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SCIENCE MEDICINES HEALTH

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Human Medicines Division

Pharmacovigilance Risk Assessment Committee (PRAC) Minutes of PRAC meeting on 5-8 February 2024

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 ongoing 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, alternates¹ 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 5-8 February 2024

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

1.3. Minutes of the previous meeting on 8-11 January 2024

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

Post-meeting note: the PRAC minutes of the meeting held on 8-11 January 2024 were published on the EMA website on 05 March 2024 ([EMA/PRAC/68905/2024](#)).

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

2.1. Newly triggered procedures

None

¹ No alternates for COMP

2.2. Ongoing procedures

None

2.3. Procedures for finalisation

None

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

3.1. Newly triggered procedures

None

3.2. Ongoing procedures

None

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

Applicant(s): various

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

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

Background

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

Summary of recommendation(s)/conclusions

- PRAC noted the feedback provided by the ad-hoc expert group (AHEG) Chair following the AHEG meeting held on 22 January 2024.
- 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/194263/2023 rev.3](#)).

² Murphy CC, et al. In utero exposure to 17 α -hydroxyprogesterone caproate and risk of cancer in offspring. *Am J Obstet Gynecol*. 2022 Jan;226(1):132.e1-132.e14. doi:10.1016/j.ajog.2021.10.035

³ Blackwell, S. C. et al. 17-OHPC to prevent recurrent preterm birth in singleton gestations (PROLONG Study): A multicenter, international, randomised double-blind trial. *Am J Perinatol*. 2020 Jan;37(2):127-136. doi:10.1055/s-0039-3400227

3.3. Procedures for finalisation

None

3.4. Re-examination procedures⁴

None

3.5. Others

None

4. Signals assessment and prioritisation⁵

For further details, see also the adopted [PRAC recommendations on signals](#) under the corresponding month.

4.1. New signals detected from EU spontaneous reporting systems

See also Annex I 14.1.

4.1.1. Adagrasib – KRAZATI (CAP)

Applicant: Mirati Therapeutics B.V.

PRAC Rapporteur: Kimmo Jaakkola

Scope: Signal of serious cutaneous adverse reactions (SCARs)

EPITT 20051 – New signal

Lead Member State(s): FI

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 SCARs was identified by the French National Agency for the Safety of Medicines and Health Products (ANSM) as part of a national surveillance monitoring in the context of an EU Early Access Program, based on cases retrieved from EudraVigilance and 6 cases (including five cases from clinical trials) identified by the MAH upon ANSM request as well as data from 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 SCARs is warranted.

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

⁵ Each signal refers to a substance or therapeutic class. The route of marketing authorisation is indicated in brackets (CAP for Centrally Authorised Products; NAP for Nationally Authorised Products including products authorised via Mutual Recognition Procedures and Decentralised Procedure). Product names are listed for reference Centrally Authorised Products (CAP) only. PRAC recommendations will specify the products concerned in case of any regulatory action required

Summary of recommendation(s)

- The MAH for Krazati (adagrasib) should submit to EMA, within 30 days, a cumulative review of all cases of Severe Cutaneous Adverse Reactions (SCARs) associated with adagrasib as suspect drug. The review should include all relevant data covered by the Standardised MedDRA Query (SMQ) SCARs with data lock point (DLP) 31 January 2024 and with an analysis of updated patient exposure estimation, a review of the published literature, data from spontaneous reports and reports from studies, as well as a discussion on possible biological plausibility and mechanism of this association. The MAH should also discuss the need for any potential amendment to the product information (PI) and/ or the risk management plan (RMP).
- A 30-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.2. New signals detected from other sources

See also Annex I 14.2.

4.2.1. Ceftriaxone (NAP)

Applicant: various

PRAC Rapporteur: to be appointed

Scope: Signal of precipitation when administered with calcium-containing solutions in infants between 29 days and 1 year

EPITT 1964 – New signal

Lead Member State(s): LV

Background

Ceftriaxone is cephalosporin antibiotic indicated for the treatment of several infections in adults and children including term neonates (from birth) like bacterial meningitis, community acquired pneumonia, hospital acquired pneumonia, acute otitis media, intra-abdominal infections, complicated urinary tract infections (including pyelonephritis), infections of bones and joints, complicated skin and soft tissue infections, gonorrhoea, syphilis, bacterial endocarditis, as well as for treatment of acute exacerbations of chronic obstructive pulmonary disease in adults, for treatment of disseminated Lyme borreliosis (early (stage II) and late (stage III)) in adults and children including neonates from 15 days of age and for pre-operative prophylaxis of surgical site infections, subject to certain conditions.

Following the publication by *Christensen ML et al.*⁶, a signal of precipitation when administered with calcium-containing solutions in infants between 29 days and 1 year was identified by EMA. Latvia confirmed that the signal needed initial analysis and prioritisation by PRAC.

Discussion

⁶ Concomitant Ceftriaxone and Intravenous Calcium Therapy in Infants". J Pediatr Pharmacol Ther 2021;26(7):702–707. DOI: 10.5863/1551-6776-26.7.702

Having considered the available evidence from the literature, PRAC agreed that further evaluation on the signal of precipitation when administered with calcium-containing solutions in infants between 29 days and 1 year is warranted.

PRAC appointed Zane Neikena as Rapporteur for the signal.

Summary of recommendation(s)

- The MAH Roche for the innovator ceftriaxone-containing medicinal product should submit to EMA, within 60 days, an analysis and discussion on the causal relationship of paediatric death cases and cases posing a life-threatening risk with the concomitant use of ceftriaxone and IV calcium in which ceftriaxone and IV calcium were used within 48 hours or more in children aged between more than 28 days and 1 year old from clinical trials, observational studies, scientific literature and post-marketing setting, focusing also on the time of administration and how ceftriaxone and IV calcium were administered, providing data on autopsy results, if available. In addition, the MAH Roche should provide a discussion of the article by *Christensen ML et al* in the context of the analysed data from other sources, as well as the available published evidence on the pathophysiological mechanism of this interaction in different patient age groups. Finally, the MAH Roche should discuss the need for any potential amendment to the product information (PI) and/ or the risk management plan (RMP).
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.3. Signals follow-up and prioritisation

4.3.1. [Atezolizumab - TECENTRIQ \(CAP\) - EMEA/H/C/004143/SDA/025](#); [Avelumab - BAVENCIO \(CAP\) - EMEA/H/C/004338/SDA/011](#); [Cemiplimab - LIBTAYO \(CAP\) - EMEA/H/C/004844/SDA/010](#); [Dostarlimab - JEMPERLI \(CAP\) - EMEA/H/C/005204/SDA/005](#); [Durvalumab - IMFINZI \(CAP\) - EMEA/H/C/004771/SDA/012](#); [Ipilimumab - YERVOY \(CAP\) - EMEA/H/C/002213/SDA/048](#); [Nivolumab - OPDIVO \(CAP\) - EMEA/H/C/003985/SDA/056](#); [Nivolumab, relatlimab - OPDUALAG \(CAP\) - EMEA/H/C/005481/SDA/006](#); [Pembrolizumab - KEYTRUDA \(CAP\) - EMEA/H/C/003820/SDA/040](#); [Tislelizumab - TEVIMBRA \(CAP\) - EMEA/H/C/005919/SDA/002](#); [Tremelimumab - IMJUDO \(CAP\) - EMEA/H/C/006016/SDA/003](#)

Applicant: AstraZeneca AB (Imjudo)⁷, Bristol-Myers Squibb Pharma EEIG (Imfinzi, Opdivo, Opdualag), GlaxoSmithKline (Ireland) Limited (Jemperli), Merck Europe B.V. (Bavencio), Merck Sharp & Dohme B.V.(Keytruda), Novartis Europharm Limited (Tevimbra), Regeneron Ireland Designated Activity Company (Libtayo), Roche Registration GmbH (Tecentriq)

PRAC Rapporteur: Bianca Mulder

Scope: Signal of coeliac disease

EPITT 19958 – Follow-up to September 2023⁸

Background

For background information, see [PRAC minutes September 2023](#).

⁷ Tremelimumab AstraZeneca Marketing Authorisation has been withdrawn at the request of the MAH

⁸ Held 28 August – 31 August 2023

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

Discussion

Having considered the available evidence in EudraVigilance and literature, the response from the MAHs, as well as a biologically plausible mechanism, PRAC considered that a causal association between immune-checkpoint inhibitors and coeliac disease is at least a reasonable possibility and that the product information should be updated to add coeliac disease as an undesirable effect.

Summary of recommendation(s)

- The MAHs for nivolumab-containing products Opdivo and Opdualag, for Keytruda (pembrolizumab), Imfinzi (durvalumab), Bavencio (avelumab), Tecentriq (atezolizumab), Libtayo (cemiplimab), Jemperli (dostarlimab), Tevimbra (tislelizumab), Yervoy (ipilimumab), and for Imjudo (tremelimumab) should submit to EMA, within 30 days, their comments on PRAC's proposal to amend⁹ the product information, providing also the relevant frequency calculations.

4.3.2. [Atezolizumab - TECENTRIQ \(CAP\) - EMEA/H/C/004143/SDA/024](#); [Avelumab - BAVENCIO \(CAP\) - EMEA/H/C/004338/SDA/010](#); [Cemiplimab - LIBTAYO \(CAP\) - EMEA/H/C/004844/SDA/009](#); [Dostarlimab - JEMPERLI \(CAP\) - EMEA/H/C/005204/SDA/004](#); [Durvalumab - IMFINZI \(CAP\) - EMEA/H/C/004771/SDA/011](#); [Ipilimumab - YERVOY \(CAP\) - EMEA/H/C/002213/SDA/047](#); [Nivolumab - OPDIVO \(CAP\) - EMEA/H/C/003985/SDA/055](#); [Nivolumab, relatlimab - OPDUALAG \(CAP\) - EMEA/H/C/005481/SDA/005](#); [Pembrolizumab - KEYTRUDA \(CAP\) - EMEA/H/C/003820/SDA/039](#); [Tislelizumab - TEVIMBRA \(CAP\) - EMEA/H/C/005919/SDA/001](#); [Tremelimumab - IMJUDO \(CAP\) - EMEA/H/C/006016/SDA/002](#)

Applicant(s): AstraZeneca AB (Imjudo)¹⁰, Bristol-Myers Squibb Pharma EEIG (Imfinzi, Opdivo, Opdualag), GlaxoSmithKline (Ireland) Limited (Jemperli), Merck Europe B.V. (Bavencio), Merck Sharp & Dohme B.V. (Keytruda), Novartis Europharm Limited (Tevimbra), Regeneron Ireland Designated Activity Company (Libtayo), Roche Registration GmbH (Tecentriq)

PRAC Rapporteur: Martin Huber

Scope: Signal of pancreatic failure

EPITT 19955 – Follow-up to September 2023¹¹

Background

For background information, see [PRAC minutes September 2023](#).

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

Discussion

⁹ Update of SmPC section 4.8. The package leaflet is updated accordingly.

¹⁰ Tremelimumab AstraZeneca Marketing Authorisation has been withdrawn at the request of the MAH

¹¹ Held 28 August – 31 August 2023

Having considered the available evidence in EudraVigilance and literature, the response from the MAHs, as well as a biologically plausible mechanism, PRAC considered that a causal association between immune-checkpoint inhibitors and pancreatic exocrine insufficiency is at least a reasonable possibility and that the product information should be updated to add pancreatic exocrine insufficiency as an undesirable effect.

Summary of recommendation(s)

- The MAHs for nivolumab-containing products Opdivo and Opdualag, for Keytruda (pembrolizumab), Imfinzi (durvalumab), Bavencio (avelumab), Tecentriq (atezolizumab), Libtayo (cemiplimab), Jemperli (dostarlimab), Tevimbra (tislelizumab), Yervoy (ipilimumab), and for Imjudo (tremelimumab) should submit to EMA, within 30 days, their comments on PRAC's proposal to amend¹² the product information, also providing the relevant frequency calculations.

4.3.3. Chlorhexidine (NAP)¹³ and other relevant fixed-dose combinations¹⁴

Applicant: various

PRAC Rapporteur: Lina Seibokiene

Scope: Signal of persistent corneal injury and significant visual impairment

EPITT 19970 – Follow-up to October 2023¹⁵

Background

For background information, see [PRAC minutes October 2023](#).

The MAHs replied to the request for information on the signal of persistent corneal injury and significant visual impairment and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence in EudraVigilance, literature and the response from the MAHs, PRAC considered that there is sufficient evidence to establish a causal association between chlorhexidine and persistent corneal injury and significant visual impairment and agreed that the product information of chlorhexidine-containing products, indicated for skin disinfection and intended for cutaneous use, should be updated to add corneal erosion, epithelium defect/corneal injury and significant permanent visual impairment as a warning and as an undesirable effect with a frequency 'not known'.

¹² Update of SmPC section 4.8. The package leaflet is updated accordingly.

¹³ For cutaneous use only

¹⁴ 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, alphanatocopherol 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 Held 25 September – 29 September 2023

Summary of recommendation(s)

- The MAHs for chlorhexidine-containing medicinal products indicated for skin disinfection and intended for cutaneous use should submit to EMA, within 30 days, their comments on PRAC's proposal to amend¹⁶ the product information.
- A 30-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.4. Variation procedure(s) resulting from signal evaluation

None

5. Risk management plans (RMPs)

5.1. Medicines in the pre-authorisation phase

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

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

See also Annex I 15.1.

5.1.1. Capiwasertib - (CAP MAA) - EMEA/H/C/006017

Scope (pre D-180 phase): Indicated in combination with fulvestrant for the treatment of adult patients with hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative (defined as IHC 0 or 1+, or IHC 2+/ISH-) locally advanced or metastatic breast cancer following recurrence or progression on or after an endocrine based regimen

5.1.2. Chikungunya virus, strain CHIKV LR2006-OPY1, live attenuated - (CAP MAA) - EMEA/H/C/005797, PRIME

Scope (pre D-120 phase, accelerated assessment): prevention of disease caused by chikungunya (CHIKV) virus

5.1.3. Fruquintinib - (CAP MAA) - EMEA/H/C/005979

Scope (pre D-180 phase): treatment of metastatic colorectal cancer

5.1.4. Insulin icodec - (CAP MAA) - EMEA/H/C/005978

Scope (pre D-180 phase): treatment of diabetes mellitus in adults

¹⁶ Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly.

5.1.5. Iptacopan - (CAP MAA) - EMEA/H/C/005764, PRIME, Orphan

Applicant: Novartis Europharm Limited

Scope (pre D-180 phase): treatment of paroxysmal nocturnal haemoglobinuria

5.1.6. Vibegron - (CAP MAA) - EMEA/H/C/005957

Scope (pre D-180 phase): treatment of micturition frequency and/or urgency incontinence as may occur in adult patients with Over Active Bladder (OAB) syndrome.

