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SCIENCE MEDICINES HEALTH

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Human Medicines Division

Pharmacovigilance Risk Assessment Committee (PRAC) Minutes of PRAC meeting on 08-11 April 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 on-going procedures for which a final decision has not yet been adopted. They will become public when adopted or considered public according to the principles stated in the Agency policy on access to documents ([EMA/127362/2006, Rev. 1](#)).

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1. Introduction

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

The Chairperson opened the 08-11 April 2024 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 that no restriction in the involvement of meeting participants for agenda topics was identified. 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 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 08-11 April 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 04-07 March 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 04-07 March 2024 were published on the EMA website on 14 May 2024. ([Minutes of the PRAC meeting on 04-07 March 2024 \(europa.eu\)](#)).

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

3.3. Procedures for finalisation

None

3.4. Re-examination procedures²

None

3.5. Others

None

4. Signals assessment and prioritisation³

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

See also Annex I 14.1.

4.1.1. Eptinezumab - VYEPTI (CAP); erenumab – AIMOVIG (CAP); galcanezumab – EMGALITY (CAP); – AJОВI (CAP)

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

PRAC Rapporteur: Kirsti Villikka

² Re-examination of PRAC recommendation under Article 32 of Directive 2001/83/EC

³ 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

Scope: Signal of erectile dysfunction

EPITT 20074 – New signal

Lead Member State(s): FI, NL

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 erectile dysfunction was identified by the Italian Medicines Agency, based on 59 cases (29 cases for erenumab, 15 cases for galcanezumab, 13 cases for fremanezumab, 2 cases for eptinezumab) retrieved from EudraVigilance and national databases, as well as 1 case for galcanezumab retrieved 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 of the signal of erectile dysfunction following administration of eptinezumab, erenumab, galcanezumab and fremanezumab is warranted.

PRAC appointed Kirsti Villikka as Rapporteur for the signal.

Summary of recommendation(s)

- The MAHs for Vyepti (eptinezumab), Aimovig (erenumab), Emgality (galcanezumab) and Ajovy (fremanezumab) should submit to EMA, within 60 days, a cumulative review of cases of erectile dysfunction including but not limited to the MedDRA-PTs 'male sexual dysfunction', 'sexual dysfunction', as well as the MedDRA HLT 'Erection and ejaculation conditions and disorders' associated with galcanezumab, erenumab, fremanezumab or eptinezumab (each MAH only on their own product) as suspect drug. This analysis should include 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 MAHs should also provide a causality assessment, together with a discussion on the need for any amendment to the product information and/or risk management plan.
- A 90-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.2. Signals follow-up and prioritisation

4.2.1. Adagrasib – KRAZATI (CAP)

Applicant: Mirati Therapeutics B.V.

PRAC Rapporteur: Kimmo Jaakkola

Scope: Signal of serious cutaneous adverse reactions (SCARs)

EPITT 20051 – Follow-up to February 2024

Background

For background information, see [PRAC minutes February 2024](#).

The MAH replied to the request for information on the signal of serious cutaneous adverse reactions (SCARs) and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence in EudraVigilance, literature and responses submitted by the MAHs, PRAC agreed that there is insufficient evidence to establish a causal relationship between Krazati (adagrasib) and SCARs at present; however, PRAC considered warranted to advise about an increased risk of SCARs following adagrasib administration. Therefore, the product information should be amended to add a warning on serious cutaneous adverse reactions (SCARs).

Summary of recommendation(s)

- The MAH for Krazati (adagrasib) should submit to EMA, within 60 days, a variation to amend⁴ the product information.
- In the next PSUR, the MAH should provide a cumulative review of all cases of serious and non-serious skin reactions using the MedDRA SOC Skin and subcutaneous tissue disorders with adagrasib. This analysis should include 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 and/ or the risk management plan as well as a proposal for a direct healthcare professional communication (DHPC) and a communication plan.

For the full PRAC recommendation, see [EMA/PRAC/147679/2024](#) published on 06 May 2024 on the EMA website.

4.2.2. [Atezolizumab - TECENTRIQ \(CAP\) - EMEA/H/C/004143/SDA/025.1](#); [Avelumab - BAVENCIO \(CAP\) - EMEA/H/C/004338/SDA/011.1](#); [Cemiplimab - LIBTAYO \(CAP\) - EMEA/H/C/004844/SDA/010.1](#); [Dostarlimab - JEMPERLI \(CAP\) - EMEA/H/C/005204/SDA/005.1](#); [Durvalumab - IMFINZI \(CAP\) - EMEA/H/C/004771/SDA/012.1](#); [Ipilimumab - YERVOY \(CAP\) - EMEA/H/C/002213/SDA/048.1](#); [Nivolumab - OPDIVO \(CAP\) - EMEA/H/C/003985/SDA/056.1](#); [Nivolumab, relatlimab - OPDUALAG \(CAP\) - EMEA/H/C/005481/SDA/006.1](#); [Pembrolizumab - KEYTRUDA \(CAP\) - EMEA/H/C/003820/SDA/040.1](#); [Tislelizumab - TEVIMBRA \(CAP\) - EMEA/H/C/005919/SDA/002.1](#); [Tremelimumab - IMJUDO \(CAP\) - EMEA/H/C/006016/SDA/003.1](#)

Applicant: AstraZeneca AB (Imjudo), 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 February 2024

⁴ Update of SmPC section 4.4. The package leaflet is updated accordingly.

Background

For background information, see [PRAC minutes February 2024](#).

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, clinical studies and the literature, and responses submitted by the MAHs, PRAC agreed that there is sufficient evidence to amend the product information of immune-check inhibitors to add coeliac disease as undesirable effect (for the products where cases of coeliac disease have been reported: atezolizumab, durvalumab, ipilimumab, nivolumab, pembrolizumab, tislelizumab, tremelimumab) and to add that coeliac disease have been reported during treatment with other immune-checkpoint inhibitors (for the products where cases of coeliac disease have not been reported: cemiplimab, avelumab, and dostarlimab).

Summary of recommendation(s)

- The MAHs for atezolizumab, durvalumab, ipilimumab, nivolumab, nivolumab/relatlinib, pembrolizumab, tislelizumab, tremelimumab, cemiplimab, avelumab and dostarlimab should submit to EMA, within 30 days, their comments on the proposed amendments to the product information, together with the relevant frequency calculations.

