTRADA (CAP) - EMEA/H/C/003718/MEA 007.14

Applicant: Sanofi Belgium

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: MAH’s response to MEA 007.13 [protocol for study OBS13434: a prospective, multicentre, observational, PASS to evaluate the long term safety profile of alemtuzumab treatment in patients with relapsing forms of multiple sclerosis (RMS)] as per the request for supplementary information (RSI) adopted in March 2023

17.2.4. Avalglucosidase alfa - NEXVIADYME (CAP) - EMEA/H/C/005501/MEA 007.2

Applicant: Sanofi B.V.

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: MAH’s response to MEA 007.1 [Protocol for study OBS17445 (listed as category 3 study in the RMP): a PASS to assess long term safety in patients with Pompe disease treated with avalglucosidase alfa in the commercial setting] as per request for supplementary information (RSI) adopted in June 2023

17.2.5. Cinacalcet - MIMPARA (CAP) - EMEA/H/C/000570/MEA 035.7

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Mari Thorn

Scope: To evaluate the risk of hypocalcaemia (e.g., clinical characteristics, laboratory variables [PTH, Ca, and P], hospitalisation due to hypocalcaemia, co-medication, cinacalcet doses) in paediatric patients treated with cinacalcet

17.2.6. Cipaglucosidase alfa - POMBILITI (CAP) - EMEA/H/C/005703/MEA 001.1

Applicant: Amicus Therapeutics Europe Limited

PRAC Rapporteur: Mari Thorn

Scope: MAH’s response to MEA 001 [protocol for study POM-005 of a non-imposed/non-interventional, listed as category 3 in the RMP: a global prospective observational registry of patients with Pompe disease] as per the request for supplementary information (RSI) as adopted in June 2023

17.2.7. Cladribine - MAVENCLAD (CAP) - EMEA/H/C/004230/MEA 003.4

Applicant: Merck Europe B.V.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: MAH's responses to MEA 003.3 [submission of a revised protocol for study MS700568-0004: pregnancy outcomes in women exposed to oral cladribine: a multi-country cohort database study – CLEAR] as per the request for supplementary information (RSI) adopted in June 2023

17.2.8. Coronavirus (COVID-19) vaccine (ChAdOx1-S [recombinant]) - VAXZEVRIA (CAP) - EMEA/H/C/005675/MEA 007.8

Applicant: AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

Scope: From Initial MAA, RMP Category 3: A post-authorisation/post-marketing observational study using existing secondary health data sources to evaluate the association between exposure to AZD1222 and safety concerns (D8111R00006)

17.2.9. Coronavirus (COVID-19) vaccine (B.1.351 variant, prefusion Spike delta TM protein, recombinant) - VIDPREVTYN BETA (CAP) - EMEA/H/C/005754/MEA 002.2

Applicant: Sanofi Pasteur

PRAC Rapporteur: Jana Lukacisinova

Scope: MAH's response to MEA 002.1 [Submission of a protocol for study VAT 00007: Post-authorisation, observational study to assess the safety of VidPrevtyn Beta using routinely collected secondary data in Europe through VAC4EU. A non-interventional PASS to assess the occurrence of pre-specified AESIs and safety concerns following administration of VidPrevtyn Beta as a booster dose in a real-world setting] as per the request for supplementary information (RSI) adopted in June 2023

17.2.10. Elasomeran - SPIKEVAX (CAP) - EMEA/H/C/005791/MEA 065.3

Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: From II/0028: Study mRNA-1273-P910 Clinical course, outcomes and risk factors of myocarditis following administration of mRNA-1273

17.2.11. Elasomeran - SPIKEVAX (CAP) - EMEA/H/C/005791/MEA 072.2

Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: MAH's response to MEA 0072.1 [protocol for study mRNA-1273-P919 (listed as category 3 study in the RMP): an observational study to assess maternal and infant outcomes following exposure to Spikevax during pregnancy and to assess whether the rate of pregnancy complications, adverse pregnancy outcomes, or adverse neonatal outcomes is

associated with prenatal exposure to Spikevax] as per the request to supplementary information (RSI) adopted in May 2023

17.2.12. Empagliflozin - JARDIANCE (CAP) - EMEA/H/C/002677/MEA 004.7

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Maria del Pilar Rayon

Scope: MAH's response to MEA 004.6 and submission of a revised protocol for study 1245.97: a non-interventional PASS assessing the risk of urinary tract malignancies in relation to empagliflozin exposure in patients with type 2 diabetes mellitus (T2DM): a multi-database European study as per the request for supplementary information (RSI) adopted in October 2022