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

See also Annex I 15.2.

5.2.1. Afamelanotide - SCENESSE (CAP) - EMEA/H/C/002548/II/0049, Orphan

Applicant: Clinuvel Europe Limited

PRAC Rapporteur: Martin Huber

Scope: Submission of the final report from study CUV-RCR-001 (Scenesse (Afamelanotide 16mg) Retrospective Chart Review) listed as an obligation in the Annex II of the product information. This is a retrospective study comparing long term safety data and outcome endpoints in patients receiving and not receiving Scenesse, or having discontinued Scenesse use. The Annex II and the RMP (version 9.6) 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.

PRAC is evaluating a type II variation procedure for Scenesse, a centrally authorised medicine containing afamelanotide, to update the RMP upon submission of the final report from CUV-RCR-001 study in order to delete it as an obligation from the RMP and Annex II. PRAC is responsible for adopting an outcome based on the assessment report from the PRAC Rapporteur, to be further considered at the level of CHMP, responsible for adopting an opinion on this variation.

Summary of advice

- The RMP for Scenesse (afamelanotide) in the context of the variation procedure under evaluation by PRAC and CHMP could be considered acceptable provided that an update to RMP version 9.6 is submitted.
- PRAC considered that the MAH should provide information what concrete efforts were made to include untreated patients in both PASSs (EEDR and RCR). The MAH should also discuss the further need to enrol untreated (control) patients and whether further measures to improve enrolment of untreated patients from participating sites are indicated. In addition, PRAC considered that since CUV052 category 3 study is not subject of this variation, changes regarding this study should be removed from the RMP and applied for in a separate procedure, and therefore a revised RMP should be submitted accordingly.

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

See also Annex I 15.3.

5.3.1. Sotrovimab - XEVUDY (CAP) - EMEA/H/C/005676/II/0026

Applicant: Glaxosmithkline Trading Services Limited

PRAC Rapporteur: Liana Martirosyan

Scope: To update sections 4.2, 4.8 and 5.2 of the SmPC in order to update information on paediatric population based on final results from study COMET-PACE (215226), a category 3 study in the RMP; this is an open-label, non-comparator, multicentre study to describe the pharmacokinetics (PK), pharmacodynamics (PD; viral load) and safety following a single intravenous or intramuscular dose of sotrovimab in paediatric participants with mild to moderate COVID-19 at high risk of disease progression. The updated RMP version 1.1 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 Xevudy, a centrally authorised product containing sotrovimab, to update the product information based on results from study COMET-PACE (215226). PRAC is responsible for providing advice to CHMP on the necessary updates to the RMP to support this procedure.

Summary of advice

- The RMP version 1.1 for Xevudy (sotrovimab) in the context of the variation under evaluation by CHMP is considered acceptable.
- PRAC considered that use in children ≥ 12 to < 18 years old is considered sufficiently characterised and agreed to delete it as missing information from the RMP relevant sections. In addition, in light of the current knowledge and since the MAH will continue to evaluate sotrovimab effectiveness through non-clinical data and literature reports, PRAC agreed to remove the targeted follow-up questionnaire in place to address treatment failure due to emerging variants from Annex 4 in the RMP.

6. Periodic safety update reports (PSURs)

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

See also Annex I 16.1.

6.1.1. Avanafil - SPEDRA (CAP) - PSUSA/00010066/202306

Applicant: Menarini International Operations Luxembourg S.A.

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

Background

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

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Spedra, a centrally authorised medicine containing avanafil 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 Spedra (avanafil) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the warning on visual problems in order to add central serous chorioretinopathy. Therefore, the current terms of the marketing authorisation(s) should be varied¹⁷.
- In the next PSUR, the MAH should provide cumulative reviews of cases of non-arteritic anterior ischaemic optic neuropathy (NAION), as well as of cases of sudden hearing loss, tinnitus and vertigo, including data from clinical trials, literature and post-marketing setting) and discuss the need for updating the product information, as warranted. Moreover, the MAH should closely monitor cases of seizures, arrhythmia and serious adverse events related to recreational use and off-label use of avanafil, as well as to continue with the close monitoring of chorioretinal disorders.

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.

6.1.2. [Brexucabtagene autoleucl - TECARTUS \(CAP\) - PSUSA/00010903/202307](#)

Applicant: Kite Pharma EU B.V., ATMP

PRAC Rapporteur: Bianca Mulder

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 Tecartus, a centrally authorised medicine containing brexucabtagene autoleucl and issued a recommendation on its marketing authorisation(s).

Summary of recommendation(s) and conclusions

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 review of the data on safety and efficacy, the benefit-risk balance of Tecartus (brexucabtagene autoleucl) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add immune effector cell-associated neurotoxicity syndrome (ICANS) as an undesirable effect with a frequency 'very common'. Moreover, Annex II should be updated to include ICANS in the key elements of the educational materials. Therefore, the current terms of the marketing authorisation(s) should be varied¹⁸.
- In the next PSUR, the MAH should provide a more extensive cumulative review and justifications for including status epilepticus (SE) as an undesirable effect in the product information, including a thorough discussion of the literature review and an extensive causality assessment of the retrieved cases, as well as provide the data from the ZUMA-3 clinical trial which led to the inclusion of this ADR in the product information.
- The MAH should update the RMP to amend the important identified risk 'serious neurological events including cerebral edema' to 'serious neurological events including cerebral edema and ICANS'.

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. Human C1-esterase inhibitor - CINRYZE (CAP) - PSUSA/00010104/202306

Applicant: Takeda Manufacturing Austria AG

PRAC Rapporteur: Gabriele Maurer

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 Cinryze, a centrally authorised medicine containing human C1-esterase inhibitor 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 Cinryze (human C1-esterase inhibitor) 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 review of all new cases related to the risk '*transmission of infection*', including a causality assessment and full case reports/narratives.
- The MAH should submit to EMA, as a post-authorisation measure, a comprehensive presentation of the reported case of 'Creutzfeldt-Jakob disease', including a causality

¹⁸ Update of SmPC section 4.8 and Annex II-D Conditions or restrictions with regard to the safe and effective use of the medicinal product. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion

assessment and a justified evaluation of any potential implication(s) on the benefit-risk balance of Cinryze (human C1-esterase inhibitor).

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

6.1.4. Nirmatrelvir, ritonavir - PAXLOVID (CAP) - PSUSA/00010984/202306

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

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

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Paxlovid, a centrally authorised medicine containing nirmatrelvir/ritonavir 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 Paxlovid (nirmatrelvir/ritonavir) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAH should provide cumulative review of cases of renal disorders, pancreatitis, gastrointestinal bleeding, hepatobiliary disorders and eye disorders, together with respective causality assessments. In addition, the MAH should provide further data on the origin of cases of medication errors leading to incorrect dose administered and propose appropriate measures to limit these errors. The MAH should also provide a review of cases of drug-drug-interaction between nirmatrelvir/ritonavir and immunosuppressants and evaluate the effectiveness of RMMs currently in place. Moreover, the MAH should provide a detailed review with a focus on urticaria as a part of the evaluation of cutaneous reactions and discuss the need for updating the product information, as warranted. The MAH should also provide a cumulative review of cases of dizziness, including a causality assessment and discuss the need to update the product information, as warranted. The MAH should also continue to monitor cases of confusional state.

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. Tedizolid phosphate - SIVEXTRO (CAP) - PSUSA/00010369/202306

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

Background

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

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Sivextro, a centrally authorised medicine containing tedizolid phosphate 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 Sivextro (tedizolid phosphate) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a drug-drug interaction between tedizolid phosphate and serotonergic drugs leading to serotonin syndrome, and to amend the warning on serotonin syndrome. Therefore, the current terms of the marketing authorisation(s) should be varied¹⁹.
- In the next PSUR, the MAH should comment on the publication by *Deng F et al.*²⁰ and discuss on the need for an update of the product information. The MAH should also continue to monitor cases of angioedema.

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

6.1.6. Voretigene neparvovec - LUXTURNA (CAP) - PSUSA/00010742/202307

Applicant: Novartis Europharm Limited, ATMP

PRAC Rapporteur: Gabriele Maurer

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 Luxturna, a centrally authorised medicine containing voretigene neparvovec, 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 Luxturna (voretigene neparvovec) in the approved indication(s) remains unchanged.

¹⁹ Update of SmPC sections 4.4 and 4.5. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion

²⁰ Deng F, Sjöstedt N, Santo M, Neuvonen M, Niemi M, Kidron H. Novel inhibitors of breast cancer resistance protein (BCRP, ABCG2) among marketed drugs. *Eur J Pharm Sci.* 2023 Feb 1;181:106362. doi: 10.1016/j.ejps.2022.106362. Epub 2022 Dec 15. PMID: 36529162

- Nevertheless, the product information should be updated to add chorioretinal atrophy as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied²¹.
- The MAH should submit to EMA, within 6 months, a protocol for a sub-study of the ongoing PASS PERCEIVE (registry-base study assessing long-term safety and effectiveness of voretigene neparvovec in a real world setting), aiming to further characterise the development of new atrophies and the progression of atrophies in the macula region but also in the periphery in patients treated with voretigene neparvovec.
- The MAH should also update the RMP to re-classify the risk of 'vision loss due to progressive chorioretinal atrophy' as an important identified risk, as well as to include in the pharmacovigilance plan of the RMP the sub-study of the ongoing PASS which aims at further characterising this risk.

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. Ibuprofen, pseudoephedrine (NAP) - PSUSA/00001711/202307

Applicant(s): various

PRAC Lead: Nathalie Gault

Scope: Evaluation of a PSUSA procedure

Background

Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID) with anti-pyretic, analgesic, and anti-inflammatory properties, while pseudoephedrine is an alpha agonist acting as a decongestant. In combination, ibuprofen/pseudoephedrine is indicated for the symptomatic relief of nasal/sinus congestion with headache, fever and pain associated with the common cold and flu in adults and adolescents over 12 or 15 years old, subject to certain conditions.

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

Summary of recommendation(s) and conclusions

²¹ Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion

- Based on the review of the data on safety and efficacy, the benefit-risk balance of ibuprofen/pseudoephedrine-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add Kounis syndrome as a warning and as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied²².
- In the next PSUR, the MAH(s) for ibuprofen/pseudoephedrine-containing products should provide a cumulative review of cases of generalised fixed drug eruption, of eosinophilic pneumonia and of severe hypokalaemia and renal tubular acidosis, and discuss the need for updating the product information, if warranted. In addition, the MAH(s) should pursue the close monitoring of "ischaemic events". The MAHs should perform a close monitoring of cases of symmetrical drug-related intertriginous and flexural exanthema with pseudoephedrine and discuss the need for updating the product information, as warranted. The MAH(s) should provide comprehensive and detailed information on the review of all cases of off-label use, as well as a cumulative review on the risk of abuse and misuse with pseudoephedrine from post marketing spontaneous reports, clinical studies, literature, and poisoning centres reports, together with a discussion on the need for an update of the product information, as warranted.

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

This PRAC recommendation is without prejudice to the final conclusions of the referral procedure under Article 31 for pseudoephedrine containing medicinal products (EMA/H/A-31/1526).

6.3.2. Nimesulide²³ (NAP) - PSUSA/00002165/202306

Applicant(s): various

PRAC Lead: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

Background

Nimesulide is a selective cyclooxygenase-2 (COX-2) inhibitor non-steroidal anti-inflammatory drug (NSAID) and it is indicated, as topical formulation, for the symptomatic relief of pain associated with sprains and acute traumatic tendinitis.

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

Summary of recommendation(s) and conclusions

²² Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position

²³ Topical formulation(s) only

- Based on the review of the data on safety and efficacy, the benefit-risk balance of nimesulide-containing medicinal products (as topical formulation) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a contraindication for use during the last trimester of pregnancy, as well as a warning to avoid use during the first and second trimester of pregnancy, unless clearly necessary, and if so the lowest possible dose should be used, and for the shortest treatment duration. Therefore, the current terms of the marketing authorisation(s) should be varied²⁴.

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. Oxycodone hydrochloride, paracetamol (NAP) - PSUSA/00002256/202307

Applicant(s): various

PRAC Lead: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

Background

Oxycodone is an opioid analgesic and paracetamol is a non-opioid analgesic. In combination oxycodone/paracetamol it is indicated in the treatment of moderate to severe degenerative muscle-osteoarticular pain not treated by single administration of non-steroidal anti-inflammatory drugs (NSAIDs)/paracetamol and in the relief of moderate to severe pain in patients with cancer.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of oxycodone/paracetamol-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated in order to further minimise the risk of opioid use disorder (OUD), to include a warning about hepatobiliary disorders sphincter of Oddi dysfunction and to add sphincter of Oddi dysfunction as an undesirable effect with a frequency 'not known'. Moreover, the product information should be updated to add a warning regarding the storage in a safe and secure place. In addition, the product information should be updated to add toxic leukoencephalopathy as a possible symptom of overdose. Therefore, the current terms of the marketing authorisation(s) should be varied²⁵.
- In the next PSUR, the MAH(s) should provide a cumulative review of cases of liver injury, including data from post-marketing setting and literature and discuss the need

²⁴ Update of SmPC sections 4.3 and 4.6. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position

²⁵ Update of SmPC sections 4.2, 4.4., 4.8 and 4.9. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position

for updating the product information, as warranted. The MAH(s) should also discuss in the next PSUR the risk of opioid-induced hyperalgesia (OIH), or an increased sensitivity to pain as a signal present the outcome of this evaluation. In addition, the MAH(s) should discuss the publication by Šarac *et*²⁶ 2022, where a case report concerning craniocervical dystonia induced by oxycodone-escitalopram is described, and discuss the need for risk minimisation measures, if warranted. The MAH(s) should also provide follow-up trend analyses about off-label use in paediatric population as well as of cases of abuse, drug dependence and withdrawal.

The frequency of PSUR submission should be revised from five-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.

6.3.4. Oxytocin²⁷ (NAP) - PSUSA/00010913/202306

Applicant(s): various

PRAC Lead: Karen Pernille Harg

Scope: Evaluation of a PSUSA procedure

Background

Oxytocin, identical to the natural oxytocin hormone released by the posterior lobe of the pituitary, is indicated for the induction of labour for medical reasons, the enhancement of labour in selected cases of uterine inertia, as well as in early stages of pregnancy as adjunctive therapy for management of incomplete, inevitable or missed abortion. Oxytocin is also indicated during caesarean section but after the delivery of the child and for the prevention and treatment of post-partum uterine atony and haemorrhage.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing oxytocin (for systemic use) 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 oxytocin-containing medicinal products (for systemic use) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.