Post-meeting note: the MAHs provided their responses and the full PRAC recommendation, can be found under [EMA/PRAC/147679/2024](#) published on 06 May 2024 on the EMA website.

4.2.3. [Atezolizumab - TECENTRIQ \(CAP\) - EMEA/H/C/004143/SDA/024.1](#); [Avelumab - BAVENCIO \(CAP\) - EMEA/H/C/004338/SDA/010.1](#); [Cemiplimab - LIBTAYO \(CAP\) - EMEA/H/C/004844/SDA/009.1](#); [Dostarlimab - JEMPERLI \(CAP\) - EMEA/H/C/005204/SDA/004.1](#); [Durvalumab - IMFINZI \(CAP\) - EMEA/H/C/004771/SDA/011.1](#); [Ipilimumab - YERVOY \(CAP\) - EMEA/H/C/002213/SDA/047.1](#); [Nivolumab - OPDIVO \(CAP\) - EMEA/H/C/003985/SDA/055.1](#); [Nivolumab, relatlimab - OPDUALAG \(CAP\) - EMEA/H/C/005481/SDA/005.1](#); [Pembrolizumab - KEYTRUDA \(CAP\) - EMEA/H/C/003820/SDA/039.1](#); [Tislelizumab - TEVIMBRA \(CAP\) - EMEA/H/C/005919/SDA/001.1](#); [Tremelimumab - IMJUDO \(CAP\) - EMEA/H/C/006016/SDA/002.1](#)

Applicant(s): AstraZeneca AB (Imjudo), 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 February 2024

Background

For background information, see PRAC minutes February 2024.

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

Discussion

Having considered the available evidence in EudraVigilance, clinical studies and the literature, and responses submitted by the MAHs, PRAC agreed that there is sufficient evidence to amend the product information of immune-checkpoint inhibitors and to include a reference to pancreatic failure. Therefore, the product information for nivolumab, ipilimumab, nivolumab/relatlimab and pembrolizumab should be amended to add pancreatic exocrine insufficiency as an undesirable effect with a frequency 'rare' and 'not known', respectively, depending on the number of cases reported from clinical trials. For products where cases of pancreatic failure were not reported (atezolizumab, avelumab, cemiplimab, dostarlimab, tislelizumab, durvalumab, tremelimumab), the product information should be amended to add the information that pancreatic exocrine insufficiency was reported during treatment with other immune-checkpoint inhibitors.

Summary of recommendation(s)

- The MAHs for nivolumab, ipilimumab, nivolumab/relatlimab, pembrolizumab, atezolizumab, avelumab, cemiplimab, dostarlimab, tislelizumab, durvalumab, tremelimumab should submit to EMA, within 60 days, a variation to amend⁵ the product information.

For the full PRAC recommendation, see [EMA/PRAC/147679/2024](#) published on 06 May 2024 on the EMA website.

4.2.4. [Axicabtagene ciloleucel – YESCARTA \(CAP\) - EMEA/H/C/004480/SDA/015;](#)
[idecabtagene vicleucel – ABECMA \(CAP\) - EMEA/H/C/004662/SDA/020;](#)
[lisocabtagene maraleucel – BREYANZI \(CAP\) - EMEA/H/C/004731/SDA/019;](#)
[ciltabtagene autoleucel – CARVYKTI \(CAP\) - EMEA/H/C/005095/SDA/016;](#)
[tisagenlecleucel – KYMRIA \(CAP\) - EMEA/H/C/004090/SDA/024;](#) [brexucabtagene autoleucel – TECARTUS \(CAP\) - EMEA/H/C/005102/SDA/013](#)

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

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of secondary malignancy of T-cell origin

EPITT 20040 – follow up to January 2024

Background

For background information, see PRAC minutes January 2024.

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

Discussion

⁵ Update of SmPC section 4.4. The package leaflet is updated accordingly.

Having considered the available evidence in EudraVigilance and the responses submitted by the MAHs, PRAC considered that further information is needed before a final recommendation is adopted.

Summary of recommendation(s)

- The MAHs for Abecma, Breyanzi, Carvykti, Kymriah, Tecartus and Yescarta should submit to EMA, within 60 days, a response to the list of questions adopted by PRAC, as well to comment on the proposal for amending the product information, Annex II-D, and on the proposed direct healthcare professional communication (DHPC) and communication plan.
- A 30-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.2.5. Chlorhexidine (NAP)⁶ and other relevant fixed-dose combinations⁷

Applicant: various

PRAC Rapporteur: Lina Seibokiene

Scope: Signal of persistent corneal injury and significant visual impairment

EPITT 19970 – Follow-up to February 2024

Background

For background information, see PRAC minutes February 2024.

The MAHs Becton Dickinson France, 3m Deutschland GmbH and Mölnlycke Health Care for Chlorhexidine, both for monocomponent and fixed-combination chlorhexidine containing products 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 data submitted by the MAHs, PRAC agreed that there is sufficient evidence to establish a causal relationship between chlorhexidine-containing medicinal products and persistent corneal injury and significant visual impairment. Therefore, the product information of chlorhexidine monocomponent and fixed-combination containing products indicated for skin disinfection and intended for cutaneous use should be updated to add a warning on persistent corneal injury following accidental ocular exposure to chlorhexidine containing medicinal products, as

⁶ For cutaneous use only

⁷ Chlorhexidine, chlorocresol, hexamidine; chlorhexidine gluconate, chlorocresol, hexamidine; chlorocresol, hexamidine, chlorhexidine digluconate; benzalkonium chloride, chlorhexidine gluconate; chlorhexidine gluconate, benzoxonium chloride, retinol; benzalkonium chloride, chlorhexidine gluconate, benzyl alcohol; chlorhexidine gluconate; chlorhexidine gluconate, cetrimonium; chlorhexidine gluconate, chlorocresol, hexamidine; chlorhexidine gluconate, dexpanthenol; chlorhexidine gluconate, hydrocortisone; chlorhexidine gluconate, hydrogen peroxide, isopropyl alcohol; chlorhexidine gluconate, isopropyl alcohol; chlorhexidine gluconate, ethanol; chlorhexidine gluconate, phenol; benzalkonium chloride, chlorhexidine gluconate; benzalkonium chloride, chlorhexidine digluconate; chlorhexidine digluconate; chlorhexidine digluconate, ethanol; chlorhexidine digluconate, isopropyl alcohol; chlorhexidine dihydrochloride; benzalkonium chloride, chlorhexidine dihydrochloride, isopropyl myristate, liquid paraffin; chlorhexidine dihydrochloride, dexpanthenol; chlorhexidine dihydrochloride, nystatin; chlorhexidine dihydrochloride, nystatin, dexamethasone; chlorhexidine dihydrochloride, nystatin, hydrocortisone; chlorhexidine dihydrochloride, zinc oxide, pramocaine hydrochloride; triamcinolone acetonide; chlorhexidine dihydrochloride, dexpanthenol, alphatocopherol acetate, vitamin A; chlorhexidine gluconate; cetrimide, chlorhexidine digluconate; chlorhexidine acetate; cetrimide, chlorhexidine acetate; retinol palmitate, chlorhexidine acetate; retinol palmitate, benzocaine, retinol, chlorhexidine acetate; bacitracin zinc, chlorhexidine acetate; nystatin, hydrocortisone, chlorhexidine acetate.