17.2.13. Empagliflozin, metformin - SYNJARDY (CAP) - EMEA/H/C/003770/MEA 006.9

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Maria del Pilar Rayon

Scope: MAH's response to MEA 006.8 and submission of a revised protocol for study 1245.97: a non-interventional PASS assessing the risk of urinary tract malignancies in relation to empagliflozin exposure in patients with type 2 diabetes mellitus (T2DM): a multi-database European study as per the request for supplementary information (RSI) adopted in October 2022

17.2.14. Eptinezumab - VYEPTI (CAP) - EMEA/H/C/005287/MEA 004.3

Applicant: H. Lundbeck A/S

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: MAH's response to MEA 004.2 as per request for supplementary information adopted in May 2023 together with an updated protocol for an observational, historical cohort study of patients initiating eptinezumab in routine clinical practice and is investigating the long-term cardiovascular safety and real-world use of Eptinezumab

17.2.15. Givosiran - GIVLAARI (CAP) - EMEA/H/C/004775/MEA 006.5

Applicant: Alnylam Netherlands B.V.

PRAC Rapporteur: Martin Huber

Scope: MAH's response to MEA 006.4 as per request for supplementary information adopted in May 2023 together with an updated protocol for PASS Study ALN-AS1-006: Company Sponsored AHP Registry: A global observational longitudinal prospective registry of patients with acute hepatic porphyria (AHP)

17.2.16. Golimumab - SIMPONI (CAP) - EMEA/H/C/000992/MEA 033.7

Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Mari Thorn

Scope: MAH's response to MEA 003.6 as per request for supplementary information adopted in March 2023 together with an updated protocol for an observational post-approval safety study of golimumab in treatment of polyarticular Juvenile Idiopathic Arthritis (pJIA) using the German Biologics JIA Registry (BiKeR)

17.2.17. Linzagolix choline - YSELTY (CAP) - EMEA/H/C/005442/MEA 002.1

Applicant: Theramex Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: MAH's response to MEA 002 as per request for supplementary information adopted in April 2023 together with an updated protocol for study YSELTY PASS: A multinational PASS on real-world treatment in patients receiving YSELTY (linzagolix choline) for moderate to severe symptoms of uterine fibroids, to evaluate routinely collected data on bone mineral density and to assess safety during long term (>12 months) use for linzagolix 200mg (with ABT) and 100mg (with and without ABT) dosing regimen

17.2.18. Naldemedine - RIZMOIC (CAP) - EMEA/H/C/004256/MEA 001.5

Applicant: Shionogi B.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: MAH's response to MEA 001.4 as per request for supplementary information adopted in April 2023 for an Observational PASS of Patients with Chronic Opioid Use for Non-Cancer and Cancer Pain who have Opioid-Induced Constipation (OIC)

17.2.19. Pitolisant - OZAWADE (CAP) - EMEA/H/C/005117/MEA 003.1

Applicant: Bioprojet Pharma

PRAC Rapporteur: Kirsti Villikka

Scope: MAH's response to MEA 003 as per request for supplementary information adopted in April 2023 together with an updated protocol for study: a multi-center, observational prospective PASS to compare the cardiovascular risks and long-term safety of OZAWADE in patients with obstructive sleep apnoea treated or not by primary therapy and exposed or not to OZAWADE when used in routine medical practice

17.2.20. Risankizumab - SKYRIZI (CAP) - EMEA/H/C/004759/MEA 010.1

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Title: 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)

17.2.21. Somatrogon - NGENLA (CAP) - EMEA/H/C/005633/MEA 001.1

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Submission of a revised protocol for study C0311023: an active surveillance study to monitor the real-world long-term safety of somatrogon among paediatric patients in Europe

17.2.22. Spesolimab - SPEVIGO (CAP) - EMEA/H/C/005874/MEA 003.1

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Nathalie Gault

Scope: From Initial MAA: A 5-year active surveillance, PASS to characterise the safety of spesolimab for flare treatment in patients with GPP. Objectives: To evaluate the risks serious or opportunistic infections, systemic hypersensitivity reaction, malignancy, and peripheral neuropathy in adult patients (aged ≥18 years) experiencing a GPP flare who are treated with spesolimab or other treatments in the routine clinical care setting