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. Paracetamol, pseudoephedrine (NAP) - PSUSA/00002307/202306

Applicant(s): various

PRAC Lead: Jo Robays

²⁶ Šarac *et al* Craniocervical Dystonia Induced by Oxycodone-Escitalopram: Possible Role of Gene Polymorphism and Drug-Drug Interactions *Psychiatr Danub*. 2022 Fall;34(3):506-508

²⁷ Systemic use only

Scope: Evaluation of a PSUSA procedure

Background

Paracetamol is a non-opioid analgesic and pseudoephedrine is an alpha agonist acting as a decongestant. In combination, paracetamol/pseudoephedrine is indicated for the relief of the symptoms of cold and flu symptoms and nasal/sinus congestion.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing paracetamol/pseudoephedrine 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 paracetamol/pseudoephedrine-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add a warning regarding the risk of abuse. Therefore, the current terms of the marketing authorisation(s) should be varied²⁸.
- In the next PSUR, the MAH(s) should provide a cumulative review of cases of symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) and discuss the need for updating the product information, as warranted. The MAH(s) should include 'high anion gap metabolic acidosis (HAGMA) (excluding cases of interaction paracetamol/flucloxacillin) and hepatotoxicity at therapeutic doses (paracetamol)' as an important potential risk in the list of safety concerns in the PSUR.

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.

This recommendation is without prejudice to the final conclusions of the referral procedure under Article 31 for pseudoephedrine containing medicinal products (EMA/H/A-31/1526).

6.3.6. Pseudoephedrine (NAP); acetylsalicylic acid, pseudoephedrine (NAP) - PSUSA/00010667/202306

Applicant(s): various

PRAC Lead: Maia Uusküla

Scope: Evaluation of a PSUSA procedure

Background

Pseudoephedrine is an alpha agonist acting as a decongestant and acetylsalicylic acid is a non-steroidal anti-inflammatory drug (NSAID). Pseudoephedrine-containing medicinal products are used for the symptomatic relief of nasal or sinus congestion caused by common cold, flu, sinusitis, allergic rhinosinusitis, vasomotor rhinitis and aerotitis. In combination, acetylsalicylic acid/pseudoephedrine is indicated for symptomatic treatment of nasal/sinus congestion with pain and fever associated with the common cold and/or flu-like symptoms.

²⁸ 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

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing pseudoephedrine, acetylsalicylic acid/pseudoephedrine 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 pseudoephedrine, acetylsalicylic acid/pseudoephedrine-containing medicinal products in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAH should provide cumulative reviews of cases of fixed drug eruption, of glaucoma and of baboon syndrome/ symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) induced by pseudoephedrine. In addition, the MAH(s) should provide a cumulative review of cases related to the risk of abuse and misuse with pseudoephedrine, including data from post-marketing setting, clinical trials, literature and poisoning centre reports together with a causality assessment, and discuss the need for updating the product information, if warranted.

The frequency of PSUR submission should be revised from five-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.

This recommendation is without prejudice to the final conclusions of the referral procedure under Article 31 for pseudoephedrine containing medicinal products (EMEA/H/A-31/1526).

6.3.7. Rizatriptan (NAP) - PSUSA/00002655/202306

Applicant(s): various

PRAC Lead: Liana Martirosyan

Scope: Evaluation of a PSUSA procedure

Background

Rizatriptan is a selective 5-HT receptor antagonist and it is indicated in adults for the acute treatment of migraine attacks with or without aura.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing rizatriptan 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 rizatriptan-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the warning regarding the use during pregnancy and breastfeeding. Therefore, the current terms of the marketing authorisation(s) should be varied²⁹.

²⁹ Update of SmPC section 4.6. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position

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

6.3.8. Tramadol (NAP) - PSUSA/00003002/202306

Applicant(s): various

PRAC Lead: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

Background

Tramadol is an opioid analgesic indicated for the treatment of moderate to severe pain.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing tramadol 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 tramadol-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, in view of available data on drug abuse and dependence (opioid use disorder) from the literature and recent assessments of PSUSA procedures for other opioids, the existing warning on drug dependence and potential for abuse should be further strengthened by adding negative consequences of opioid use disorder and risk factors identified in accordance with wordings already implemented for other opioids. The product information should also be updated to reflect the drug-drug interaction between tramadol and gabapentinoids. Therefore, the current terms of the marketing authorisation(s) should be varied³⁰.
- In the next PSUR, the MAH(s) should provide a cumulative review of cases of restless legs syndrome (RLS) and of tinnitus, as well as a review of cases of opioid-induced hyperalgesia (OIH) and allodynia, and discuss the need for updating the product information, if warranted.

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

6.4. Follow-up to PSUR/PSUSA procedures

See also Annex I 16.4.

6.4.1. Abatacept - ORENCIA (CAP) - EMEA/H/C/000701/LEG 071

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Kimmo Jaakkola

³⁰ Update of SmPC sections 4.2, 4.4, 4.5 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position

Scope: From /PSUSA/00000013/202212:

1. updated cumulative review about progressive multifocal leukoencephalopathy (PML), including information from post-marketing cases, clinical trials, real-world data and literature.
2. cumulative review on the association between abatacept and sarcoidosis, including information from post-marketing cases, clinical trials, real world data, and literature

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 further data on progressive multifocal leukoencephalopathy (PML) and sarcoidosis.

Summary of advice/conclusion(s)

- PRAC concurred that the current evidence is insufficient to establish a causal association between abatacept and sarcoidosis, therefore, PRAC agreed that no update of the product information is warranted at this stage and that the MAH should continue to monitor cases of sarcoidosis as part of the routine pharmacovigilance surveillance.
- Based on the available data, PRAC agreed that although a causality association between abatacept and PML cannot be established at present, a contributory role of abatacept in development of PML cannot be excluded either. The MAH should submit to EMA, within 60 days, a variation to amend the product information to update the existing warning on PML in the SmPC and to include a new warning in the PIL.

6.5. Variation procedure(s) resulting from PSUSA evaluation

See also Annex I 16.5.

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

Applicant: Orexigen Therapeutics Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: Submission of an update of sections 4.3, 4.4 and 4.5 of the SmPC to update and streamline the relevant wording on opioids as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00010366/202209) adopted in April 2023. The package leaflet is updated accordingly. The RMP version 12.9 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.

Following the evaluation of the most recently submitted PSUR(s) for the above-mentioned medicine(s), PRAC requested the MAH to submit a variation to update the product information as requested in the conclusions of the PSUSA procedure. PRAC is responsible for

adopting an outcome based on the assessment report from the PRAC Rapporteur, to be further considered at the level of CHMP, responsible for adopting an opinion on this variation.

Summary of recommendation(s)

- Based on the available data, the Rapporteur's assessment and the MAH's responses, PRAC agreed that the risk minimisation measures related to the interaction with opioids should be enhanced. Therefore, PRAC agreed that a DHPC and a patient card are warranted in order to inform HCPs and patients about the risks and precautions associated with possible opioid interactions. Furthermore, PRAC agreed that the product information, the prescriber checklist and the RMP should be amended accordingly.
- The MAH should submit, to EMA, within 30 days, responses to the request for supplementary information (RSI).

6.6. Expedited summary safety reviews³¹

None

7. Post-authorisation safety studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)³²

None

7.2. Protocols of PASS non-imposed in the marketing authorisation(s)³³

See Annex I 17.2.

7.3. Results of PASS imposed in the marketing authorisation(s)³⁴

None

7.4. Results of PASS non-imposed in the marketing authorisation(s)³⁵

See also Annex I 17.4.

7.4.1. Vedolizumab - ENTYVIO (CAP) - EMEA/H/C/002782/II/0081

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Adam Przybylkowski

Scope: Update of section 4.6 of the SmPC in order to update information on pregnancy based on final results from study Vedolizumab-5001 (OTIS Entyvio Pregnancy Exposure Registry); this is a non-interventional study to monitor planned and unplanned pregnancies

³¹ 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

³² In accordance with Article 107n of Directive 2001/83/EC

³³ 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

³⁴ In accordance with Article 107p-q of Directive 2001/83/EC

³⁵ 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

in female patients with ulcerative colitis or Crohn's disease. The package leaflet is updated accordingly. In addition, the MAH took the opportunity to introduce minor changes and corrections to the product information and bring it in line with the latest QRD template

Background

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

The MAH conducted a non-interventional PASS (OTIS Entyvio Pregnancy Exposure Registry) conducted in the United States and Canada to monitor planned and unplanned pregnancies in female patients with ulcerative colitis or Crohn's disease. The Rapporteur assessed the final study results.

Summary of advice

- Based on the available data and the Rapporteur's review, PRAC considered that the ongoing variation to amend the existing information related to the use in pregnancy to reflect the final results of the study Vedolizumab-5001 could be considered acceptable provided that the MAH submits satisfactory responses to a RSI.
- A 30-day assessment timetable will be followed.

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

See Annex I 17.5.

7.6. Others

None

7.7. New Scientific Advice

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

7.8. Ongoing Scientific Advice

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

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

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

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

8.1. Annual reassessments of the marketing authorisation

See Annex I 18.1.

8.2. Conditional renewals of the marketing authorisation

See Annex I 18.2.

8.3. Renewals of the marketing authorisation

See Annex I 18.3.

9. Product related pharmacovigilance inspections

9.1. List of planned pharmacovigilance inspections

None

9.2. Ongoing or concluded pharmacovigilance inspections

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

9.3. Others

None

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

10.1. Safety related variations of the marketing authorisation

None

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

None

10.3. Other requests

None

10.4. Scientific Advice

Information related to this section cannot be released at the present time as it is deemed to

contain commercially confidential information.

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

11.1. Safety related variations of the marketing authorisation

11.1.1. Methotrexate (NAP) - SE/H/1442/01-02/II/27, SE/H/1422/01/II/20

Applicant(s): Orion Corporation

PRAC Lead: Mari Thorn

Scope: PRAC consultation on type II national variations to update the product information of methotrexate-containing products in order to add a warning on photosensitivity based on the MHRA review of methotrexate and photosensitivity reactions, on request of Sweden

Background

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

In the context of the evaluation of a type II variation procedure on the update of the product information of methotrexate-containing products in order to add a warning on photosensitivity based on the MHRA review, Sweden requested PRAC advice on its assessment.

Summary of advice

- Based on the review of the available information, PRAC agreed with the Lead Member State (LMS) conclusions that further data is needed to make a proper assessment of the risk for photosensitivity reactions associated with methotrexate. Therefore, PRAC agreed that the MAH should submit a cumulative review on the risk for photosensitivity reactions associated with methotrexate from post marketing spontaneous reports, clinical studies and published literature, stratified by indication (oncology, dermatology, and other autoimmune-related indications) and dose, including a discussion on the mechanism and type of photosensitivity with methotrexate. Based on this review, the MAH should propose risk minimisation measures, if warranted, considering that methotrexate may be used concomitantly with UV treatment in certain indications such as in some cases of psoriasis.

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 Barbara Kovacic Bytyqi as the new alternate for Croatia, replacing Petar Mas, who took over the role of the member for Croatia (replacing Nikica Mirosevic Svrce whose mandate ended on 25 January 2024). The Chair also thanked Valentina di Giovanni for her contribution as the alternate for Italy.

12.1.2. Vote by proxy

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

12.1.3. PRAC working group - Best practice guide on using PRAC plenary time efficiently and effectively – update on the implementation of quantitative goals – Q4 2023

In line with the adopted PRAC best practice guidance (BPG) on Committee efficiency (see PRAC minutes May 2016 and PRAC minutes June 2018) and the adopted implementation plan for the BPG including goals to measure compliance with the recommendations (see PRAC minutes June 2016 and PRAC minutes June 2018), PRAC was informed on the quantitative measures collected for Q4 2023 of PRAC meetings during the organisational, regulatory and methodological matters (ORGAM) meeting on 22 February 2024. For previous update, see [PRAC minutes December 2023](#).

12.2. Coordination with EMA Scientific Committees or CMDh-v

None

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

None

12.4. Cooperation within the EU regulatory network

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

The EMA Secretariat provided PRAC with an update on the response of immune system in the COVID-19 vaccines, on the COVID-19 and Monkey pox vaccine effectiveness, and on the EMA-funded observational study concerning the efforts in data collection vaccine monitoring platform which is included as specific obligation in the Monkeypox vaccine, as well as on the risk mitigation strategy concerning Zika virus. PRAC was also informed on the [ETF statement on use of recently updated COVID-19 vaccines](#) and on the revision of the [guidance on use of medicinal product for the treatment and prophylaxis of biological agents that might be used as weapons of bioterrorism](#) along with an upcoming meeting with a panel of European experts where members can nominate experts .

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. EU Pharmacovigilance system - quarterly workload measures and performance indicators – Q4 2023 and predictions

At the organisational, regulatory and methodological matters (ORGAM) meeting on 22 February 2024, the EMA Secretariat presented to PRAC an overview of the quarterly figures on the EMA pharmacovigilance system-related workload and performance indicators. For previous update, see [PRAC minutes December 2023](#).

12.8.2. PRAC workload statistics – Q4 2023

At the organisational, regulatory and methodological matters (ORGAM) meeting on 22 February 2023, PRAC was informed on the quarterly and cumulative figures to estimate the evolution of the PRAC workload for Q4 2023, by reflecting on the number of procedures and agenda items covered at each PRAC plenary meeting. For previous update, see [PRAC minutes December 2023](#).

12.9. Pharmacovigilance audits and inspections

12.9.1. Pharmacovigilance systems and their quality systems

None

12.9.2. Pharmacovigilance inspections

None

12.9.3. Pharmacovigilance audits

None

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

12.10.1. Periodic safety update reports

None

12.10.2. Granularity and Periodicity Advisory Group (GPAG)

PRAC lead: Jana Lukacisinova

The EMA Secretariat provided to PRAC an update on the membership of GPAG and a brief update on the first meeting under the new PRAC lead Jana Lukacisinova. Petar Mas became also a member of the group.

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

Post-meeting note: following the PRAC meeting of February 2024, the updated EURD list was adopted by CHMP and CMDh at their February 2024 meetings and published on the EMA website, see: [Home> Human Regulatory>Post-authorisation>Pharmacovigilance>Periodic safety update reports>> List of Union reference dates and frequency of submission of periodic safety update reports \(PSURs\)](#)

12.11. Signal management

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

PRAC lead: Martin Huber

The EMA Secretariat presented an update on a SMART Methods stream meeting held on 7 December 2023 summarising the provided update on the work for clinical quality of various primary data collection for pregnancy pharmacovigilance, on the masking effect survey and on the Health Data Lab pilot.

12.11.2. Signals and safety analytics project – update on activities

The EMA Secretariat presented to PRAC the signals and safety analytics (SSA) project aiming to replace the technology behind EVDAS, eRMR, and adrreports.eu website, along with improving the system performance, enhancing the user interface, and implementing a more user-oriented approach to interrogating adverse drug reaction (ADR) data. The implementation will follow a phased approach with the first phase aiming to deliver the core functionalities for signal detection for EMA and NCAs. A call was launched via HMA for the roles of Network Product Owner (PO) and Subject Matter Experts (SMEs) who will be the designated representatives and participate in the implementation on behalf of the Network. The network can still express their interest for the PO role by 16 February 2024.