well as to add corneal erosion, epithelium defect/corneal injury, significant permanent visual impairment as undesirable effects with a frequency 'not known'.

Summary of recommendation(s)

- The MAHs for chlorhexidine monocomponent and fixed-combination containing products indicated for skin disinfection and intended for cutaneous use should submit to national competent authorities, within 60 days, a variation to update the product information.

For the full PRAC recommendation, see [EMA/PRAC/147679/2024](#) published on 06 May 2024 on the EMA website.

4.2.6. Doxycycline (NAP)

Applicant: various

PRAC Rapporteur: Liana Martirosyan

Scope: Signal of suicidality

EPITT 19997 – follow up to December 2023⁸

Background

For background information, see PRAC minutes December 2023.

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

Discussion

Having reviewed the available evidence from EudraVigilance and the literature, including the data submitted by the MAH, PRAC considered that further information is needed before a final recommendation is adopted.

Summary of recommendation(s)

- The MAH Pfizer Limited as the market leader for doxycycline should submit to EMA, within 3 months, a cumulative review of cases from EudraVigilance related to SMQ Depression and suicide/self-injury with doxycycline as suspect drug, including a causality assessment of all cases using the WHO-UMC causality assessment criteria per case. In addition, the MAH should provide a critical discussion of available published literature including all published case reports, and other relevant scientific literature, as well as on potential mechanisms, and a discussion on the need to update the product information and/or RMP.
- A 90-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.2.7. Ethambutol (NAP)

Applicant: various

PRAC Rapporteur: Sonja Hrabcik

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

⁸ Held on 27-30 November 2023

EPITT 20018 – follow up to December 2023⁹

Background

For background information, see PRAC minutes December 2023.

The MAH Teofarma S.R.L. replied to the request for information on the signal of DRESS and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence in EudraVigilance, literature, including the responses submitted by the MAH, PRAC agreed that there is sufficient evidence to establish a causal relationship between ethambutol and DRESS. Therefore, the product information should be updated to add DRESS as a warning and as an undesirable effect with a frequency 'not known'.

Summary of recommendation(s)

- The MAHs for ethambutol containing products, including in monocomponent and fixed-combinations should submit to national competent authorities, within 60 days, a variation to amend the product information.

For the full PRAC recommendation, see [EMA/PRAC/147679/2024](#) published on 06 May 2024 on the EMA website.

4.2.8. [Exenatide - BYDUREON \(CAP\) - EMEA/H/C/002020/SDA/030.1](#), [BYETTA \(CAP\) - EMEA/H/C/000698/SDA/050.1](#); [Dulaglutide - TRULICITY \(CAP\) - EMEA/H/C/002825/SDA/010.1](#); [Insulin glargine, lixisenatide - SULIQUA \(CAP\) - EMEA/H/C/004243/SDA/009.1](#); [Lixisenatide - LYXUMIA \(CAP\) - EMEA/H/C/002445/SDA/017.1](#); [liraglutide - SAXENDA \(CAP\) - EMEA/H/C/003780/SDA/020.1](#), [VICTOZA \(CAP\) - EMEA/H/C/001026/SDA/040.1](#), [XULTOPHY \(CAP\) - EMEA/H/C/002647/SDA/006.1](#); [Semaglutide - OZEMPIC \(CAP\) - EMEA/H/C/004174/SDA/008.1](#), [RYBELSUS \(CAP\) - EMEA/H/C/004953/SDA/013.1](#), [WEGOVY \(CAP\) - EMEA/H/C/005422/SDA/007.1](#)

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

PRAC Rapporteur: Bianca Mulder

Scope: Signal of suicidal ideation and self-injurious ideation

EPITT 19946 – follow up to December 2023¹⁰

Background

For background information, see PRAC minutes December 2023.

The MAHs replied to the request for information on the signal of suicidal ideation and self-injurious ideation and the responses were assessed by the Rapporteur.

Discussion

⁹ Held on 27-30 November 2023

¹⁰ Held on 27-30 November 2023

Having considered the available evidence from EudraVigilance, literature including the observational studies, non-clinical data, clinical and post-marketing data, as well as the responses from the MAHs, PRAC concluded that current evidence is insufficient evidence to establish a causal relationship between suicidal ideation and the glucagon-like peptide-1 receptor agonists, namely exenatide, liraglutide, dulaglutide, semaglutide, and lixisenatide and that no updates to the product information and/or risk management plan are warranted at present.

Summary of recommendation(s)

- The MAHs for liraglutide-containing products, including Victoza, Saxenda, Xultophy, semaglutide-containing products including Ozempic, Rybelsus, Wegovy (Novo Nordisk A/S), exenatide-containing products including Bydureon, Byetta (AstraZeneca AB), dulaglutide-containing products including Trulicity (Eli Lilly Nederland B.V.) and lixisenatide-containing products incl. Lyxumia, Suliqua (Sanofi Winthrop Industrie) should continue to monitor these events closely including new publications on the subject, as part of routine pharmacovigilance.

For the full PRAC recommendation, see [EMA/PRAC/147679/2024](#) published on 06 May 2024 on the EMA website.