17.2.23. Tezepelumab - TEZSPIRE (CAP) - EMEA/H/C/005588/MEA 001.1

Applicant: AstraZeneca AB

PRAC Rapporteur: Eva Jirsová

Scope: PASS Study D5180R00010 (TREATY): A Non-Interventional Multi-Database Post-Authorisation Study to Assess Pregnancy-Related Safety Data from Women with Severe Asthma Exposed to Tezepelumab

17.2.24. Ublituximab - BRIUMVI (CAP) - EMEA/H/C/005914/MEA 001

Applicant: Propharma Group The Netherlands B.V.

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: 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

17.2.25. Ublituximab - BRIUMVI (CAP) - EMEA/H/C/005914/MEA 002

Applicant: Propharma Group The Netherlands B.V.

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Protocol for PASS Study No TG1101-RMS403 (cat. 3): a registry study of pregnancy and infant outcomes in patients treated with ublituximab, to characterise the safety of

ublituximab use in pregnancy, including maternal, foetal and neonate/infant outcomes, in female patients with relapsing forms of multiple sclerosis

17.2.26. Ublituximab - BRIUMVI (CAP) - EMEA/H/C/005914/MEA 003

Applicant: Propharma Group The Netherlands B.V.

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Protocol for PASS Study No TG1101-RMS404 (cat. 3): a study using data from an administrative healthcare claims database to characterise the safety to characterise the safety of ublituximab use in pregnancy, including maternal, foetal and neonate/infant outcomes, in female patients with relapsing forms of multiple sclerosis

17.3. Results of PASS imposed in the marketing authorisation(s)[54]

None

17.4. Results of PASS non-imposed in the marketing authorisation(s)[55]

17.4.1. Cabozantinib - CABOMETYX (CAP) - EMEA/H/C/004163/II/0033

Applicant: Ipsen Pharma

PRAC Rapporteur: Menno van der Elst

Scope: Final report from study F-FR-60000-001 (CASSIOPE) listed as a category 3 study in the RMP: a prospective, non-imposed and non-interventional study of cabozantinib tablets in adults with advanced renal cell carcinoma (RCC) following prior vascular endothelial growth factor (VEGF)-targeted therapy. The RMP version 7.0 has also been submitted

17.4.2. Guanfacine - INTUNIV (CAP) - EMEA/H/C/003759/II/0033/G

Applicant: Takeda Pharmaceuticals International AG Ireland Branch

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Submission of the final reports from the drug utilisation study of Intuniv (guanfacine extended release) in European countries: a prescriber survey (EUPAS18739) and a retrospective database study (EUPAS18735), listed as category 3 studies in the RMP. The RMP version 4.0 has also been submitted

17.4.3. Hydrocortisone - PLENADREN (CAP) - EMEA/H/C/002185/II/0043

Applicant: Takeda Pharmaceuticals International AG Ireland Branch

PRAC Rapporteur: Mari Thorn

Scope: Submission of the final report from study SHP617-400 (EU AIR) listed as a category 3 PASS in the RMP; this is a European multi-centre, multi-country, post-authorisation, observation study (registry) of patients with chronic adrenal insufficiency. The RMP version

[54] In accordance with Article 107p-q of Directive 2001/83/EC
[55] 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

4.0 has also been submitted

17.4.4. 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 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 HCP checklist as routine aRMM. The Annex II is updated accordingly

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

Applicant: Alfasigma S.p.A.

PRAC Rapporteur: Martin Huber

Scope: 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 with a submission of an updated RMP version 16.1 in order to delete 'severe malaria' from the Missing Information

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

Applicant: Daiichi Sankyo Europe GmbH

PRAC Rapporteur: Ana Sofia Diniz Martins

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

17.4.7. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/II/0101/G

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: Update of section 4.4 of the SmPC in order to remove a warning on cardiovascular events based on final results from non-interventional PASS studies NDI-MACE (CNTO1275PSO4005) and Quantify MACE (PCSIMM004697), listed as category 3 studies in the RMP (MEA/053 and MEA/054). NDI-MACE is a Nordic database initiative for exposure to ustekinumab: a review and analysis of major adverse cardiovascular events (MACE) from the Swedish and Danish national registry systems; Quantify MACE is an observational longitudinal PASS of STELARA in the treatment of psoriasis and psoriatic arthritis: analysis of major adverse cardiovascular events (MACE) using Swedish national health registers. The

package leaflet is updated accordingly. The RMP version 27.1 has also been submitted