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. Covid-19 infection and medicines in pregnancy (CONSIGN) - final study results

PRAC lead(s): Sabine Straus, Ulla Wändel Liminga

The EMA Secretariat along with the invited speakers presented to PRAC the results of the EMA funded study on the use and impact of COVID-19 treatment in pregnant women. For further background information, see [PRAC minutes September 2020](#), [PRAC minutes December 2020](#), [PRAC minutes February 2021](#) and [PRAC minutes June 2022](#). PRAC noted the information.

12.21.2. Direct healthcare professional communications (DHPCs) process review and publication on EMA website

At the organisational, regulatory and methodological matters (ORGAM) meeting on 22 February 2023, the EMA Secretariat presented to PRAC the updated DHPC review process to include that medical writers' review is done in parallel with the review performed by PRAC Rapporteurs and Communication experts. The process has also been updated to reflect the publication of DHPCs on the EMA website. PRAC noted the information.

12.21.3. Drafting group on multiple sclerosis and use of disease modifying drugs (DMDs) in women of childbearing potential – update

PRAC lead: Nathalie Gault

Following the presentation of the drafting group activities the previous month (see [PRAC minutes January 2024](#)), the EMA Secretariat provided to PRAC an update on the work of the group related to a DRAFT PRAC Assessor's Guide on PASS and PRIM in multiple sclerosis in order to start the PRAC consultation. PRAC noted the information and was requested to provide comments by 5 April 2024 in writing.

Post meeting note: Based on feedback received from the PRAC Chair and from the PRAC topic lead on the PRAC workplan activities related to pregnancy, and considering the multiple currently ongoing PRAC work related to pregnancy guidance (e.g. GVP P.III), the consultation phase for the assessors' guidance on PASS and PRIM was paused.

12.21.4. [Drafting group on standard product information wording - Haemophagocytic Lymphohistiocytosis \(HLH\) -update](#)

PRAC lead: Bianca Mulder

Following the discussions during the recent plenary meetings, PRAC proposed to work on a standard wording for haemophagocytic lymphohistiocytosis (HLH) as an adverse reaction to be used for future updates of the product information for various medicinal products, if warranted. At the organisational, regulatory and methodological matters (ORGAM) meeting on 22 February 2023, the EMA Secretariat presented to PRAC the results of this drafting group composed by EMA and PRAC delegates/NCA representatives. With the use of artificial intelligence (AI) tools, the group concluded the exercise and proposed a final wording for PRAC consideration, while presented also the challenges this exercise encompasses. PRAC noted the information and members were requested to provide any further comments on the wording proposal in writing along with any other proposals for future similar exercises.

12.21.5. [EMA-HMA Lessons Learned from COVID-19 Pandemic](#)

At the organisational, regulatory and methodological matters (ORGAM) meeting on 22 February 2023, the EMA Secretariat presented to PRAC the [joint EMA-HMA report on the response to the public health emergency](#), and covered the activities during this phase of the pandemic, i.e., between 30 January 2020 and 5 May 2023. The ultimate goal of the lessons learned was to draw from the experiences of the emergency phase of the COVID-19 pandemic to strengthen the European Medicines Regulatory Network's (EMRN) crisis preparedness and its ability to respond rapidly if the EU were confronted with another pandemic or health crisis of this magnitude, as well as to improve other future activities. PRAC noted the information.

12.21.6. [International Conference on Harmonisation \(ICH\) E2D\(R1\) - Post-approval safety data management: definitions and standards for expedited reporting - update](#)

PRAC Lead(s): Sabine Straus

At the organisational, regulatory and methodological matters (ORGAM) meeting on 22 February 2023, PRAC was informed on ICH E2D(R1) guideline which is currently going through Step 2 endorsement by ICH Management Committed and is expected to be released soon for public consultation. For background information see [PRAC Minutes July 2023](#). Since July, editorial updates and minor changes requested by US FDA have been implemented and therefore PRAC was provided with a summary of changes introduced through the revision of the guideline. PRAC was invited to send any comments in the frame

of the public consultation by 24 May 2024.

Post meeting note: the draft [ICH E2D\(R1\) Guideline was released for EU public consultation until 22 June 2024](#)

12.21.7. Pharmacovigilance business team - activities and work plan

At the organisational, regulatory and methodological matters (ORGAM) meeting on 22 February 2023, the EMA Secretariat presented to PRAC an overview of the activities done by the Pharmacovigilance business team (PBT) throughout 2023 based on the agreed workplan. For background information, see [PRAC minutes March 2022](#). The EMA Secretariat also presented to PRAC the PBT workplan for 2024 and PRAC members were invited to provide comments by 15 March 2024.

Post meeting note: The workplan was endorsed on 15 of March 2024 with no further comments.

12.21.8. PRAC Assessors trainings - update

PRAC Lead(s): Martin Huber, Sabine Straus

The EMA Secretariat provided the proposed plan for the 2024 PRAC Assessors training with several short webinar sessions scheduled around the year. PRAC welcomed the proposal and noted the information.

12.21.9. Rules for granting companies extended clock-stops – proposal for review

PRAC lead: Ulla Wändel Liminga

At the organisational, regulatory and methodological matters (ORGAM) meeting on 22 February 2023, the EMA Secretariat presented to PRAC the report on the outcomes and proposals to CHMP concerning the rules for granting companies extended clock stops. PRAC noted the information and was invited to provide any comments in writing by 29 February 2024.

Post meeting note: The updated Guidance document for pre-submission meetings was adopted at CHMP of March 2024.

13. Any other business

Next meeting on: 04-07 March 2024

14. Annex I – Signals assessment and prioritisation³⁶

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 timetables³⁷.

14.1. New signals detected from EU spontaneous reporting systems

14.1.1. Methotrexate – NORDIMET (CAP), JYLAMVO (CAP), NAP

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

PRAC Rapporteur: Martin Huber

Scope: Signal of hyperhomocysteinaemia

EPITT 20031 – New signal

Lead Member State(s): DE

14.1.2. Valaciclovir (NAP)

Applicant: various

PRAC Rapporteur: Jana Lukačičinová

Scope: Signal of acute hepatitis

EPITT 20047 – New signal

Lead Member State(s): CZ

14.2. New signals detected from other sources

14.2.1. Medroxyprogesterone acetate (NAP)

Applicant: various

PRAC Rapporteur: Bianca Mulder

Scope: Signal of meningioma

EPITT 20030 – New signal

Lead Member State(s): NL

³⁶ Each signal refers to a substance or therapeutic class. The route of marketing authorisation is indicated in brackets (CAP for Centrally Authorised Products; NAP for Nationally Authorised Products including products authorised via Mutual Recognition Procedures and Decentralised Procedure). Product names are listed for reference Centrally Authorised Products (CAP) only. PRAC recommendations will specify the products concerned in case of any regulatory action required

³⁷ Either MAH(s)'s submission within 60 days followed by a 60 day-timetable assessment or MAH's submission cumulative review within an ongoing or upcoming PSUR/PSUSA procedure (if the DLP is within 90 days), and no disagreement has been raised before the meeting

15. Annex I – Risk management plans

15.1. Medicines in the pre-authorisation phase

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

15.1.1. Eribulin - (CAP MAA) - EMEA/H/C/006191

Scope (pre D-180 phase): treatment of breast cancer and liposarcoma

15.1.2. Omalizumab - (CAP MAA) - EMEA/H/C/005958

Scope (pre D-180 phase): treatment of asthma

15.1.3. Ustekinumab - (CAP MAA) - EMEA/H/C/006415

Scope (pre D-180 phase): treatment of moderate to severe plaque psoriasis in adults, children and adolescents, active psoriatic arthritis in adults, treatment of Crohn's Disease

15.1.4. Ustekinumab - (CAP MAA) - EMEA/H/C/006132

Scope (pre D-180 phase): treatment of moderate to severe plaque psoriasis in adults, children and adolescents, active psoriatic arthritis in adults, treatment of Crohn's Disease and ulcerative colitis

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

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

15.2.1. Esketamine - SPRAVATO (CAP) - EMEA/H/C/004535/II/0021

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Kirsti Villikka

Scope: Submission of an updated RMP version 5.2 in order to remove "use during pregnancy" as missing information from the list of safety concerns, with the consequential removal of the associated category 3 additional pharmacovigilance activity, the National Pregnancy Registry for Antidepressants ("Massachusetts General Hospital (MGH) pregnancy registry)

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

Applicant: Corza Medical GmbH

PRAC Rapporteur: Gabriele Maurer

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

15.2.3. [Infliximab - ZESLY \(CAP\) - EMEA/H/C/004647/II/0033](#)

Applicant: Sandoz GmbH

PRAC Rapporteur: Mari Thorn

Scope: Submission of an updated RMP version 4.0 in order to remove the UKIBD (UK) registry from the additional pharmacovigilance activities

15.2.4. [Lasmiditan - RAYVOW \(CAP\) - EMEA/H/C/005332/II/0005](#)

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Anna Mareková

Scope: Submission of an updated RMP version 1.1 in order to include a descriptive interim analysis in the study design of study H8H-MC-B006, listed as a category 3 study in the RMP. This is a non-interventional study titled 'Lasmiditan Use and Motor Vehicle Accidents in Real-World Settings in the US'

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. [Abrocitinib - CIBINQO \(CAP\) - EMEA/H/C/005452/II/0010](#)

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Petar Mas

Scope: Extension of indication to include treatment of adolescents 12 to < 18 years of age with moderate to severe atopic dermatitis for CIBINQO based on final results from non-clinical study 00655292 [21GR211] and interim results from clinical study B7451015; this is a Phase III multi-centre, long-term extension study investigating the efficacy and safety of abrocitinib, with or without topical medications, administered to subjects aged 12 years and older with moderate to severe atopic dermatitis. As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The package leaflet is updated in accordance. Version 4.1 of the RMP has also been submitted

15.3.3. [Alpelisib - PIQRAY \(CAP\) - EMEA/H/C/004804/II/0022/G](#)

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Bianca Mulder

Scope: Grouped application comprising two type II variations (C.I.4) as follows:

- Update of sections 4.2, 4.4, 4.8 of the SmPC in order to update information on prophylactic use of metformin for hyperglycaemia based on the results from study CBYL719CES01T (METALLICA). METALLICA is a Phase II study aimed to evaluate the effect of prophylactic use of metformin for hyperglycaemia in HR-positive, HER2-negative, PIK3CA-mutated advanced breast cancer patients treated with alpelisib plus endocrine therapy.

- Update of section 4.8 of the SmPC in order to add "uveitis" to the list of adverse drug reactions (ADRs) with frequency "Not known" based on a cumulative review of the MAH safety database and literature.

The package leaflet and Annex II are updated accordingly. The RMP version 7.0 has also been submitted

15.3.4. [Atezolizumab - TECENTRIQ \(CAP\) - EMEA/H/C/004143/II/0083/G](#)

Applicant: Roche Registration GmbH

PRAC Rapporteur: Carla Torre

Scope: A grouped application comprising of 2 Type II variations, as follows:

C.I.4: Update of section 5.1 of the SmPC in order to update efficacy information based on final results from study IMvigor210 (GO29293) listed as a PAES in the Annex II; this is a Phase II, multicentre, single-arm study of atezolizumab in patients with locally advanced or metastatic urothelial bladder cancer. The Annex II is updated accordingly. In addition, the MAH took the opportunity to introduce minor editorial changes to the product information and to bring it in line with the latest QRD template.

C.I.13: Submission of the final report from study SAUL (MO29983) listed as a category 3 study in the RMP. This is an open-label, single arm, multicentre, safety study of atezolizumab in locally advanced or metastatic urothelial or non-urothelial carcinoma of the urinary tract. The RMP version 30.0 has also been submitted

15.3.5. [Bedaquiline - SIRTURO \(CAP\) - EMEA/H/C/002614/II/0056, Orphan](#)

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension of indications by removal of the restriction for use of SIRTURO (bedaquiline [BDQ]), based on final results from study STREAM Stage 2; this is an multicentre, open-label, parallel-group, randomised, active-controlled study in participants aged 15 years or older with RR/MDR-TB to evaluate an investigational BDQ-containing, all-oral, 40-week regimen of anti-TB drugs (Regimen C) compared to an injectable-containing 40-week control regimen (Regimen B). As a consequence of the data emerging from the submitted study, sections 2, 4.1, 4.2, 4.4, 4.5, 4.8, 4.9, 5.1, 5.2 and 5.3 of the SmPC are updated. In addition, section E of Annex II has also been updated. The Labelling and package leaflet are updated in accordance. Version 10.1 of the RMP has also been submitted. Furthermore, the product information is brought in line with the latest QRD template version 10.3. As part of the application, the MAH is requesting the switch from a conditional MA to standard MA

15.3.6. Bempedoic acid - NILEMDO (CAP) - EMEA/H/C/004958/II/0031

Applicant: Daiichi Sankyo Europe GmbH

PRAC Rapporteur: Kimmo Jaakkola

Scope: Extension of indication to include treatment of adults with established or at high risk for atherosclerotic cardiovascular disease to reduce cardiovascular risk, based on results from study 1002-043 (CLEAR [Cholesterol Lowering via Bempedoic Acid, an ATP citrate lyase (ACL) Inhibiting Regimen]). CLEAR outcomes study is a phase 3 multi-centre randomised, double-blind, placebo-controlled study to evaluate whether long-term treatment with bempedoic acid reduces the risk of major adverse cardiovascular events (MACE) in patients with, or at high risk for, cardiovascular disease who are statin intolerant. As a consequence, sections 4.1, 4.8 and 5.1 of the SmPC are updated. The package leaflet is updated accordingly. Version 4.0 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce minor formatting changes to the product information. As part of the application, the MAH is requesting a 1-year extension of the market protection

15.3.7. Bempedoic acid, ezetimibe - NUSTENDI (CAP) - EMEA/H/C/004959/II/0035

Applicant: Daiichi Sankyo Europe GmbH

PRAC Rapporteur: Kimmo Jaakkola

Scope: Extension of indication to include treatment of adults with established or at high risk for atherosclerotic cardiovascular disease to reduce cardiovascular risk for NUSTENDI, based on results from Study 1002-043, known as the CLEAR [Cholesterol Lowering via Bempedoic Acid, an ATP citrate lyase (ACL) Inhibiting Regimen] outcomes trial, a phase 3, randomised, double-blind, placebo-controlled study to assess the effects of bempedoic acid (ETC-1002) on the occurrence of major cardiovascular events (MACE) in patients with, or at high risk for, cardiovascular disease who are statin intolerant. As a consequence, sections 4.1, 4.8 and 5.1 of the SmPC are updated. The package leaflet is updated in accordance. Version 4.0 of the RMP has also been submitted. As part of the application the MAH is requesting a 1-year extension of the market protection