4.2.9. Teriparatide – FORSTEO (CAP) – EMEA/H/C/000425/SDA/053, MOVYMIA (CAP) - EMEA/H/C/004368/SDA/003, TERROSA (CAP) - EMEA/H/C/003916/SDA/003, LIVOGIVA (CAP) - EMEA/H/C/005087/SDA/002, SONDELBAY (CAP) - EMEA/H/C/005827/SDA/002, KAULIV (CAP) - EMEA/H/C/004932/SDA/002, TERIPARATIDE SUN (CAP); NAP - EMEA/H/C/005793/SDA/002

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

PRAC Rapporteur: Tiphaine Vaillant

Scope: Signal of alopecias

EPITT 19972 – Follow-up to October 2023¹¹

Background

For background information, see PRAC minutes October 2023.

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

Discussion

Having considered the available evidence from EudraVigilance, literature and the responses from the MAHs, PRAC concluded that current evidence is insufficient evidence to establish a causal relationship between teriparatide and alopecia and that no updates to the product information and/or risk management plan are warranted at present.

Summary of recommendation(s)

¹¹ Held on 25-28 September 2023

- The MAHs for teriparatide-containing products should continue to monitor these events closely as part of routine pharmacovigilance.

For the full PRAC recommendation, see [EMA/PRAC/147679/2024](https://www.ema.europa.eu/en/PRAC/147679/2024) published on 06 May 2024 on the EMA website.

4.3. Variation procedure(s) resulting from signal evaluation

See Annex I 0

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. Autologous cartilage-derived articular chondrocytes, in-vitro expanded - (CAP MAA) - EMEA/H/C/004594

Scope (pre D-120 phase): repair of symptomatic, localised, full-thickness cartilage defects of the knee joint grade III or IV

5.1.2. Crovalimab - (CAP MAA) - EMEA/H/C/006061

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

5.1.3. Donanemab - (CAP MAA) - EMEA/H/C/006024

Scope (pre D-180 phase): to slow disease progression in adult patients with Alzheimer's disease (AD)

5.1.4. Erdafitinib - (CAP MAA) - EMEA/H/C/006050

Scope (pre D-180 phase): treatment of adult patients with locally advanced unresectable or metastatic urothelial carcinoma (UC)

5.1.5. Macitentan, tadalafil - (CAP MAA) - EMEA/H/C/005001

Scope (pre D-180 phase): treatment of pulmonary arterial hypertension (PAH) in adults patients

5.1.6. Odronextamab - (CAP MAA) - EMEA/H/C/006215, Orphan

Applicant: Regeneron Ireland Designated Activity Company

Scope (pre D-180 phase): treatment of blood cancers (follicular lymphoma (FL) or diffuse large B cell lymphoma (DLBCL) and large B cell lymphoma)

5.1.7. Single-stranded 5' capped mRNA encoding the Respiratory syncytial virus glycoprotein F stabilized in the prefusion conformation - (CAP MAA) - EMEA/H/C/006278

Scope (pre D-180 phase): prevention of lower respiratory tract disease (LRTD) and acute respiratory disease (ARD) caused by respiratory syncytial virus (RSV)

5.1.8. Vorasidenib - (CAP MAA) - EMEA/H/C/006284, Orphan

Applicant: Les Laboratoires Servier

Scope (pre D-120 phase, accelerated assessment): treatment of predominantly non-enhancing astrocytoma or oligodendroglioma with a IDH1 R132 mutation or IDH2 R172 mutation

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

See Annex I 15.2.

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

See also Annex I 15.3.

5.3.1. Filgotinib - JYSELECA (CAP) - EMEA/H/C/005113/II/0031/G

Applicant: Galapagos N.V.

PRAC Rapporteur: Petar Mas

Scope: Grouped application comprising two variations as follows:

Type II (C.I.4): Update of sections 4.8 and 5.1 of the SmPC to update the safety mean duration exposure and efficacy information based on final results (up to Week 432) from study GLPG0634-CL-205 (DARWIN 3) listed as a category 3 study in the RMP (MEA/009); this is a phase II, open-label, long-term follow-up safety and efficacy study to evaluate the long-term safety and tolerability of filgotinib for the treatment of rheumatoid arthritis in patients who received treatment in their parent studies. The RMP version 6.1 has also been submitted.

Type IA (A.6): To change the ATC code for Janus-associated kinase (JAK) inhibitor from L04AA45 filgotinib to L04AF04 filgotinib

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 Jyseleca, a centrally authorised product containing filgotinib, to update the product information based on final results (up to Week 432) from study GLPG0634-CL-205 (DARWIN 3). 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 6.1 for Jyseleca (filgotinib) in the context of the variation under evaluation by CHMP is considered acceptable.
- In addition, PRAC considered that the product information (SmPC section 4.7) should be updated to be in line with QRD v10.4 template.

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.

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.

6.1.1. Abemaciclib - VERZENIOS (CAP) - PSUSA/00010724/202309

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Carla Torre

Scope: Evaluation of a PSUSA procedure

Background

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Verzenios, a centrally authorised medicine containing abemaciclib 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 Verzenios (abemaciclib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include photopsia as an undesirable effect with a frequency 'uncommon'. Therefore, the current terms of the marketing authorisation(s) should be varied¹².
- In the next PSUR, the MAH should perform an analysis of the ratio of serious/non-serious cases of interstitial lung disease (ILD)/pneumonitis, overall ratio from clinical trial sources and yearly post-marketing ratios adjusted for estimated yearly exposure, overall and regional over the years from all sources. In addition, the MAH should continue monitoring and provide updated cumulative reviews of corneal disorders and

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

events of cataracts. Finally, the MAH should discuss the need for update of the product information, as warranted.

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

6.1.2. Avacopan - TAVNEOS (CAP) - PSUSA/00010967/202309

Applicant: Vifor Fresenius Medical Care Renal Pharma France

PRAC Rapporteur: Liana Martirosyan

Scope: Evaluation of a PSUSA procedure

Background

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Tavneos (avacopan) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the existing warning and add drug-induced liver injury (DILI) and vanishing bile duct syndrome (VBDS) as undesirable effects with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied¹³.
- In the next PSUR, the MAH should further analyse the available data with regard to timing of detected abnormal liver function tests and to discuss whether the monitoring advices are adequate to allow early detection of liver toxicity. The MAH should also discuss the need for update of the product information, as warranted.