17.4.8. Voriconazole - VFEND (CAP) - EMEA/H/C/000387/WS2270/0147

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Update of Annex II and RMP to version 6.0 to include the results from final clinical study report (CSR) following the completion of a non-interventional (NI) PASS A1501103: an active safety surveillance program to monitor selected events in patients with long-term voriconazole use - MEA091. In addition, the MAH is also taking this opportunity to introduce editorial changes

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

17.5.1. Apremilast - OTEZLA (CAP) - EMEA/H/C/003746/MEA 008.3

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Monica Martinez Redondo

Scope: Fourth yearly report for study CC 10004 PSA-012: evaluation of the long-term safety and safety outcomes for psoriatic arthritis patients treated with Otezla (apremilast) in the British Society for Rheumatology Psoriatic Arthritis Register (BSRBR-PsA) [final clinical study report (CSR) expected in Q2 2026]

17.5.2. Azathioprine - JAYEMPI (CAP) - EMEA/H/C/005055/MEA 001.1

Applicant: Nova Laboratories Ireland Limited

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Second annual report for category 3 study in the RMP: Monitoring of medication error reports specifically due to 'conversion of patients from tablet to liquid formulation and two dosing syringes' annually and submitted as post authorisation measure (PAM outside the context of azathioprine PSUR) (from initial opinion/MA)

17.5.3. Blinatumomab - BLINCYTO (CAP) - EMEA/H/C/003731/ANX 010.1

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Jana Lukacisinova

Scope: Interim study results for Observational PASS to describe the long-term safety profile of first-relapse B-precursor acute lymphocytic leukaemia (ALL) paediatric patients who have been treated with blinatumomab or chemotherapy prior to undergoing haemopoietic stem cell transplant / Study 20180130

17.5.4. Coronavirus (COVID-19) vaccine (recombinant, adjuvanted) - NUVAXOVID (CAP) - EMEA/H/C/005808/MEA 004.4

Applicant: Novavax CZ, a.s.

PRAC Rapporteur: Gabriele Maurer

Scope: Interim report for study 2019nCoV-402: UK PASS Using the Clinical Practice Research Datalink (CPRD): A surveillance study to characterise the safety profile of Nuvaxovid in adults aged 18 years and older in the real-world setting using the UK CPRD

17.5.5. Dimethyl fumarate - SKILARENCE (CAP) - EMEA/H/C/002157/MEA 001.7

Applicant: Almirall S.A

PRAC Rapporteur: Mari Thorn

Scope: Fifth annual interim results for study M-41008-40 (listed as a category 3 study in the RMP): an observational PASS in European psoriasis registers to evaluate the long-term safety of Skilarence (dimethyl fumarate) used for the treatment of patients with moderate to severe psoriasis

17.5.6. Eliglustat - CERDELGA (CAP) - EMEA/H/C/003724/ANX 001.4

Applicant: Sanofi B.V.

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Interim results for study OBS14009: A prospective multicentre observational post authorisation safety sub-registry to characterise the long-term safety profile of commercial use of eliglustat (Cerdelga) in adult patients with Gaucher disease

17.5.7. Elosulfase alfa - VIMIZIM (CAP) - EMEA/H/C/002779/ANX 005.8

Applicant: BioMarin International Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Ninth annual report for the Morquio A Registry Study (MARS): A voluntary observational registry study (MPS IVA)

17.5.8. Ravulizumab - ULTOMIRIS (CAP) - EMEA/H/C/004954/MEA 008.1

Applicant: Alexion Europe SAS

PRAC Rapporteur: Kimmo Jaakkola

Scope: Paroxysmal Nocturnal Hemoglobinuria (PNH) Registry Biennial Interim Report, Protocol M07-001

17.5.9. Siponimod - MAYZENT (CAP) - EMEA/H/C/004712/MEA 004.3

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Interim study report for the survey among healthcare professionals and MS patients/caregivers (study CBAF312A2006)