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

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Bianca Mulder

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

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

Applicant: Gilead Sciences Ireland Unlimited Company

PRAC Rapporteur: Adam Przybylkowski

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

15.3.10. Cariprazine - REAGILA (CAP) - EMEA/H/C/002770/II/0034

Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Update of sections 4.3 and 4.5 of the SmPC in order to update an existing contraindication and update drug-drug interaction information with CYP3A4 inhibitors, based on final results from study RGH-188-301 (CYPRESS) listed as a category 3 study in the RMP; this is an open-label, single-arm, fixed-sequence study to investigate the effect of erythromycin, a moderate CYP3A4 inhibitor on the pharmacokinetics of cariprazine in male patients with schizophrenia. The package leaflet is updated accordingly. The RMP version 4.0 has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the product information

15.3.11. Ciltacabtagene autoleucel - CARVYKTI (CAP) - EMEA/H/C/005095/II/0021, Orphan

Applicant: Janssen-Cilag International NV, ATMP

PRAC Rapporteur: Jo Robays

Scope: Extension of indication to include treatment of adult patients with relapsed and refractory multiple myeloma, who have received at least 1 prior therapy, including an IMiD and a product information, have demonstrated disease progression on or after the last therapy and are refractory to lenalidomide for CARVYKTI, based on interim results from

study MMY3002 listed as a specific obligation (SOB/006) in the Annex II. This is an ongoing, Phase 3, randomised, open-label, multicentre study to determine whether treatment with cilta-cel provides an efficacy benefit compared to standard therapy in participants with relapsed and lenalidomide-refractory multiple myeloma. As a consequence, sections 4.1, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet is updated in accordance. Version 4.1 of the RMP has also been submitted. In addition, the MAH took the opportunity to update Annex II of the product information. As part of the application the MAH is requesting a 1-year extension of the market protection

15.3.12. [Coronavirus \(COVID-19\) vaccine \(ChAdOx1-S \[recombinant\]\) - VAXZEVRIA \(CAP\) - EMEA/H/C/005675/II/0096](#)

Applicant: AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

Scope: Update of sections 4.8 and 5.1 of the SmPC based on final results from study D7220C00001; this is a phase 2/3 partially double-blinded, randomised, multinational, active-controlled study in both previously vaccinated and unvaccinated adults to determine the safety and immunogenicity of AZD2816, a vaccine for the prevention of COVID-19 caused by variant strains of SARS-CoV-2. The RMP version 8 s1 has also been submitted

15.3.13. [Coronavirus \(COVID-19\) vaccine \(ChAdOx1-S \[recombinant\]\) - VAXZEVRIA \(CAP\) - EMEA/H/C/005675/II/0097](#)

Applicant: AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

Scope: Submission of the final report from study D8110C00001 listed as a category 3 study in the RMP (SOB/020). This is a phase III, randomised, placebo-controlled study of AZD1222 (Vaxzevria) conducted in the US, Peru and Chile. The purpose of the final CSR addendum is to provide long-term safety data through to study completion and include the second year of follow-up post-first dose and final day 730 visit. The RMP version 8 s2 has also been submitted

15.3.14. [Entrectinib - ROZLYTREK \(CAP\) - EMEA/H/C/004936/X/0017/G](#)

Applicant: Roche Registration GmbH

PRAC Rapporteur: Bianca Mulder

Scope: Grouped application consisting of: 1) Extension application to: a) Introduce a new pharmaceutical form (coated granules) associated with a new strength (50 mg); b) Introduce a new route of administration (gastroenteral use) for the already authorised 100 mg and 200 mg hard capsules presentations based on final results from studies CO40778 (STARTRK-NG), GO40782 (STARTRK-2) and BO41932 (TAPISTRY). Study CO40778 is a Phase I/II open-label, dose-escalation and expansion study of entrectinib in pediatrics with locally advanced or metastatic solid or primary CNS tumors and/or who have no satisfactory treatment options; Study GO40782 is an open-label, multicenter, global Phase II basket study of entrectinib for the treatment of patients with solid tumors that harbor an NTRK1/2/3, ROS1, or ALK gene rearrangement (fusion), and Study BO41932 is a Phase II, global, multicenter, open-label, multi-cohort study designed to evaluate the safety and

efficacy of targeted therapies or immunotherapy as single agents or in rational, specified combinations in participants with unresectable, locally advanced or metastatic solid tumors determined to harbor specific oncogenic genomic alterations or who are tumor mutational burden (TMB)-high as identified by a validated next-generation sequencing (NGS) assay; 2) grouped with the following type II variations:

a) to extend the currently approved indication in solid tumours with NTRK gene fusion to patients from birth to 12 years of age (both for the coated granules and already approved hard capsules presentations);

b) to add a new paediatric indication from birth to 18 years of age for patients with solid tumours with a ROS1 gene fusion (both for the coated granules and already approved hard capsules presentations).

As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2, 6.3, 6.4 and 6.6 of the SmPC are updated accordingly. The package leaflet and Labelling are updated in accordance.

c) to add wording regarding the option of suspension in water of the content of the capsules to be used orally or via the e.g. gastric or nasogastric tube (in sections 4.2 and 5.2 of the SmPC).

The RMP (version 5) is updated in accordance. The MAH took the opportunity to introduce minor editorial changes to the product information and to update Annex II of the SmPC

15.3.15. Epcoritamab - TEPKINLY (CAP) - EMEA/H/C/005985/II/0001, Orphan

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Monica Martinez Redondo

Scope: Extension of indication to include treatment of adult patients with relapsed or refractory (R/R) follicular lymphoma (FL) after two or more lines of systemic therapy for TEPKINLY, based on results from the indolent Non-Hodgkins Lymphoma (iNHL) expansion cohort of Study GCT3013-01, the First In Human (FIH) Phase 1/2 study in R/R B-NHL, with key supportive data from the Phase 1b/2 Study GCT3013-04 in Japanese subjects. Study GCT3013-01 is an ongoing global, single-arm, phase 1/2 study designed to evaluate epcoritamab as monotherapy in R/R B-NHL. As a consequence, sections 1, 3, 4.1, 4.2, 4.4, 4.8, 5.1, 5.2, 6.3, 6.4, 6.5 and 6.6 of the SmPC are updated. The package leaflet and Labelling are updated in accordance. Version 2.0 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce minor changes to the product information

15.3.16. Faricimab - VABYSMO (CAP) - EMEA/H/C/005642/II/0009

Applicant: Roche Registration GmbH

PRAC Rapporteur: Carla Torre

Scope: Update of section 4.8 of the SmPC in order to add 'Retinal Vasculitis' and 'Retinal Occlusive Vasculitis' to the list of adverse drug reactions (ADRs) with frequency not known, based on a drug safety report and post-marketing data; the package leaflet is updated accordingly. The RMP version 4.0 has also been submitted. In addition, the MAH took the opportunity to add study CR45271 as a category 3 study in the RMP, to introduce minor changes and corrections to the product information and to update the list of local

representatives in the package leaflet

15.3.17. Fedratinib - INREBIC (CAP) - EMEA/H/C/005026/II/0019, Orphan

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Sonja Hrabcik

Scope: Update of sections 4.2 and 5.2 of the SmPC in order to update posology recommendations in patients with severe hepatic impairment and to update pharmacokinetic information based on final results from study FEDR-CP-001 listed as a category 3 study in the RMP; this is a phase 1, open-label, single-dose study to assess the pharmacokinetics, safety, and tolerability of fedratinib in subjects with moderate and severe hepatic impairment compared with healthy subjects. The RMP version 2.0 has also been submitted

15.3.18. Hydroxycarbamide - XROMI (CAP) - EMEA/H/C/004837/II/0019

Applicant: Nova Laboratories Ireland Limited

PRAC Rapporteur: Jo Robays

Scope: Extension of indication to include the prevention of vaso-occlusive complications of sickle cell disease in children from 6 months to 2 years of age for Xromi, based on final results from the paediatric study INV543, listed as a category 3 study in the RMP; this is a single-arm, open-label, multi-centre study in children with sickle cell anaemia over 6 months of age. 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 4.1 of the RMP has also been submitted

15.3.19. Isatuximab - SARCLISA (CAP) - EMEA/H/C/004977/II/0026

Applicant: Sanofi Winthrop Industrie

PRAC Rapporteur: Monica Martinez Redondo

Scope: Update of sections 4.2, 4.4 and 5.2 of the SmPC based on final results from study TED16414, listed as a category 3 study in the RMP; this is a phase 1b/2 open label, non-randomised, multi center study to evaluate the safety, pharmacokinetics, and preliminary efficacy of isatuximab (SAR650984) in patients awaiting kidney transplantation. The package leaflet is updated accordingly. The RMP version 1.4 has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the product information

15.3.20. Ivacaftor, tezacaftor, elexacaftor - KAFTRIO (CAP) - EMEA/H/C/005269/WS2551/0043; Ivacaftor - KALYDECO (CAP) - EMEA/H/C/002494/WS2551/0121

Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Martin Huber

Scope: Extension of the indication for Kaftrio (ivacaftor/tezacaftor/elexacaftor) and Kalydeco (ivacaftor) in a combination regimen to include the treatment of patients with

cystic fibrosis (CF) aged 2 years and older who do not carry any F508del mutations and have at least one ivacaftor/tezacaftor/elexacaftor-responsive mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene based on study VX21-445-124, study VX21-445-125 and study VX22-CFD-016. As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the Kaftrio SmPC are updated; sections 4.1 and 5.1 of the Kalydeco SmPC are updated. The package leaflet is updated in accordance. In addition, the MAH took this opportunity to introduce editorial changes to the product information

15.3.21. Lenvatinib - KISPLYX (CAP) - EMEA/H/C/004224/WS2631/0059; LENVIMA (CAP) - EMEA/H/C/003727/WS2631/0054

Applicant: Eisai GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of sections 4.2, 4.8, 5.1 and 5.2 of the SmPC for Kisplyx and sections 4.8 and 5.1 of the SmPC for Lenvima, in order to reflect the results of two completed paediatric clinical studies E7080-G000-216 and E7080-G000-231. Study 231 is a Phase 2, open-label, multicenter basket study to evaluate the antitumor activity and safety of Lenvatinib in children, adolescents, and young adults with relapsed or refractory solid malignancies. Study 216 is a Phase 1/2, multicentre, open-label, single arm study of lenvatinib in combination with everolimus in paediatric subjects (and young adults aged ≤ 21 years) with relapsed or refractory malignant solid tumors. The package leaflet for Kisplyx is updated accordingly. The RMP version 15.3 has also been submitted

15.3.22. 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

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

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Extension application to introduce a new pharmaceutical form associated with new strengths (1 and 2.5 mg dispersible tablet) grouped with an extension of indication (C.I.6.a) to include, as monotherapy or in combination, the long-term treatment of pulmonary arterial hypertension (PAH) in paediatric patients aged 1 month to less than 18 years of age of WHO Functional Class (FC) I to III for OPSUMIT, based on interim results from AC-055-

312 study (TOMORROW). This is a multicentre, open-label, randomised study with single-arm extension period to assess the pharmacokinetics, safety, and efficacy of macitentan versus standard of care in children with pulmonary arterial hypertension. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 4.9, 5.1 and 5.2 of the SmPC for film-coated tablets are updated. The package leaflet and Labelling are updated in accordance. Version 14.1 of the RMP has also been submitted.

15.3.24. Mirabegron - BETMIGA (CAP) - EMEA/H/C/002388/X/0039/G

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Grouped variations consisting of: 1) extension application to introduce a new pharmaceutical form associated with new strength (8 mg/mL prolonged-release granules for oral suspension); 2) extension of indication to include treatment of neurogenic detrusor overactivity (NDO) in paediatric patients aged 3 to less than 18 years. The RMP (version 9.0) is updated accordingly

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

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Petar Mas

Scope: Extension application to add a new strength of 25 mg hard capsules, grouped with an extension of indication (C.I.6.a) to include treatment of fibrosing interstitial lung diseases (ILDs) in children and adolescents from 6 to 17 years of age for Ofev, following the assessment of procedure X/0052/G, based on final results from study 1199-0337 (a double blind, randomised, placebo-controlled trial to evaluate the dose-exposure and safety of nintedanib per os on top of standard of care for 24 weeks, followed by open label treatment with nintedanib of variable duration, in children and adolescents (6 to 17 year-old) with clinically significant fibrosing ILD), which is supplemented by the currently ongoing prospective phase III extension trial 1199-0378 (an open-label trial of the long-term safety and tolerability of nintedanib per os, on top of standard of care, over at least 2 years, in children and adolescents with clinically significant fibrosing ILD). The main objective of the study 1199-0337 was to evaluate dose-exposure and safety of nintedanib in children and adolescents with fibrosing ILD. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and Labelling are updated in accordance. Version 12.0 of the RMP has also been submitted

15.3.26. Nirsevimab - BEYFORTUS (CAP) - EMEA/H/C/005304/II/0018/G

Applicant: Sanofi Winthrop Industrie

PRAC Rapporteur: Kimmo Jaakkola

Scope: Grouped application comprising two type II variations as follows:
C.I.13: Submission of the final report from study D5290C00004 (MELODY) listed as a category 3 study in the RMP. This is a phase III, randomised, double-blind, placebo-controlled study to evaluate the safety and efficacy of MEDI8897, a monoclonal antibody with an extended half-life against respiratory syncytial virus, in healthy late preterm and term infants.

C.I.13: Submission of the final report from study D5290C00005 (MEDLEY) listed as a category 3 study in the RMP. This is a phase II/III study, randomised, double-blind, placebo-controlled study to evaluate the safety of Beyfortus (nirsevimab) in high-risk children. The RMP version 2.3 has also been submitted

15.3.27. 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

15.3.28. Peginterferon alfa-2a - PEGASYS (CAP) - EMEA/H/C/000395/II/0119/G

Applicant: Pharmaand GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Grouped application consisting of extension of indication to include treatment of polycythaemia vera (PV) and essential thrombocytopenia (ET) for PEGASYS, based on published data of clinical studies conducted in support of the efficacy and safety of Pegasys for the treatment of ET and PV. As a consequence, sections 4.1, 4.2, 4.8 and 5.2 of the SmPC are updated. The package leaflet is updated in accordance. Version 10.1 of the RMP has also been submitted. Furthermore, the product information is brought in line with the latest QRD template version 10.3

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

Applicant: Accord Healthcare S.L.U.