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

6.1.3. Caplacizumab - CABLIVI (CAP) - PSUSA/00010713/202308

Applicant: Ablynx NV

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

Background

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

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Cablivi, a centrally authorised medicine containing caplacizumab 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 Cablivi (caplacizumab) 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 an analysis about the impact on the risk benefit including a discussion on the reason for delayed ADAMTS13 normalization which is unclear and requires further investigation with respect to the presented literature *Prasannan N, et al, 2023*¹⁴. In addition, the MAH should continue to closely monitor major serious and non-serious bleeding events including information to concomitant medication and provide information on the risk minimization measures effectiveness (i.e. PAC) of (major) bleeding events. The MAH should also continue to closely monitor cardiac disorders and provide a review on serious case reports including presentation of the cases with concomitant medication that might contribute to cardiac disorders, as well as a discussion on the need for update of the product information, as warranted.

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

6.1.4. Cobicistat, elvitegravir, emtricitabine, tenofovir disoproxil - STRIBILD (CAP) - PSUSA/00010082/202308

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

Background

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Stribild, a centrally authorised medicine containing cobicistat/elvitegravir/emtricitabine/tenofovir disoproxil 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 Stribild (cobicistat/elvitegravir/emtricitabine/tenofovir disoproxil) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend a warning/precaution regarding bone effects and add 'bone mineral density decreased' as an undesirable effect with frequency 'common'. Therefore, the current terms of the marketing authorisation(s) should be varied¹⁵.

¹⁴ Prasannan N, Thomas M, Stubbs M, et al. Delayed normalization of ADAMTS13 activity in acute thrombotic thrombocytopenic purpura in the caplacizumab era. *Blood*. 2023 May 4;141(18):2206-2213. doi: 10.1182/blood.2022018847

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

- In the next PSUR, the MAH should continue to closely monitor the risks of 'renal toxicity' and 'bone events due to proximal renal tubulopathy/loss of BMD', focusing also on patients without clear risk factors.

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. [Ebola vaccine \(rDNA, replication-incompetent\) - MVABEA \(CAP\); ZABDENO \(CAP\) - PSUSA/00010857/202309](#)

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

Background

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Mvabea and Zabdeno, centrally authorised medicines containing Ebola vaccine (rDNA, replication-incompetent) 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 Mvabea (Ebola vaccine (rDNA, replication-incompetent)) and Zabdeno (Ebola vaccine (rDNA, replication-incompetent)) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained for Mvabea (Ebola vaccine (rDNA, replication-incompetent)).
- Nevertheless, the product information for Zabdeno (Ebola vaccine (rDNA, replication-incompetent)) should be updated to add a warning/precaution regarding thrombosis with thrombocytopenia syndrome (TTS). Therefore, the current terms of the marketing authorisation(s) should be varied¹⁶.
- In the next PSUR, the MAH should provide a cumulative analysis of thromboembolic events, including potential TTS cases, for the Ad26.ZEBOV program, including TTS/ vaccine-induced immune thrombotic thrombocytopenia (VITT) cases assessed as possible, probable or confirmed per PRAC case definition of TTS.

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. [Emtricitabine, rilpivirine, tenofovir disoproxil - EVIPLERA \(CAP\) - PSUSA/00009142/202308](#)

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Liana Martirosyan

Scope: Evaluation of a PSUSA procedure

¹⁶ 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.

Background

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Eviplera, a centrally authorised medicine containing emtricitabine/rilpivirine/tenofovir disoproxil 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 Eviplera (emtricitabine/rilpivirine/tenofovir disoproxil) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend a warning/precaution regarding bone effects and add 'bone mineral density decreased' as an undesirable effect with frequency 'common'. Therefore, the current terms of the marketing authorisation(s) should be varied¹⁷.
- In the next PSUR, the MAH should monitor fatal outcome cases, including the MedDRA preferred term (PT) death and associated PTs.

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

6.1.7. Enzalutamide - XTANDI (CAP) - PSUSA/00010095/202308

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

Background

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Xtandi, a centrally authorised medicine containing enzalutamide 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 Xtandi (enzalutamide) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add a warning/precaution regarding severe cutaneous adverse reactions (SCARs), and Stevens-Johnson syndrome and hepatic enzymes increased as undesirable effects with a frequency 'not known' and 'uncommon' respectively. Therefore, the current terms of the marketing authorisation(s) should be varied¹⁸.
- In the next PSUR, the MAH should further investigate and discuss the medication error cases, keep monitoring cases of second primary malignancy, acute renal failure, administration of enzalutamide in combination with antiresorptive therapy, seizures, drug reaction with eosinophilia and systemic symptoms (DRESS), interstitial lung

¹⁷ Update of SmPC sections 4.4. and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion.

¹⁸ Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion.

disease (ILD) focusing on the non-Japanese cases, depression including any new cases related to suicide ideation, suicide attempt, completed suicide, intentional overdose, depression suicidal, major depression, and self-injurious ideation, as well as cases of acute hepatic failure and drug-induced liver injury (DILI). In addition, the MAH should provide a summary of cases of non-pathological fractures in which there is concomitant use radium-enzalutamide, as well as cases of fall separated by indication (monotherapy vs combination), if available, including a discussion on the potential mechanism by which enzalutamide may cause fall. The MAH should also provide a discussion on the need for update of the product information, as warranted.

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

6.1.8. Eravacycline - XERAVA (CAP) - PSUSA/00010718/202308

Applicant: Paion Deutschland GmbH

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

Background

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Xerava, a centrally authorised medicine containing eravacycline 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 Xerava (eravacycline) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add a warning/precaution regarding coagulopathy, as well as to add the hypofibrinogenaemia, increased international normalised ratio (INR), prolonged activated partial thromboplastin time (aPTT) and prolonged prothrombin time (PT) as undesirable effects with a frequency 'common'. Therefore, the current terms of the marketing authorisation(s) should be varied¹⁹.

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.

6.1.9. Idecabtagene vicleucel - ABECMA (CAP) - PSUSA/00010954/202309

Applicant: Bristol-Myers Squibb Pharma EEIG, ATMP

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

Background

¹⁹ Update of SmPC sections 4.4 and 4.8. The package leaflet and Annex II are updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion.