17.5.10. Teduglutide - REVESTIVE (CAP) - EMEA/H/C/002345/ANX 003.10

Applicant: Takeda Pharmaceuticals International AG Ireland Branch

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: MAH response to ANX 003.9 [Fourth interim report for study TED-R-13-002: an international short bowel syndrome registry - a prospective, long-term observational cohort study of patients with short bowel syndrome] as per request for supplementary information adopted in March 2023

17.5.11. Tozinameran - COMIRNATY (CAP) - EMEA/H/C/005735/MEA 041.3

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: MAH's responses to MEA 041.2 [Justification for not submitting an interim study report for study C4591036 (former paediatric heart network study): a safety surveillance study of myocarditis and myopericarditis associated with Comirnaty (tozinameran) in persons less than 21 years of age to characterize the clinical course, risk factors, long-term sequelae, and quality of life in children and young adults under 21 years with acute post-vaccine myocarditis, including a protocol amendment] as per request for supplementary information (RSI) adopted in March 2023

17.6. Others

17.6.1. Avatrombopag - DOPTELET (CAP) - EMEA/H/C/004722/MEA 002.6

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Monica Martinez Redondo

Scope: MAH’s responses to MEA 002.5 [feasibility assessment for study AVA-CLD-402: evaluation of the feasibility of conducting a PASS of Doptelet (avatrombopag) in patients with severe chronic liver disease (CLD) and of the use of potential European electronic health care databases] as per request for supplementary information adopoted in January 2023

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. Dinutuximab beta - QARZIBA (CAP) - EMEA/H/C/003918/S/0053 (without RMP)

Applicant: Recordati Netherlands B.V.

PRAC Rapporteur: Gabriele Maurer

Scope: Annual reassessment of the marketing authorisation

18.1.2. Ebola vaccine (rDNA, replication-incompetent) - MVABEA (CAP) - EMEA/H/C/005343/S/0019 (without RMP)

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Jean-Michel Dogné

Scope: Annual reassessment of the marketing authorisation

18.1.3. Ebola vaccine (rDNA, replication-incompetent) - ZABDENO (CAP) - EMEA/H/C/005337/S/0017 (without RMP)

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Jean-Michel Dogné

Scope: Annual reassessment of the marketing authorisation

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

Applicant: SIGA Technologies Netherlands B.V.

PRAC Rapporteur: Martin Huber

Scope: Annual reassessment of the marketing authorisation

18.2. Conditional renewals of the marketing authorisation

18.2.1. Bedaquiline - SIRTURO (CAP) - EMEA/H/C/002614/R/0054 (without RMP)

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Conditional renewal of the marketing authorisation

18.2.2. Etranacogene dezaparvovec - HEMGENIX (CAP) - EMEA/H/C/004827/R/0007 (without RMP)

Applicant: CSL Behring GmbH, ATMP[56]

PRAC Rapporteur: Menno van der Elst

Scope: Conditional renewal of the marketing authorisation

18.2.3. Ex vivo expanded autologous human corneal epithelial cells containing stem cells - HOLOCLAR (CAP) - EMEA/H/C/002450/R/0058 (with RMP)

Applicant: Holostem Terapie Avanzate s.r.l., ATMP[57]

PRAC Rapporteur: Rhea Fitzgerald

Scope: Conditional renewal of the marketing authorisation

18.2.4. Selpercatinib - RETSEVMO (CAP) - EMEA/H/C/005375/R/0026 (with RMP)

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Conditional renewal of the marketing authorisation

18.3. Renewals of the marketing authorisation

18.3.1. Atazanavir - ATAZANAVIR KRKA (CAP) - EMEA/H/C/004859/R/0004 (with RMP)

Applicant: KRKA, d.d., Novo mesto

PRAC Rapporteur: Nathalie Gault

Scope: 5-year renewal of the marketing authorisation

18.3.2. Brexucabtagene autoleucel - TECARTUS (CAP) - EMEA/H/C/005102/R/0034 (with RMP)

Applicant: Kite Pharma EU B.V., ATMP[58]

PRAC Rapporteur: Menno van der Elst

Scope: 5-year renewal of the marketing authorisation

18.3.3. Dacomitinib - VIZIMPRO (CAP) - EMEA/H/C/004779/R/0011 (without RMP)

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Menno van der Elst

Scope: 5-year renewal of the marketing authorisation

[56] Advanced therapy medicinal product
[57] Advanced therapy medicinal product
[58] Advanced therapy medicinal product

18.3.4. Febuxostat - FEBUXOSTAT KRKA (CAP) - EMEA/H/C/004773/R/0008 (with RMP)

Applicant: KRKA, d.d., Novo mesto

PRAC Rapporteur: Jan Neuhauser

Scope: 5-year renewal of the marketing authorisation

18.3.5. Influenza vaccine (surface antigen, inactivated, prepared in cell cultures) - FLUCELVAX TETRA (CAP) - EMEA/H/C/004814/R/0040 (without RMP)

Applicant: Seqirus Netherlands B.V.