PRAC Rapporteur: Martin Huber

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

15.3.30. Tisagenlecleucel - KYMRIA (CAP) - EMEA/H/C/004090/II/0075, Orphan

Applicant: Novartis Europharm Limited, ATMP

PRAC Rapporteur: Gabriele Maurer

Scope: Update of sections 5.1 and 5.2 of the SmPC in order to update efficacy and pharmacokinetic information based on final results from study CCTL019C2201 PAES in the Annex II (ANX008); this is a phase II, single arm, multicentre trial to determine the efficacy and safety of CTL019 in adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL). The RMP version 6 has also been submitted. In addition, the MAH took the opportunity to update Annex II.D of the product information

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. Aclidinium bromide - BRETARIS GENUAIR (CAP); EKLIRA GENUAIR (CAP) - PSUSA/00009005/202307

Applicant: Covis Pharma Europe B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.2. Ambrisentan - VOLIBRIS (CAP) - PSUSA/00000129/202306

Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

16.1.3. Asfotase alfa - STRENSIQ (CAP) - PSUSA/00010421/202307

Applicant: Alexion Europe SAS

PRAC Rapporteur: Eamon O'Murchu

Scope: Evaluation of a PSUSA procedure

16.1.4. Avapritinib - AYVAKYT (CAP) - PSUSA/00010878/202307

Applicant: Blueprint Medicines (Netherlands) B.V.

PRAC Rapporteur: Bianca Mulder

Scope: Evaluation of a PSUSA procedure

16.1.5. Beclometasone, formoterol, glycopyrronium bromide - RIARIFY (CAP); TRIMBOW (CAP); TRYDONIS (CAP) - PSUSA/00010617/202307

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.1.6. Birch bark extract³⁸ - FILSUEZ (CAP) - PSUSA/00010446/202307

Applicant: Amryt Pharmaceuticals DAC

PRAC Rapporteur: Zane Neikena

Scope: Evaluation of a PSUSA procedure

16.1.7. Budesonide³⁹ - JORVEZA (CAP) - PSUSA/00010664/202307

Applicant: Dr. Falk Pharma GmbH

PRAC Rapporteur: Zane Neikena

Scope: Evaluation of a PSUSA procedure

16.1.8. Carfilzomib - KYPROLIS (CAP) - PSUSA/00010448/202307

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Petar Mas

Scope: Evaluation of a PSUSA procedure

16.1.9. Casirivimab, imdevimab - RONAPREVE (CAP) - PSUSA/00010963/202307

Applicant: Roche Registration GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.10. Cenegermin - OXERVATE (CAP) - PSUSA/00010624/202307

Applicant: Dompe farmaceutici S.p.A.

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.1.11. Cladribine⁴⁰ - MAVENCLAD (CAP) - PSUSA/00010634/202307

Applicant: Merck Europe B.V.

PRAC Rapporteur: Carla Torre

Scope: Evaluation of a PSUSA procedure

16.1.12. Daridorexant - QUVIVIQ (CAP) - PSUSA/00010993/202307

Applicant: Idorsia Pharmaceuticals Deutschland GmbH

³⁸ Centrally authorised product(s) only

³⁹ For centrally authorised product(s) indicated for eosinophilic esophagitis only

⁴⁰ Multiple sclerosis indication only

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.1.13. Eptacog beta (activated) - CEVENFACTA (CAP) - PSUSA/00011006/202307

Applicant: Laboratoire Francais du Fractionnement et des Biotechnologies

PRAC Rapporteur: Bianca Mulder

Scope: Evaluation of a PSUSA procedure

16.1.14. Faricimab - VABYSMO (CAP) - PSUSA/00011016/202307

Applicant: Roche Registration GmbH

PRAC Rapporteur: Carla Torre

Scope: Evaluation of a PSUSA procedure

16.1.15. Finerenone - KERENDIA (CAP) - PSUSA/00010978/202307

Applicant: Bayer AG

PRAC Rapporteur: Bianca Mulder

Scope: Evaluation of a PSUSA procedure

16.1.16. Glucagon⁴¹ - BAQSIMI (CAP); OGLUO (CAP) - PSUSA/00010826/202307

Applicant: Eli Lilly Nederland B.V. (BAQSIMI), Tetris Pharma B.V. (Ogluo)

PRAC Rapporteur: Eamon O'Murchu

Scope: Evaluation of a PSUSA procedure

16.1.17. Glucarpidase - VORAXAZE (CAP) - PSUSA/00010968/202307

Applicant: SERB S.A.S.

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.18. Guselkumab - TREMFYA (CAP) - PSUSA/00010652/202307

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Gabriele Maurer

Scope: Evaluation of a PSUSA procedure

16.1.19. Icosapent ethyl - VAZKEPA (CAP) - PSUSA/00010922/202307

Applicant: Amarin Pharmaceuticals Ireland Limited

⁴¹ For centrally authorised product(s) only

PRAC Rapporteur: Bianca Mulder

Scope: Evaluation of a PSUSA procedure

16.1.20. Imipenem, cilastatin, relebactam - RECARBRIO (CAP) - PSUSA/00010830/202307

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.21. Indacaterol, glycopyrronium, mometasone - ENERZAIR BREEZHALER (CAP); ZIMBUS BREEZHALER (CAP) - PSUSA/00010861/202307

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.1.22. Inotersen - TEGSEDI (CAP) - PSUSA/00010697/202307

Applicant: Akcea Therapeutics Ireland Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

16.1.23. L-lysine hydrochloride, l-arginine hydrochloride - LYSAKARE (CAP) - PSUSA/00010786/202307

Applicant: Advanced Accelerator Applications

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.24. Neratinib - NERLYNX (CAP) - PSUSA/00010712/202307

Applicant: Pierre Fabre Medicament

PRAC Rapporteur: Bianca Mulder

Scope: Evaluation of a PSUSA procedure

16.1.25. Nonacog gamma - RIXUBIS (CAP) - PSUSA/00010320/202306

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Gabriele Maurer

Scope: Evaluation of a PSUSA procedure

16.1.26. Odevixibat - BYLVAY (CAP) - PSUSA/00010949/202307

Applicant: Albireo

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.27. Peginterferon alfa-2a - PEGASYS (CAP) - PSUSA/00009254/202307

Applicant: Pharmaand GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.28. Pneumococcal polysaccharide conjugate vaccine (15 valent, adsorbed) - VAXNEUVANCE (CAP) - PSUSA/00010975/202307

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Gabriele Maurer

Scope: Evaluation of a PSUSA procedure

16.1.29. Relugolix - ORGOVYX (CAP) - PSUSA/00010994/202307

Applicant: Accord Healthcare S.L.U.

PRAC Rapporteur: Karin Ernehalm

Scope: Evaluation of a PSUSA procedure

16.1.30. Remimazolam - BYFAVO (CAP) - PSUSA/00010924/202307

Applicant: Paion Deutschland GmbH

PRAC Rapporteur: Eamon O Murchu

Scope: Evaluation of a PSUSA procedure

16.1.31. Spheroids of human autologous matrix-associated chondrocytes - SPHEROX (CAP) - PSUSA/00010630/202307

Applicant: Co.Don GmbH, ATMP

PRAC Rapporteur: Gabriele Maurer

Scope: Evaluation of a PSUSA procedure

16.1.32. Tasimelteon - HETLIOZ (CAP) - PSUSA/00010394/202307

Applicant: Vanda Pharmaceuticals Netherlands B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.33. Tebentafusp - KIMMTRAK (CAP) - PSUSA/00010991/202307

Applicant: Immunocore Ireland Limited

PRAC Rapporteur: Bianca Mulder
Scope: Evaluation of a PSUSA procedure

16.1.34. Tecovirimat - TECOVIRIMAT SIGA (CAP) - PSUSA/00010971/202307

Applicant: SIGA Technologies Netherlands B.V.
PRAC Rapporteur: Martin Huber
Scope: Evaluation of a PSUSA procedure

16.1.35. Tigecycline - TYGACIL (CAP) - PSUSA/00002954/202306

Applicant: Pfizer Europe MA EEIG
PRAC Rapporteur: Maria del Pilar Rayon
Scope: Evaluation of a PSUSA procedure

16.1.36. Vericiguat - VERQUVO (CAP) - PSUSA/00010950/202307

Applicant: Bayer AG
PRAC Rapporteur: Kimmo Jaakkola
Scope: Evaluation of a PSUSA procedure

16.1.37. Voclosporin - LUPKYNIS (CAP) - PSUSA/00011020/202307

Applicant: Otsuka Pharmaceutical Netherlands B.V.
PRAC Rapporteur: Adam Przybylkowski
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. Caffeine⁴² - GENCEBOK (CAP); PEYONA (CAP); NAP - PSUSA/00000482/202307

Applicant: Gennisium Pharma (Gencebok), Chiesi Farmaceutici S.p.A. (Peyona), various
PRAC Rapporteur: Sonja Hrabcik
Scope: Evaluation of a PSUSA procedure

⁴² Apnea indication only

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

16.3.1. Acetylsalicylic acid, rosuvastatin (NAP) - PSUSA/00010893/202306

Applicant(s): various

PRAC Lead: Polona Golmajer

Scope: Evaluation of a PSUSA procedure

16.3.2. Allergen for therapy: betula verrucosa⁴³ (NAP) - PSUSA/00010815/202307

Applicant(s): various

PRAC Lead: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

16.3.3. Almotriptan (NAP) - PSUSA/00000101/202306

Applicant(s): various

PRAC Lead: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

16.3.4. Cyproterone (NAP) - PSUSA/00000905/202307

Applicant(s): various

PRAC Lead: Petar Mas

Scope: Evaluation of a PSUSA procedure

16.3.5. Diclofenac, misoprostol (NAP) - PSUSA/00001040/202307

Applicant(s): various

PRAC Lead: Karin Erneholm

Scope: Evaluation of a PSUSA procedure

16.3.6. Epirubicin (NAP) - PSUSA/00001234/202306

Applicant(s): various

PRAC Lead: Marie Louise Schougaard Christiansen

Scope: Evaluation of a PSUSA procedure

16.3.7. Ferucarbotran (NAP) - PSUSA/00001382/202306

Applicant(s): various

⁴³ Sublingual use only

PRAC Lead: Mari Thörn

Scope: Evaluation of a PSUSA procedure

16.3.8. Hepatitis A (inactivated), typhoid polysaccharide vaccine (adsorbed) (NAP) - PSUSA/00001594/202306

Applicant(s): various

PRAC Lead: Gabriele Maurer

Scope: Evaluation of a PSUSA procedure

16.3.9. Levocetirizine (NAP) - PSUSA/00001850/202307

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.3.10. Misoprostol⁴⁴ (NAP) - PSUSA/00010291/202306

Applicant(s): various

PRAC Lead: Marie Louise Schougaard Christiansen

Scope: Evaluation of a PSUSA procedure

16.3.11. Octreotide (NAP) - PSUSA/00002201/202306

Applicant(s): various

PRAC Lead: Eamon O'Murchu

Scope: Evaluation of a PSUSA procedure

16.3.12. Oxytocin⁴⁵ (NAP) - PSUSA/00010914/202306

Applicant(s): various

PRAC Lead: Karen Pernille Harg

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

16.3.13. Phentermine, topiramate (NAP) - PSUSA/00010956/202307

Applicant(s): various

PRAC Lead: Mari Thörn

Scope: Evaluation of a PSUSA procedure

⁴⁴ Gastrointestinal indication only

⁴⁵ Nasal spray only

16.4. Follow-up to PSUR/PSUSA procedures

16.4.1. Piperaquine tetraphosphate, arteminol - EURARTESIM (CAP) - EMEA/H/C/001199/LEG 018.1

Applicant: Alfasigma S.p.A.

PRAC Rapporteur: Martin Huber

Scope: MAH's response to LEG 018 request for supplementary information as adopted in October 2023. In view of the available data regarding "autoimmune haemolytic anaemia" and "delayed haemolytic anaemia" the MAH is requested to propose a wording to update the product information of arteminol / piperaquine tetraphosphate (Eurartesim) with the new information regarding "autoimmune haemolytic anaemia" and "delayed haemolytic anaemia" in section 4.4 and 4.8 of the SmPC and corresponding sections of the PL

16.4.2. Tocilizumab - ROACTEMRA (CAP) - EMEA/H/C/000955/LEG 063.1

Applicant: Roche Registration GmbH

PRAC Rapporteur: Gabriele Maurer

Scope: MAH's response to LEG 063 [to perform cumulative reviews of reports from clinical trials, post-marketing studies, literature and spontaneous reports concerning (i) psychiatric disorders including depression and related disorders, (ii) ulcerative keratitis, and (iii) pyoderma gangrenosum. To discuss potential pathomechanisms.] as adopted in September 2023

16.4.3. Vernakalant - BRINAVESS (CAP) - EMEA/H/C/001215/LEG 034

Applicant: Correvio

PRAC Rapporteur: Bianca Mulder

Scope: Vernakalant hypotension notification for case number 202311010464: To perform a parallel submission of serious special interest case reports associated with Brinavess

16.5. Variation procedure(s) resulting from PSUSA evaluation

16.5.1. Blinatumomab - BLINCYTO (CAP) - EMEA/H/C/003731/II/0054, Orphan

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Jana Lukacisinova

Scope: To update sections 4.2, 4.4, 4.8 of the SmPC to include immune effector cell-associated neurotoxicity syndrome (ICANS); and to update section D of Annex II to remove educational materials for physicians, pharmacists and nurses and to include ICANS within neurologic events in educational material for patient/caregivers and patient alert card following the outcome of PSUR procedure EMEA/H/C/PSUSA/00010460/202212. The package leaflet is updated accordingly. The RMP version 17.0 has also been submitted

16.5.2. Rituximab - MABTHERA (CAP) - EMEA/H/C/000165/II/0201/G

Applicant: Roche Registration GmbH

PRAC Rapporteur: Karin Erneholm

Scope: A grouped application comprising of:

Type II (C.I.3.b): Update of sections 4.1, 4.2, 4.3, 4.8, 5.1, 6.2, 6.4 and 6.5 of the SmPC in order to introduce several structural and editorial changes to align with the current SmPC guideline and to remove the educational materials for healthcare professionals (HCPs) and patients, following the request by PRAC in the assessment report for the PSUSA procedure EMA/PRAC/257005/2023. The Annex II, Labelling and package leaflet are updated accordingly. The RMP version 25.0 has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the product information and to update the list of local representatives in the package leaflet.

Type I (A.6): To change the ATC Code of rituximab from L01XC02 to L01FA01

16.6. Expedited summary safety reviews⁴⁶

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)⁴⁷

None

17.2. Protocols of PASS non-imposed in the marketing authorisation(s)⁴⁸

17.2.1. Agalsidase beta - FABRAZYME (CAP) - EMEA/H/C/000370/MEA 065

Applicant: Sanofi B.V.