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Abecma, a centrally authorised medicine containing idecabtagene vicleucel 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 Abecma (idecabtagene vicleucel) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add immune effector cell-associated neurotoxicity syndrome (ICANS) as a warning and undesirable effect with a frequency 'uncommon'. Therefore, the current terms of the marketing authorisation(s) should be varied²⁰.
- In the next PSUR, the MAH should provide reporting cumulative rates for secondary malignancy.
- The MAH is requested to amend in the RMP the important identified risk from 'neurologic toxicity' to 'neurologic toxicity including ICANS', since ICANS is considered a CAR T cell-specific adverse drug reaction (ADR) which overlaps but remains distinct from overall neurologic toxicity.

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

6.1.10. Maralixibat - LIVMARLI (CAP) - PSUSA/00011032/202309

Applicant: Mirum Pharmaceuticals International B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

Background

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Livmarli, a centrally authorised medicine containing maralixibat 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 Livmarli (maralixibat) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add ALT increased and AST increased as warnings and undesirable effects with a frequency 'common'. Therefore, the current terms of the marketing authorisation(s) should be varied²¹.
- In the next PSUR, the MAH should provide an in-depth discussion of all cases of bleeding events (haemorrhage) and all cases of coagulation disorders, including abnormal results

²⁰ Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion.

²¹ Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion.

of coagulation tests with the data lock point to be 28 March 2024. Moreover, the MAH should discuss the need to update the product information, as warranted.

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

6.1.11. [Mepolizumab - NUCALA \(CAP\) - PSUSA/00010456/202309](#)

Applicant: GlaxoSmithKline Trading Services Limited

PRAC Rapporteur: Gabriele Maurer

Scope: Evaluation of a PSUSA procedure

Background

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Nucala, a centrally authorised medicine containing mepolizumab 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 Nucala (mepolizumab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add Herpes Zoster and arthralgia as undesirable effects with frequency 'uncommon' and 'common' respectively. Therefore, the current terms of the marketing authorisation(s) should be varied²².
- In the next PSUR, the MAH should present a review of the safety topic 'sleep disorder and sleep disturbances', including a review of cases from spontaneous reporting, clinical trials and scientific literature, a statistical analysis and a discussion of a potential pathomechanism. In addition, the MAH should continue monitoring and report on cases of life-threatening and fatal cases in EGPA patients including a comparison of reporting rates over the different indications, as well as of the rate of fatal cases in patients treated with the diagnosis HES. The MAH should also propose methods to improve the approach regarding the inquiry with questionnaires for the important potential risk 'alterations in cardiovascular safety'.

The frequency of PSUR submission should be revised from six-monthly 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.

6.1.12. [Nonacog alfa - BENEFIX \(CAP\) - PSUSA/00002183/202308](#)

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Gabriele Maurer

Scope: Evaluation of a PSUSA procedure

²² 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.

Background

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Benefix, a centrally authorised medicine containing nonacog alfa 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 Benefix (nonacog alfa) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.

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.

6.1.13. Ofatumumab - KESIMPTA (CAP) - PSUSA/00010927/202309

Applicant: Novartis Ireland Limited

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

Background

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Kesimpta, a centrally authorised medicine containing ofatumumab 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 Kesimpta (ofatumumab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend a warning regarding injection-related reactions and to add nausea and vomiting as undesirable effects with a frequency common. Therefore, the current terms of the marketing authorisation(s) should be varied²³.
- In the next PSUR, the MAH should continue monitoring cases of cytopenia including neutropenia, cardiovascular events, severe mucocutaneous reactions, bowel obstruction including appendicitis, immunogenicity, loss of consciousness and cardiac events occurring <48 hours after ofatumumab injection, as well as sepsis and pneumonia including an explanation of the term 'non-serious sepsis' used in clinical studies, an in-depth discussion on the role of diabetes as a strong confounding factor and follow up information on Case NVSC2022US241260. In addition, the MAH should discuss nausea and vomiting events to characterise the occurrence, timing and co-reported events. The MAH should also conduct separate assessment of cases reporting PML cases and JCV infection, as well as to retrieve new information on pregnancy cases which outcome is pending.

²³ Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion.

The 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.

6.1.14. Vosoritide - VOXZOGO (CAP) - PSUSA/00010952/202308

Applicant: BioMarin International Limited

PRAC Rapporteur: Zane Neikena

Scope: Evaluation of a PSUSA procedure

Background

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Voxzogo, a centrally authorised medicine containing vosoritide 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 Voxzogo (vosoritide) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add hypertrichosis as an undesirable effect with a frequency 'uncommon'. 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.

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

See also Annex I 16.2.

6.2.1. Duloxetine - CYMBALTA (CAP); DULOXETINE LILLY (CAP); YENTREVE (CAP); NAP - PSUSA/00001187/202308

Applicant: Eli Lilly Nederland B.V. (Cymbalta, Duloxetine Lilly, Yentreve), various

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

Background

Duloxetine is an oral dual serotonin and norepinephrine reuptake inhibitor (SNRI) that enhances serotonin and norepinephrine neurotransmission, indicated for adult patients with depression, generalised anxiety disorder (GAD), diabetic peripheral neuropathic pain (DPNP) and stress urinary incontinence (SUI) in women.

²⁴ Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of Cymbalta, Duloxetine Lilly and Yentreve, centrally authorised medicines containing duloxetine, and nationally authorised medicines containing duloxetine 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 duloxetine-containing product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the warning about serotonergic syndrome and to add the information about the neuroleptic malignant syndrome (NMS), as well as to add stress cardiomyopathy (Takotsubo cardiomyopathy) as an undesirable effect with frequency 'not known'. Therefore, the current terms of the marketing authorisations should be varied²⁵.
- In the next PSUR, the MAHs should provide a cumulative review of rhabdomyolysis cases in which a potential interaction with statins could be referred, and of cases of NMS related to duloxetine withdrawal. In addition, the MAHs should provide a cumulative review of cases of dry eye and of neonatal hypoglycaemia including information from all sources (clinical trials, post-marketing experience, literature) and discussing if the latter problem could be part of the neonatal withdrawal syndrome, as well as the need to update the product information about both as warranted. The MAHs should also provide a cumulative review of the use of duloxetine in the paediatric population and the associated risks (in particular suicide-related behaviours and hostility) discussing specifically risk minimisation measures (RMMs) and their effectiveness, with a focus on the risk of suicide-related behaviours and hostility discussing also any additional RMMs that would be deemed necessary to further mitigate these risks and inform competent authorities prior to the next PSUR submission if any impact on the marketing authorisations as warranted. Furthermore, the MAHs should discuss the signal of pulmonary hypertension as an important potential risk, keep providing the publications regarding fractures and spontaneous abortion, and continue to closely monitor serious cardiovascular events and events with fatal outcome due to cardiac events as important potential risk, splitting the cases by ischaemic heart disease, cardiac arrhythmias and especially QT prolongation and cardiac arrest, as well to provide the narrative of fatal cases related to the important identified risk suicidality for the next PSUR.