PRAC Rapporteur: Gabriele Maurer

Scope: 5-year renewal of the marketing authorisation

18.3.6. Macimorelin - GHRYVELIN (CAP) - EMEA/H/C/004660/R/0020 (without RMP)

Applicant: Atnahs Pharma Netherlands B.V.

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: 5-year renewal of the marketing authorisation

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

Applicant: AOP Orphan Pharmaceuticals GmbH

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: 5-year renewal of the marketing authorisation

19. Annex II – List of participants

List of participants including any restrictions with respect to involvement of members / alternates / experts following evaluation of declared interests for the 25-28 September meeting, which was held in-person. Participants marked with "a" attended the plenary session while those marked with "b" attended the ORGAM. An asterisk (*) after the role, in the second column, signals that the member/alternate attended remotely. Additional experts participated in (part of) the meeting, either in person or remotely.

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Sabine Straus [a,b]	Chair	The Netherlands	No interests declared	
Jan Neuhauser [a]	Member	Austria	No interests declared	
Sonja Hrabcik [a]	Alternate	Austria	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Jean-Michel Dogné [a,b]	Member	Belgium	No interests declared	
Jo Robays [a]	Alternate	Belgium	No interests declared	
Maria Popova-Kiradjieva [b]	Member	Bulgaria	No interests declared	
Nikica Mirošević Skvrce [a]	Member	Croatia	No interests declared	
Željana Margan Koletić [a]	Alternate*	Croatia	No interests declared	
Elena Kaisis [a,b]	Member	Cyprus	No interests declared	
Panagiotis Psaras [b]	Alternate	Cyprus	No interests declared	
Eva Jirsová [a,b]	Member	Czechia	No interests declared	
Jana Lukacisinova [a,b]	Alternate	Czechia	No interests declared	
Marie Louise Schougaard Christiansen [a,b]	Member	Denmark	No interests declared	
Karin Erneholm [a,b]	Alternate	Denmark	No restrictions applicable to this meeting	
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 (Vice-Chair)	Germany	No interests declared	
Gabriele Maurer [a,b]	Alternate*	Germany	No restrictions applicable to this meeting	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Sofia Trantza [a],[b]	Member	Greece	No interests declared	
Georgia Gkegka [a],[b]	Alternate*	Greece	No interests declared	
Julia Pallos [a],[b]	Member	Hungary	No participation in final deliberations and voting on:	4.3.1. Azacitidine – AZACITIDINE ACCORD (CAP), AZACITIDINE BETAPHARM (CAP), AZACITIDINE MYLAN (CAP), ONUREG (CAP) - EMEA/H/C/004761/SDA/002; VIDAZA (CAP) - EMEA/H/C/003820/SDA/036 7.4.1. Lenalidomide - REVLIMID (CAP) - EMEA/H/C/000717/II/0126 15.3.1. Abatacept - ORENCIA (CAP) - EMEA/H/C/000701/II/0152 15.3.16. Luspatercept - REBLOZYL (CAP) - EMEA/H/C/004444/II/0021, Orphan 16.1.23. Fedratinib - INREBIC (CAP) - PSUSA/00010909/202302 17.1.2. Lisocabtagene