PRAC Rapporteur: Liana Martirosyan

Scope: EPIDEMIOLOGY STUDY PROTOCOL, study no.: EPM0086 ; Fabrazyme (agalsidase beta) home infusion educational materials effectiveness evaluation: a survey of nurses administering home infusions

⁴⁶ 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

⁴⁷ In accordance with Article 107n of Directive 2001/83/EC

⁴⁸ 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. [Atogepant - AQUIPTA \(CAP\) - EMEA/H/C/005871/MEA 002](#)

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Rugile Pilviniene

Scope: From Initial MAA: PASS Study Protocol, study no.: P24433 (RMP version 1.0); Title: PASS to evaluate the utilisation and safety of atogepant in patients with migraine and significant cardiovascular or cerebrovascular disease in Europe

17.2.3. [Birch bark extract - FILSUEVZ \(CAP\) - EMEA/H/C/005035/MEA 001.2](#)

Applicant: Amryt Pharmaceuticals DAC

PRAC Rapporteur: Zane Neikena

Scope: REVISED PROTOCOL / [PASS (FOStER-EB) [(AEB-21)]]; Observational safety and effectiveness evaluation registry-based study in Epidermolysis Bullosa (EB) (FOStER-EB) [(AEB-21)] to evaluate the long-term safety of Filsuvez amongst patients treated for EB in relation to the incidence, severity and relatedness of skin malignancies (including squamous cell carcinoma, basal cell carcinoma and malignant melanoma, and use in patients with different skin types regarding ethnic origin

17.2.4. [Cinacalcet - MIMPARA \(CAP\) - EMEA/H/C/000570/MEA 035.8](#)

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Mari Thorn

Scope: Protocol amendment for the observational registry study (20180204) 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

17.2.5. [Coronavirus \(COVID-19\) vaccine \(B.1.351 variant, prefusion Spike delta TM protein, recombinant\) - VIDPREVTYN BETA \(CAP\) - EMEA/H/C/005754/MEA 002.3](#)

Applicant: Sanofi Pasteur

PRAC Rapporteur: Jana Lukacisinova

Scope: MAH's response to MEA 002.2 [Revised PASS Protocol / Study number: VAT 00007] RSI as adopted in October 2023. REAL WORLD AND EPIDEMIOLOGY STUDY PROTOCOL; Title: Post-authorisation, observational study to assess the safety of VidPrevtyln 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 VidPrevtyln Beta as a booster dose in a real-world setting

17.2.6. [Emicizumab - HEMLIBRA \(CAP\) - EMEA/H/C/004406/MEA 012.1](#)

Applicant: Roche Registration GmbH

PRAC Rapporteur: Amelia Cupelli

Scope: MAH's response to MEA 012 [PASS No. BO44691] as adopted in September 2023:

A revised protocol for the non-imposed non-interventional PASS to evaluate the long-term safety of Hemlibra in patients with moderate Hemophilia A and severe bleeding phenotype (safety risk: thrombo-embolic events)

17.2.7. Enfortumab vedotin - PADCEV (CAP) - EMEA/H/C/005392/MEA 003.1

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Eva Jirsová

Scope: Updated Study Protocol / Study no.: 7465-PV-0002 version 2.0; To evaluate patients understanding and awareness of the content of the patient card related to risks of skin reactions and patients behaviours to minimise the risks

17.2.8. Filgotinib - JYSELECA (CAP) - EMEA/H/C/005113/MEA 017.1

Applicant: Galapagos N.V.

PRAC Rapporteur: Petar Mas

Scope: MAH's response to MEA 017 [Protocol for study GLPG0634-CL-417: non-interventional, post-authorisation, cohort, safety study evaluating the effectiveness of the additional risk minimization measures for filgotinib (Jyseleca) use in patients with moderately to severely active ulcerative colitis within multiple European registries] as per the request for supplementary information (RSI) as adopted in September 2023

17.2.9. Linzagolix choline - YSELTY (CAP) - EMEA/H/C/005442/MEA 002.2

Applicant: Theramex Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: MAH's response to MEA 002.1 as per request for supplementary information adopted in October 2023 together with an updated protocol for study YSELTYPASS: A multinational PASS on real-world treatment in patients receiving YSELTYPASS (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

17.2.10. Mirikizumab - OMVOH (CAP) - EMEA/H/C/005122/MEA 001

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Sonja Hrabcik

Scope: From initial MAA: Protocol / I6T-MC-B003; Observational Study of Pregnancy and Infant Outcomes Among Women Exposed to Mirikizumab During Pregnancy in US-based Administrative Claims Data

17.2.11. Mirikizumab - OMVOH (CAP) - EMEA/H/C/005122/MEA 002

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Sonja Hrabcik

Scope: From initial MAA: Protocol / I6T-MC-B004; Observational Secondary Database Study to Assess the Long-Term Safety of Mirikizumab in Routine Clinical Practice Using US Administrative Claims Data

17.2.12. Naldemedine - RIZMOIC (CAP) - EMEA/H/C/004256/MEA 001.6

Applicant: Shionogi B.V.

PRAC Rapporteur: Eamon O Murchu

Scope: MAH's response to MEA 001.5 for an Observational PASS of Patients with Chronic Opioid Use for Non-Cancer and Cancer Pain who have Opioid-Induced Constipation (OIC) as per the request for supplementary information adopted in October 2023

17.2.13. Pegvaliase - PALYNZIQ (CAP) - EMEA/H/C/004744/MEA 005.7

Applicant: BioMarin International Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Protocol Amendment 4 for study 165-504: A global, multicenter study to assess maternal, fetal and infant outcomes of exposure to Palynziq (pegvaliase) during pregnancy and breastfeeding

17.2.14. Pitolisant - OZAWADE (CAP) - EMEA/H/C/005117/MEA 003.2

Applicant: Bioprojet Pharma

PRAC Rapporteur: Kirsti Villikka

Scope: Revised Protocol / Study no.: P21-02; A multi-centre, 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

17.2.15. Respiratory syncytial virus vaccine (bivalent, recombinant) - ABRYSVO (CAP) - EMEA/H/C/006027/MEA 002.1

Applicant: Pfizer Europe Ma EEIG

PRAC Rapporteur: Liana Martirosyan

Scope: Revised Protocol, Study C3671031; Title: A Post-Authorization Safety Study of Guillain-Barré Syndrome (GBS) Following ABRYSVOTM Among Older Adults in the United States. (v.1.0)

17.3. Results of PASS imposed in the marketing authorisation(s)⁴⁹

None

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

17.4. Results of PASS non-imposed in the marketing authorisation(s)⁵⁰

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

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Martin Huber

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

17.4.2. Dolutegravir, lamivudine - DOVATO (CAP) - EMEA/H/C/004909/WS2620/0047; Dolutegravir, Rilpivirine - JULUCA (CAP) - EMEA/H/C/004427/WS2620/0056; Dolutegravir - TIVICAY (CAP) - EMEA/H/C/002753/WS2620/0092; Dolutegravir, Abacavir, Lamivudine - TRIUMEQ (CAP) - EMEA/H/C/002754/WS2620/0118

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Martin Huber

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

17.4.3. Epoetin alfa - ABSEAMED (CAP) - EMEA/H/C/000727/WS2615/0108; Epoetin alfa - BINOCRIT (CAP) - EMEA/H/C/000725/WS2615/0108; Epoetin alfa - EPOETIN ALFA HEXAL (CAP) - EMEA/H/C/000726/WS2615/0108

Applicant: Sandoz GmbH

PRAC Rapporteur: Tiphaine Vaillant

Scope: Submission of the final report from Non-Interventional PASS, NI-PASS HX575-507 listed as a category 3 study in the RMP. The non-interventional study (NIS PASS) study HX575-507 was conducted to address a post-approval requirement (MEA 13.5) to evaluate the safety profile of HX575 administered s.c. in patients with CKD-induced anemia under

⁵⁰ 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

real-life conditions, in order to increase confidence on the safe use of s.c. HX575. The RMP version 19.0 has also been submitted

17.4.4. [Hepatitis B surface antigen \(rDNA\) - HEPLISAV B \(CAP\) - EMEA/H/C/005063/II/0031](#)

Applicant: Dynavax GmbH

PRAC Rapporteur: Gabriele Maurer

Scope: Update of section 4.6 of the SmPC in order to update information on pregnancy based on final results from study DV2-HBV-28 - Post-marketing observational surveillance study to evaluate pregnancy outcomes among women who receive HEPLISAV-B or Engerix-B; HBV-28 was conducted using the same patient population as two observational post-marketing surveillance studies designed to evaluate the incidence of AMI (HBV-25) or new-onset immune-mediated diseases, herpes zoster, and anaphylaxis (HBV-26) in recipients of HEPLISAV-B compared with recipients of Engerix-B. The primary objective of this study was to describe and compare pregnancy outcomes in recipients of HEPLISAV-B and recipients of Engerix-B. The package leaflet is updated accordingly. The RMP version 1.4 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

17.4.5. [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 (CNT01275PSO4005) 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

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

17.5.1. [Inotersen - TEGSEDI \(CAP\) - EMEA/H/C/004782/MEA 007.5](#)

Applicant: Akcea Therapeutics Ireland Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Interim study report for PASS No TG4005 (non-imposed/non-interventional); Pregnancy surveillance program of women and infants exposed to Tegsedi during pregnancy

17.5.2. [Naloxegol - MOVENTIG \(CAP\) - EMEA/H/C/002810/MEA 006.15](#)

Applicant: Kyowa Kirin Holdings B.V.

PRAC Rapporteur: Eamon O Murchu

Scope: MAH's response to MEA 006.14 [Final progress report for study D3820R00009 - Naloxegol Health Outcomes PASS – An observational PASS of MOVENTIG (Naloxegol) Among Patients Aged 18 Years and Older Diagnosed with Non-Cancer Pain and Cancer Pain and Treated with Opioids Chronically in Selected European Populations] as per the request for supplementary information (RSI) adopted in September 2023

17.5.3. Risdiplam - EVRYSDI (CAP) - EMEA/H/C/005145/MEA 007.4

Applicant: Roche Registration GmbH

PRAC Rapporteur: Jan Neuhauser

Scope: Second interim study report for study BN42833 (Risdiplam Pregnancy Surveillance Study): A Phase IV, non-interventional surveillance study

17.5.4. Rivaroxaban - XARELTO (CAP) - EMEA/H/C/000944/MEA 049.4

Applicant: Bayer AG

PRAC Rapporteur: Mari Thorn

Scope: First progress report for the Xarelto Paediatric VTE PASS Drug Utilization Study: an observational, longitudinal, multi-source drug utilization safety study to evaluate the drug use patterns and safety of rivaroxaban oral suspension in children under two years with venous thromboembolism (XAPAEDUS)

17.5.5. Siponimod - MAYZENT (CAP) - EMEA/H/C/004712/MEA 004.4

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Maria del Pilar Rayon

Scope: MAH's response to MEA 004.3 [Interim study report for the survey among healthcare professionals and MS patients/caregivers (study CBAF312A2006)] as per request for supplementary information adopted in October 2023

17.5.6. Tacrolimus - ADVAGRAF (CAP) - EMEA/H/C/000712/MEA 032.4

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Eamon O Murchu

Scope: Progress Report / Study No.: 2868371 v.1.0; Feasibility assessment of conducting a NI-PASS of outcomes associated with the use of tacrolimus around conception, or during pregnancy or lactation using data from available secondary use data sources to replicate the Transplant Pregnancy Registry International (TPRI) study

17.5.7. Tacrolimus - MODIGRAF (CAP) - EMEA/H/C/000954/MEA 024.4

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Mari Thorn

Scope: Progress Report / Study No.: 2868371 v.1.0; Feasibility assessment of conducting a

NI-PASS of outcomes associated with the use of tacrolimus around conception, or during pregnancy or lactation using data from available secondary use data sources to replicate the Transplant Pregnancy Registry International (TPRI) study

17.5.8. Teduglutide - REVESTIVE (CAP) - EMEA/H/C/002345/ANX 003.11

Applicant: Takeda Pharmaceuticals International AG Ireland Branch

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: MAH Response to ANX 003.10 [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 adopted in October 2023

17.6. Others

None

17.7. New Scientific Advice

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

17.8. Ongoing Scientific Advice

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

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

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

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

Based on the review of the available pharmacovigilance data for the medicine(s) listed below and the CHMP Rapporteur's assessment report, PRAC considered that either the renewal of the marketing authorisation procedure could be concluded - and supported the renewal of their marketing authorisations for an unlimited or additional period, as applicable - or no amendments to the specific obligations of the marketing authorisation under exceptional circumstances for the medicines listed below were recommended. As per the agreed criteria, the procedures were finalised at the PRAC level without further plenary discussion.

18.1. Annual reassessments of the marketing authorisation

18.1.1. Cholic acid - ORPHACOL (CAP) - EMEA/H/C/001250/S/0053 (without RMP)

Applicant: Theravia

PRAC Rapporteur: Sofia Trantza

Scope: Annual reassessment of the marketing authorisation

18.1.2. Eladocagene exuparvovec - UPSTAZA (CAP) - EMEA/H/C/005352/S/0017 (without RMP)

Applicant: PTC Therapeutics International Limited, ATMP

PRAC Rapporteur: Gabriele Maurer

Scope: Annual reassessment of the marketing authorisation

18.1.3. Fosdenopterin - NULIBRY (CAP) - EMEA/H/C/005378/S/0006 (without RMP)

Applicant: TMC Pharma (EU) Limited

PRAC Rapporteur: Martin Huber

Scope: Annual reassessment of the marketing authorisation

18.1.4. Idebenone - RAXONE (CAP) - EMEA/H/C/003834/S/0035 (without RMP)

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Amelia Cupelli

Scope: Annual reassessment of the marketing authorisation

18.1.5. Lomitapide - LOJUXTA (CAP) - EMEA/H/C/002578/S/0057 (without RMP)

Applicant: Amryt Pharmaceuticals DAC

PRAC Rapporteur: Bianca Mulder

Scope: Annual reassessment of the marketing authorisation

18.1.6. Obiltoxaximab - NYXTHRACIS (CAP) - EMEA/H/C/005169/S/0013 (without RMP)

Applicant: SFL Pharmaceuticals Deutschland GmbH

PRAC Rapporteur: Liana Martirosyan

Scope: Annual reassessment of the marketing authorisation

18.1.7. Smallpox vaccine (live modified vaccinia virus Ankara) - IMVANEX (CAP) - EMEA/H/C/002596/S/0095 (without RMP)

Applicant: Bavarian Nordic A/S

PRAC Rapporteur: Gabriele Maurer

Scope: Annual reassessment of the marketing authorisation

18.1.8. Tocofersolan - VEDROP (CAP) - EMEA/H/C/000920/S/0049 (without RMP)

Applicant: Recordati Rare Diseases

PRAC Rapporteur: Melinda Palfi

Scope: Annual reassessment of the marketing authorisation

18.2. Conditional renewals of the marketing authorisation

18.2.1. Mosunetuzumab - LUNSUMIO (CAP) - EMEA/H/C/005680/R/0008 (without RMP)

Applicant: Roche Registration GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Conditional renewal of the marketing authorisation

18.2.2. Pandemic influenza vaccine (H5N1) (live attenuated, nasal) - PANDEMIC INFLUENZA VACCINE H5N1 ASTRAZENECA (CAP) - EMEA/H/C/003963/R/0071 (without RMP)

Applicant: AstraZeneca AB

PRAC Rapporteur: Sonja Hrabcik

Scope: Conditional renewal of the marketing authorisation

18.2.3. Selumetinib - KOSELUGO (CAP) - EMEA/H/C/005244/R/0015 (without RMP)

Applicant: AstraZeneca AB

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Conditional renewal of the marketing authorisation

18.3. Renewals of the marketing authorisation

18.3.1. Idelalisib - ZYDELIG (CAP) - EMEA/H/C/003843/R/0059 (with RMP)

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Martin Huber

Scope: 5-year renewal of the marketing authorisation

18.3.2. Lacosamide - LACOSAMIDE UCB (CAP) - EMEA/H/C/005243/R/0020 (without RMP)

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: 5-year renewal of the marketing authorisation

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

Applicant: Advanced Accelerator Applications

PRAC Rapporteur: Adam Przybylkowski

Scope: 5-year renewal of the marketing authorisation

18.3.4. Pegfilgrastim - GRASUSTEK (CAP) - EMEA/H/C/004556/R/0014 (with RMP)

Applicant: Jutta Pharma GmbH

PRAC Rapporteur: Bianca Mulder

Scope: 5-year renewal of the marketing authorisation

18.3.5. Pegvaliase - PALYNZIQ (CAP) - EMEA/H/C/004744/R/0038 (without RMP)

Applicant: BioMarin International Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: 5-year renewal of the marketing authorisation

18.3.6. Posaconazole - POSACONAZOLE ACCORD (CAP) - EMEA/H/C/005005/R/0014 (with RMP)

Applicant: Accord Healthcare S.L.U.