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.

6.2.2. Mercaptopurine - XALUPRINE (CAP); NAP - PSUSA/00001988/202309

Applicant: Nova Laboratories Ireland Limited (Xaluprine), various

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

Background

²⁵ Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion.

Mercaptopurine is an inactive pro-drug which acts as a purine antagonist but requires cellular uptake and intracellular anabolism to thioguanine nucleotides (TGNs) for cytotoxicity, indicated for the treatment of acute lymphoblastic leukaemia (ALL) in adults, adolescents and children.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of Xaluprine, a centrally authorised medicine containing mercaptopurine, and nationally authorised medicines containing mercaptopurine 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 mercaptopurine-containing product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add stomatitis, cheilitis, mucosal inflammation and coagulation factors decreased as undesirable effects with a frequency 'not known', to add pellagra as a warning and undesirable effect with a frequency 'not known', amend the information regarding cholestasis of pregnancy, and to add the drug-drug interaction of infliximab and methotrexate. Therefore, the current terms of the marketing authorisations should be varied²⁶.
- In the next PSUR, the MAH Nova should closely monitor medication errors related to conversion errors discussing also in terms of root cause analysis and effectiveness of the risk minimisation measures (RMMs), while should also discuss the need for further RMMs, as warranted.

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

6.2.3. Zoledronic acid²⁷ - ZOLEDRONIC ACID HOSPIRA (SRD) (CAP); ZOLEDRONIC ACID MEDAC (CAP); ZOMETA (CAP); NAP - PSUSA/00003149/202308

Applicant: Pfizer Europe MA EEIG (Zoledronic acid Hospira (SRD)), medac Gesellschaft für klinische Spezialpräparate mbH (Zoledronic acid medac), Phoenix Labs Unlimited Company (Zometa), various

PRAC Rapporteur: Karin Erneholm

Scope: Evaluation of a PSUSA procedure

Background

Zoledronic acid is a third-generation bisphosphonate which primarily act on bone, indicated for prevention of skeletal related events in adult patients with advanced malignancies involving bone, treatment of tumour-induced hypercalcaemia and osteoporosis.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of Zoledronic Acid Hospira (SRD), Zoledronic Acid Medac and Zometa, centrally authorised

²⁶ Update of SmPC sections 4.4, 4.5, 4.6 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion.

²⁷ For cancer and fractures indications only

medicines containing zoledronic acid²⁷, and nationally authorised medicines containing zoledronic acid²⁷ 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 zoledronic acid-containing product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add tubulointerstitial nephritis as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisations should be varied²⁸.
- In the next PSUR, the MAHs should provide a cumulative review on zoledronic acid and drug-induced liver injury (DILI) and related terms, on glomerulus related adverse events including, but not restricted, to 'glomerulopathy', 'glomerulonephritis', and 'glomerulosclerosis' after treatment with zoledronic acid, as well as discuss the need to update the product information, as warranted. In addition, the MAH Ennogen should provide a revised and up-to-date list of safety concerns along with a justification for any change or not. Finally, the MAH Pfizer should continue to characterise the remaining/not agreed to be removed risks and provide a justification to request any further removal.

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

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

See also Annex I 16.2.1.

6.3.1. Bromazepam (NAP) - PSUSA/00000435/202308

Applicant(s): various

PRAC Lead: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

Background

Bromazepam is a benzodiazepine, a central nervous system (CNS)-active compound and is indicated for the management of anxiety, tension and other somatic or psychiatric complaints associated with the anxiety syndrome, for adjunctive use for treatment of anxiety or excitation associated with psychological disorders, such as mood disorders or schizophrenia, as well as for prevention and treatment of delirium tremens and other manifestations of alcohol withdrawal and insomnia.

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

Summary of recommendation(s) and conclusions

²⁸ 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 bromazepam-containing medicinal products in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAHs should provide an in-depth analysis of literature data regarding the risk of dementia including a thorough discussion of the limitations and biases of these studies in order to better characterise this important potential risk and the potential relationship between bromazepam and dementia. The MAHs are also requested to provide a cumulative review of glaucoma, intraocular pressure increased and related MedDRA preferred terms (PTs) including a literature review, an analysis of all potential confounding factors and risk factors, as well as a discussion on the need to update the product information, as warranted. In addition, the MAHs should provide a discussion on the need to add an information about the risk of small gestational age (SGA) to the product information to ensure the best possible monitoring of the foetus, analyse cases of malformations with bromazepam to assess whether or not there is an over-representation of a type of malformation, analyse the available data in cumulative period on the risk of neurodevelopmental disorders following exposure to bromazepam and benzodiazepines. Finally, the MAHs should continue to closely monitor the risk of pneumonia and related PTs (as pneumonia aspiration) as well as the risk of hepatitis and discuss any new data, and to continue closely monitor of off-label use in paediatrics and the risk of miscarriage following exposure to bromazepam and benzodiazepines.

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

6.3.2. [Dexibuprofen \(NAP\) - PSUSA/00000996/202308](#)

Applicant(s): various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

Background

Dexibuprofen is a pharmacologically active enantiomer of racemic ibuprofen, a non-steroidal substance with anti-inflammatory and analgesic effects indicated for the symptomatic treatment for the relief of pain and inflammation associated with osteoarthritis, acute symptomatic treatment of pain during menstrual bleeding (primary dysmenorrhoea) and symptomatic treatment of other forms of mild to moderate pain, such as muscular-skeletal pain or dental pain.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing dexibuprofen 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 dexibuprofen-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 an undesirable effect with a frequency 'not known' and to amend the warning on severe cutaneous adverse reactions (SCARs) and add SCARs (including erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis) and drug reaction with eosinophilia and systemic symptoms (DRESS syndrome) including acute generalised exanthematous pustulosis (AGEP) as undesirable effects with frequencies 'very rare' and 'not known', respectively. Therefore, the current terms of the marketing authorisation(s) should be varied²⁹.