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				maraleucel – BREYANZI (CAP) - EMEA/H/C/PSA /S/0105 17.1.3. Pomalidomide – IMNOVID (CAP) - EMEA/H/C/PSA /S/0106 17.4.4. Luspatercept - REBLOZYL (CAP) - EMEA/H/C/004 444/II/0023, Orphan
Melinda Palfi [a]	Alternate*	Hungary	No interests declared	
Guðrún Stefánsdóttir[b]	Member	Iceland	No participation in final deliberations and voting on:	15.3.2. Adalimumab - AMGEVITA (CAP) - EMEA/H/C/004 212/X/0036/G 17.2.5. Cinacalcet - MIMPARA (CAP) - EMEA/H/C/000 570/MEA 035.7 17.5.1. Apremilast - OTEZLA (CAP) - EMEA/H/C/003 746/MEA 008.3 17.5.3. Blinatumomab - BLINCYTO (CAP) - EMEA/H/C/003 731/ANX 010.1
Gudrun Þengilsdóttir [a]	Alternate	Iceland	No restrictions applicable to this meeting	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Rhea Fitzgerald [a,b]	Member	Ireland	No interests declared	
Eamon O Murchu [a]	Alternate	Ireland	No interests declared	
Amelia Cupelli [a,b]	Member	Italy	No interests declared	
Valentina Di Giovanni [a,b]	Alternate*	Italy	No interests declared	
Zane Neikena [a,b]	Member*	Latvia	No interests declared	
Rugile Pilviniene [a]	Member*	Lithuania	No interests declared	
Nadine Petitpain [b]	Member	Luxembourg	No participation in final deliberations and voting on:	3.2.2. – EMA/H/A-31/1526
Anne-Cécile Vuillemin [a,b]	Alternate	Luxembourg	No interests declared	
John Joseph Borg [b]	Member	Malta	No interests declared	
Benjamin Micallef [a]	Alternate	Malta	No interests declared	
Menno van der Elst [a]	Member	Netherlands	No interests declared	
Liana Gross-Martirosyan [a,b]	Alternate	Netherlands	No interests declared	
David Olsen [a,b]	Member	Norway	No participation in final deliberations and voting on:	3.2.1. Hydroxyprogesterone (NAP) - EMEA/H/A-31/1528 3.2.2. – EMA/H/A-31/1526 6.3.4. Ibuprofen, ibuprofen lysine; ibuprofen, caffeine (NAP) - PSUSA/00010649/202302

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				14.1.1. Chlorhexidine (NAP) and other relevant fixed-dose combinations
Pernille Harg [a,b]	Alternate	Norway	No interests declared	
Adam Przybylkowski [a]	Member*	Poland	No interests declared	
Katarzyna Ziolkowska [b]	Alternate	Poland	No interests declared	
Ana Sofia Diniz Martins [a,b]	Member	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	
Maria del Pilar Rayon [a,b]	Member	Spain	No interests declared	
Monica Martinez Redondo [a]	Alternate	Spain	No interests declared	
Ulla Wändel Liminga [a]	Member	Sweden	No interests declared	
Mari Thorn [a,b]	Alternate	Sweden	No restrictions applicable to this meeting	
Milou Daniel Drici [a,b]	Member	Independent scientific expert	No interests declared	
Maria Teresa Herdeiro [a,b]	Member*	Independent scientific expert	No interests declared	
Patricia McGettigan [a]	Member	Independent scientific expert	No interests declared	
Tania Schink [a,b]	Member	Independent scientific expert	No participation in final	4.1.3. Glucagon-like peptide-1 (GLP-1)

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			deliberations and voting on:	receptor agonists: dulaglutide – TRULICITY (CAP); exenatide – BYDUREON (CAP), BYETTA (CAP); insulin degludec, liraglutide – XULTOPHY (CAP); liraglutide – SAXENDA (CAP), VICTOZA (CAP); insulin glargine, lixisenatide – SULIQUA (CAP); lixisenatide - LYXUMIA (CAP); semaglutide – OZEMPIC (CAP), RYBELSUS (CAP), WEGOVY (CAP); tirzepatide – MOUNJARO (CAP) 15.3.9. Edoxaban - LIXIANA (CAP) - EMEA/H/C/002629/WS2409/0042; ROTEAS (CAP) - EMEA/H/C/004339/WS2409/0029
Hedvig Nordeng [a]	Member	Independent scientific expert	No interests declared	
Roberto Frontini [a],[b]	Member	Healthcare Professionals' Representative	No participation in final deliberations	16.1.44. Simoctocog alfa - NUWIQ (CAP); VIHUMA (CAP) -