PRAC Rapporteur: Nathalie Gault

Scope: 5-year renewal of the marketing authorisation

18.3.7. Posaconazole - POSACONAZOLE AHCL (CAP) - EMEA/H/C/005028/R/0011 (without RMP)

Applicant: Accord Healthcare S.L.U.

PRAC Rapporteur: Nathalie Gault

Scope: 5-year renewal of the marketing authorisation

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

Applicant: Alexion Europe SAS

PRAC Rapporteur: Kimmo Jaakkola

Scope: 5-year renewal of the marketing authorisation

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

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Carla Torre

Scope: 5-year renewal of the marketing authorisation

19. Annex II – List of participants

including any restrictions with respect to involvement of members/alternates/experts following evaluation of declared interests for the 5 February 2024 PRAC meeting, which was held in-person.

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	
Sonja Hrabcik ^a	Alternate	Austria	No interests declared	
Jean-Michel Dogné ^a	Member	Belgium	No interests declared	
Jo Robays ^{a,b}	Alternate	Belgium	No interests declared	
Maria Popova-Kiradjieva ^{a,b}	Member	Bulgaria	No interests declared	
Petar Mas ^{a,b}	Member	Croatia	No interests declared	
Barbara Kovacic Bytyqi ^{a,b}	Alternate*	Croatia	No interests declared	
Panagiotis Psaras ^{a,b}	Alternate	Cyprus	No interests declared	
Eva Jirsová ^{a,b}	Member	Czechia	No interests declared	
Jana Lukacisinova ^a	Alternate	Czechia	No interests declared	
Marie Louise Schougaard Christiansen ^{a,b}	Member	Denmark	No interests declared	
Karin Erneholm ^{a,b}	Alternate	Denmark	No interests declared	
Maia Uusküla ^a	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	Alternate	France	No interests declared	
Martin Huber ^{a,b}	Member (Vice-Chair)	Germany	No interests declared	
Gabriele Maurer ^{a,b}	Alternate*	Germany	No participation	4.3.1. Atezolizumab - TECENTRIQ

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			in final deliberations and voting on:	(CAP) - EMEA/H/C/004 143/SDA/025; Avelumab - BAVENCIO (CAP) - EMEA/H/C/004 338/SDA/011; Cemiplimab - LIBTAYO (CAP) - EMEA/H/C/004 844/SDA/010; Dostarlimab - JEMPERLI (CAP) - EMEA/H/C/005 204/SDA/005; Durvalumab - IMFINZI (CAP) - EMEA/H/C/004 771/SDA/012; Ipilimumab - YERVOY (CAP) - EMEA/H/C/002 213/SDA/048; Nivolumab - OPDIVO (CAP) - EMEA/H/C/003 985/SDA/056; Nivolumab, relatlimab - OPDUALAG (CAP) - EMEA/H/C/005 481/SDA/006; Pembrolizumab - KEYTRUDA (CAP) - EMEA/H/C/003 820/SDA/040; Tislelizumab - TEVIMBRA (CAP) - EMEA/H/C/005 919/SDA/002; Tremelimumab - IMJUDO (CAP) - EMEA/H/C/006 016/SDA/003 4.3.2.

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				<p>Atezolizumab - TECENTRIQ (CAP) - EMEA/H/C/004 143/SDA/024;</p> <p>Avelumab - BAVENCIO (CAP) - EMEA/H/C/004 338/SDA/010;</p> <p>Cemiplimab - LIBTAYO (CAP) - EMEA/H/C/004 844/SDA/009;</p> <p>Dostarlimab - JEMPERLI (CAP) - EMEA/H/C/005 204/SDA/004;</p> <p>Durvalumab - IMFINZI (CAP) - EMEA/H/C/004 771/SDA/011;</p> <p>Ipilimumab - YERVOY (CAP) - EMEA/H/C/002 213/SDA/047;</p> <p>Nivolumab - OPDIVO (CAP) - EMEA/H/C/003 985/SDA/055;</p> <p>Nivolumab, relatlimab - OPDUALAG (CAP) - EMEA/H/C/005 481/SDA/005;</p> <p>Pembrolizumab - KEYTRUDA (CAP) - EMEA/H/C/003 820/SDA/039;</p> <p>Tislelizumab - TEVIMBRA (CAP) - EMEA/H/C/005 919/SDA/001;</p> <p>Tremelimumab - IMJUDO (CAP) - EMEA/H/C/006 016/SDA/002</p>

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	Alternate*	Greece	No interests declared	
Julia Pallos ^{a,b}	Member	Hungary	No participation in final deliberations and voting on:	4.3.1. Atezolizumab - TECENTRIQ (CAP) - EMEA/H/C/004 143/SDA/025; Avelumab - BAVENCIO (CAP) - EMEA/H/C/004 338/SDA/011; Cemiplimab - LIBTAYO (CAP) - EMEA/H/C/004 844/SDA/010; Dostarlimab - JEMPERLI (CAP) - EMEA/H/C/005 204/SDA/005; Durvalumab - IMFINZI (CAP) - EMEA/H/C/004 771/SDA/012; Ipilimumab - YERVOY (CAP) - EMEA/H/C/002 213/SDA/048; Nivolumab - OPDIVO (CAP) - EMEA/H/C/003 985/SDA/056; Nivolumab, relatlimab - OPDUALAG (CAP) - EMEA/H/C/005 481/SDA/006; Pembrolizumab - KEYTRUDA (CAP) - EMEA/H/C/003 820/SDA/040; Tislelizumab - TEVIMBRA (CAP) -

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				EMEA/H/C/005 919/SDA/002; Tremelimumab - IMJUDO (CAP) - EMEA/H/C/006 016/SDA/003 4.3.2. Atezolizumab - TECENTRIQ (CAP) - EMEA/H/C/004 143/SDA/024; Avelumab - BAVENCIO (CAP) - EMEA/H/C/004 338/SDA/010; Cemiplimab - LIBTAYO (CAP) - EMEA/H/C/004 844/SDA/009; Dostarlimab - JEMPERLI (CAP) - EMEA/H/C/005 204/SDA/004; Durvalumab - IMFINZI (CAP) - EMEA/H/C/004 771/SDA/011; Ipilimumab - YERVOY (CAP) - EMEA/H/C/002 213/SDA/047; Nivolumab - OPDIVO (CAP) - EMEA/H/C/003 985/SDA/055; Nivolumab, relatlimab - OPDUALAG (CAP) - EMEA/H/C/005 481/SDA/005; Pembrolizuma b - KEYTRUDA (CAP) - EMEA/H/C/003 820/SDA/039; Tislelizumab -

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				<p>TEVIMBRA (CAP) - EMEA/H/C/005 919/SDA/001; Tremelimumab - IMJUDO (CAP) - EMEA/H/C/006 016/SDA/002</p> <p>6.4.1. Abatacept - ORENCIA (CAP) - EMEA/H/C/000 701/LEG 071</p> <p>15.3.1. Abatacept - ORENCIA (CAP) - EMEA/H/C/000 701/II/0152</p> <p>15.3.17. Fedratinib - INREBIC (CAP) - EMEA/H/C/005 026/II/0019, Orphan</p> <p>15.3.22. Luspatercept - REBLOZYL (CAP) - EMEA/H/C/004 444/II/0021, Orphan</p>
Gudrun Þengilsdóttir ^a	Alternate	Iceland	No restrictions applicable to this meeting	
Rhea Fitzgerald ^a	Member	Ireland	No interests declared	
Eamon O Murchu ^{a,b}	Alternate	Ireland	No interests declared	
Amelia Cupelli ^{a,b}	Member	Italy	No interests declared	
Zane Neikena ^{a,b}	Member	Latvia	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Lina Seibokiene ^{a,b}	Alternate	Lithuania	No participation in discussion, final deliberations and voting on:	17.5.4. Rivaroxaban - XARELTO (CAP) - EMEA/H/C/000 944/MEA 049.4
Nadine Petitpain ^{a,b}	Member	Luxembourg	No restrictions applicable to this meeting	
John Joseph Borg ^a	Member*	Malta	No interests declared	
Benjamin Micallef ^a	Alternate*	Malta	No interests declared	
Liana Martirosyan ^a	Member	Netherlands	No interests declared	
Bianca Mulder ^{a,b}	Alternate	Netherlands	No interests declared	
David Olsen ^{a,b}	Member	Norway	No participation in final deliberations and voting on:	3.2.1. Hydroxyprogesterone (NAP) - EMEA/H/A-31/1528 4.3.3. Chlorhexidine (NAP) and other relevant fixed-dose combinations 6.3.6. Pseudoephedrine (NAP); acetylsalicylic acid, pseudoephedrine (NAP) - PSUSA/00010 667/202306 16.1.15. Finerenone - KERENDIA (CAP) - PSUSA/00010 978/202307

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				16.1.36. Vericiguat - VERQUVO (CAP) - PSUSA/00010 950/202307 16.3.4. Cyproterone (NAP) - PSUSA/00000 905/202307 17.5.4. Rivaroxaban - XARELTO (CAP) - EMEA/H/C/000 944/MEA 049.4
Pernille Harg ^{a,b}	Alternate	Norway	No interests declared	
Adam Przybylkowski ^a	Member	Poland	No interests declared	
Ana Sofia Diniz Martins ^{a,b}	Member	Portugal	No interests declared	
Carla Torre ^a	Alternate	Portugal	No interests declared	
Roxana Dondera ^a	Member	Romania	No interests declared	
Irina Sandu ^{a,b}	Alternate*	Romania	No interests declared	
Anna Mareková ^a	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,b}	Alternate	Spain	No interests declared	
Ulla Wändel Liminga ^{a,b}	Member	Sweden	No interests declared	
Mari Thorn ^{a,b}	Alternate	Sweden	No restrictions	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			applicable to this meeting	
Annalisa Capuano ^a	Member*	Independent scientific expert	No interests declared	
Milou Daniel Drici ^{a,b}	Member	Independent scientific expert	No interests declared	
Maria Teresa Herdeiro ^{a,b}	Member	Independent scientific expert	No interests declared	
Patricia McGettigan ^a	Member*	Independent scientific expert	No interests declared	
Tania Schink ^{a,b}	Member*	Independent scientific expert	No participation in final deliberations and voting on:	16.1.1. Acridinium bromide - BRETARIS GENUAIR (CAP); EKLIRA GENUAIR (CAP) - PSUSA/00009 005/202307 17.5.4. Rivaroxaban - XARELTO (CAP) - EMEA/H/C/000 944/MEA 049.4
Hedvig Nordeng ^a	Member	Independent scientific expert	No interests declared	
Roberto Frontini ^a	Member	Healthcare Professionals' Representative	No restrictions applicable to this meeting	
Salvatore Messina ^a	Alternate	Healthcare Professionals' Representative	No interests declared	
Marko Korenjak ^a	Member	Patients' Organisation Representative	No interests declared	
Michal Rataj ^{a,b}	Alternate	Patients' Organisation Representative	No interests declared	
Laurence de Fays ^a	Expert	Belgium	No interests declared	
Michaela Dlouhá ^a	Expert	Czechia	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Michaela Dlouhá ^a	Expert	Czechia	No interests declared	
Lucie Skálová ^a	Expert	Czechia	No interests declared	
Irene Mandrup Krüger ^a	Expert	Denmark	No interests declared	
Anissa Benlazar ^a	Expert	France	No interests declared	
Pauline Dayani ^a	Expert	France	No interests declared	
Vincent Gazin ^a	Expert	France	No interests declared	
Dina Habib-Hanawy ^a	Expert	France	No interests declared	
Faustine Vidil ^a	Expert	France	No interests declared	
Dominique Gaston ^a	Expert	Germany	No interests declared	
Jelena Katic ^a	Expert	Germany	No interests declared	
Dennis Lex ^{a,b}	Expert	Germany	No interests declared	
Birte Niemann ^a	Expert	Germany	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	
Fiorella Petronzelli ^a	Expert	Italy	No restrictions applicable to this meeting	
Anja Van Haren ^b	Expert	Netherlands	No interests declared	
Susanne Dertz ^a	Expert	Norway	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Natividad Galiana ^a	Expert	Spain	No restrictions applicable to this meeting	
Consuelo Mejías ^a	Expert	Spain	No interests declared	
Isabel Olmos ^a	Expert	Spain	No interests declared	
A representative from the European Commission attended the meeting				
Observers from FDA (USA), PMDA (Japan) and WHO attended the meeting.				
Meeting run with support from relevant EMA staff				
Experts were evaluated against the agenda topics or activities they participated in.				

20. Annex III - List of acronyms and abbreviations

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

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

21. Explanatory notes

The Notes give a brief explanation of relevant minute's items and should be read in conjunction with the minutes.

EU Referral procedures for safety reasons: Urgent EU procedures and Other EU referral procedures

(Items 2 and 3 of the PRAC minutes)

A referral is a procedure used to resolve issues such as concerns over the safety or benefit-risk balance of a medicine or a class of medicines. In a referral, EMA is requested to conduct a scientific assessment of a particular medicine or class of medicines on behalf of the European Union (EU). For further detailed information on safety related referrals please see:

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>