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			and voting on:	PSUSA/00010276/202301
Salvatore Messana [a]	Alternate	Healthcare Professionals' Representative	No interests declared	
Marko Korenjak [a]	Alternate	Patients' Organisation Representative	No interests declared	
Laurence de Fays [a,b]	Expert	Belgium	No interests declared	
Flora Musuamba Tshinanu [a]	Expert	Belgium	No restrictions applicable to this meeting	
Melita Dumančić [a]	Expert	Croatia	No restrictions applicable to this meeting	
Nina Lalić [a]	Expert	Croatia	No restrictions applicable to this meeting	
Petar Mas [a]	Expert	Croatia	No interests declared	
Veronika Deščíková [a]	Expert	Czechia	No interests declared	
Michaela Dlouha [a]	Expert	Czechia	No interests declared	
Lucie Skálová [a]	Expert	Czechia	No interests declared	
Marian Hjortlund Allon [a]	Expert	Denmark	No interests declared	
Mette Hjorslev Knudgaard [a]	Expert	Denmark	No interests declared	
Jesper Kjær [a]	Expert	Denmark	No interests declared	
Kristina Laursen [a]	Expert	Denmark	No interests declared	
Annette Cleveland Nielsen [a]	Expert	Denmark	No restrictions applicable to this meeting	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Moritz Sander [a]	Expert	Denmark	No interests declared	
Aynur Sert [a]	Expert	Denmark	No interests declared	
Per Sindahl [a]	Expert	Denmark	No interests declared	
Helene Stenbaek Hansen[b]	Expert	Denmark	No restrictions applicable to this meeting	
Mette Wikkelsø [a]	Expert	Denmark	No interests declared	
Katrin Kurvits [a]	Expert	Estonia	No interests declared	
Krista Ress [a]	Expert	Estonia	No restrictions applicable to this meeting	
Indrek Soosaar [a]	Expert	Estonia	No interests declared	
Helve Vestman [a]	Expert	Estonia	No interests declared	
Pauline Dayani [a]	Expert	France	No interests declared	
Camille De-Kervasdoue [a]	Expert	France	No interests declared	
Cécile Dop [a]	Expert	France	No interests declared	
Vincent Gazin [a]	Expert	France	No interests declared	
Stéphanie Hueber [a]	Expert	France	No interests declared	
Janine Mahungu [a]	Expert	France	No interests declared	
Ludivine Martin [a]	Expert	France	No restrictions applicable to this meeting	
Dennis Lex [a],[b]	Expert	Germany	No interests declared	
Justyna Dziewiatka [a]	Expert	Ireland	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Clare Foley [a]	Expert	Ireland	No interests declared	
Adriana Ammassari [a]	Expert	Italy	No interests declared	
Patrizia Felicetti [a]	Expert	Italy	No interests declared	
Silvia Francisci [a]	Expert	Italy	No interests declared	
Carmela Macchiarulo [a]	Expert	Italy	No interests declared	
Pasquale Marchione [a]	Expert	Italy	No interests declared	
Elena Matarangolo [a]	Expert	Italy	No interests declared	
Diāna Litenboka [a]	Expert	Latvia	No interests declared	
Diāna Paegle [a]	Expert	Latvia	No interests declared	
Michal Pirozynski [a]	Expert	Malta	No interests declared	
Marloes Bazelier [a]	Expert	Netherlands	No restrictions applicable to this meeting	
Marianne Klanker [a]	Expert	Netherlands	No interests declared	
Fokaline Vroom [a]	Expert	Netherlands	No interests declared	
Esther Zagwijn [a]	Expert	Netherlands	No interests declared	
Inge Zomerdijk [a]	Expert	Netherlands	No interests declared	
Carla Torre [a]	Expert	Portugal	No interests declared	
Natividad Galiana [a]	Expert	Spain	No restrictions applicable to this meeting	
Carmen Gallego López Jurado [a]	Expert	Spain	No interests declared	
Consuelo Mejías [a]	Expert	Spain	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Eva Segovia [a]	Expert	Spain	No interests declared	
Charlotte Backman [a],[b]	Expert	Sweden	No interests declared	
Emelie Bergman Perland [a]	Expert	Sweden	No restrictions applicable to this meeting	
Sara Brandel [a]	Expert	Sweden	No restrictions applicable to this meeting	
Anders Lignell [a]	Expert	Sweden	No interests declared	
Sissela Liljeqvist [a]	Expert	Sweden	No restrictions applicable to this meeting	
Annica Nordin [a]	Expert	Sweden	No interests declared	
A representative from the European Commission attended the meeting				
Meeting run with support from relevant EMA staff				

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

20. Annex III - List of acronyms and abbreviations

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

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