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. Dienogest, estradiol³⁰ (NAP) - PSUSA/00010444/202309

Applicant(s): various

PRAC Lead: Bianca Mulder

Scope: Evaluation of a PSUSA procedure

Background

Dienogest/estradiol is a combined oral contraceptive.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing dienogest/estradiol 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 dienogest/estradiol-containing medicinal products 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.

6.3.4. Lithium (NAP) - PSUSA/00001897/202308

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

Lithium is a mood stabilising medicine indicated for the treatment of manic phase in bipolar disorder, of manic-depressive episodes in bipolar disorder, of aggressive or self-mutilating behaviour, as an adjuvant treatment in resistant major depression in patients who have not

²⁹ 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.

³⁰ For contraception indication only

had an optimal response to antidepressant treatment, as well as for prophylaxis of both the manic and depressive phases of bipolar disorder and the prevention of repeated unipolar depressive episodes.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing lithium 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 lithium-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add Brugada syndrome as a warning and an undesirable effect with a frequency 'not known', to add hypercalcaemia as an undesirable effect with a frequency 'very frequent', and hyperparathyroidism, parathyroid adenoma, parathyroid hyperplasia and drug reaction with eosinophilia and systemic symptoms (DRESS) as undesirable effects with a frequency 'not known'. In addition, the product information should be updated to amend the warning regarding lithium toxicity following bariatric surgery and add a drug-drug interaction (DDI) with topiramate. Therefore, the current terms of the marketing authorisation(s) should be varied³¹.
- In the next PSUR, the MAHs should provide a cumulative review for the DDI between topiramate and lithium, as well as on Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) cases, and for the occurrence of akathisia associated with lithium therapy. The MAHs should further review fatalities due to lithium toxicities with a view to establish a threshold for lithium plasma concentrations above which fatalities can occur, as well as to provide a cumulative review on the unmasking and/or aggravation of Brugada syndrome in association with lithium use and discuss how to best minimise this risk based on the totality of available data. In addition, the MAHs should continue to closely monitor cases of leukaemia, hyperleukocytosis, papillary thyroid cancer, sinoatrial block, sinus arrest, atrioventricular block complete and rhabdomyolysis. Finally, the MAHs should discuss any need to update the product information, as warranted.

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

6.3.5. Naloxone, oxycodone (NAP) - PSUSA/00002114/202308

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

Naloxone/oxycodone is a combination of opioid analgesics indicated in adults for the treatment of severe pain requiring the use of an opioid analgesic and as a second-line

³¹ Update of SmPC sections 4.4, 4.5 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position.

symptomatic treatment of patients with severe to very severe idiopathic restless legs syndrome (RLS) after failure of dopaminergic therapy.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of naloxone/oxycodone-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add a warning regarding hepatobiliary disorders including sphincter of Oddi dysfunction, and to add information about interactions of opioids with anticholinergics or medications with anticholinergic activity. Therefore, the current terms of the marketing authorisation(s) should be varied³².
- In the next PSUR, the MAH should provide a follow-up trend analysis of naloxone/oxycodone cases aggregately reported under the standardised MedDRA query (SMQ) 'drug abuse, dependence and withdrawal', as well as cases reported under the separate preferred terms (PTs) 'drug dependence', 'withdrawal syndrome', 'drug withdrawal syndrome' as well as 'drug abuse' and 'overdose', from 2012 onwards, within the EEA countries excluding UK and Switzerland, stratifying all data based on the indication (cancer pain and non-cancer pain, in particular in patients with rheumatic disease; restless legs syndrome). Results should be presented for all EEA countries as well as broken down by individual EEA country of origin and by year. Data should be also provided for serious, non-serious, total and fatal events.
- The MAH should also discuss the publication by *Langford et al. 2023*³³ and evaluate the need for an update of the product information (e.g., regarding information about a plan for end of treatment [SmPC Section 4.2], risk of opioid use disorder [SmPC section 4.4], etc.).
- In addition, the FDA issued a Drug Safety Communication³⁴ on 13 April 2023 requiring several updates to the prescribing information of opioid pain medicines, including a warning about opioid-induced hyperalgesia and allodynia. Currently, allodynia is not addressed in the product information of OXN. Therefore, the MAH should evaluate hyperalgesia and allodynia as a signal.
- The list of safety concerns in the next PSUR should include the important identified risks of accidental overdose, physical dependence and drug withdrawal syndrome (DWS), drug abuse, and psychological dependence, as well as the missing information use in pregnant and lactating women as safety concerns in the next PSUR.
- Finally, the MAH should discuss any need to update the product information, as warranted.

³² Update of SmPC sections 4.4 and 4.5. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position.

³³ Langford AV, Lin CC, Bero L, Blyth FM, Doctor J, Holliday S, Jeon YH, Moullin J, Murnion B, Nielsen S, Osman R, Penm J, Reeve E, Reid S, Wale J, Schneider CR, Gnjudic D. Clinical practice guideline for deprescribing opioid analgesics: summary of recommendations. *Med J Aust.* 2023 Jul 17;219(2):80-89.

³⁴ <https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-prescribing-information-all-opioid-pain-medicines-provide-additional-guidance-safe-use>

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

6.3.6. Naproxen (NAP) - PSUSA/00002125/202308

Applicant(s): various

PRAC Lead: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

Background

Naproxen is a non-steroidal anti-inflammatory (NSAID) non-selective COX1-2 inhibitor with analgesic, anti-inflammatory and antipyretic properties, indicated for the symptomatic treatment of pain and inflammation due to various conditions, dysmenorrhea and migraine, subject to certain conditions.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing naproxen 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 naproxen-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information of the systemic formulations should be updated to add drug reaction with eosinophilia and systemic symptoms (DRESS) as a warning as well as to add DRESS and fixed drug eruption (FDE) as undesirable effects with a frequency 'not known'. For naproxen-containing medicinal products for topical use, the product information should be amended to add a contraindication and a warning about the use in pregnancy. Therefore, the current terms of the marketing authorisation(s) should be varied³⁵.
- In the next PSUR, the MAHs for naproxen-containing medicines for systemic formulations should submit a cumulative review of the impact of naproxen in male fertility, of complications of infections with a treatment of naproxen for fever rheumatologic pain, of all cases of hepatic damage with naproxen using the MedDRA high level terms (HLT) hepatocellular damage and hepatitis, hepatobiliary function diagnostic procedure and the preferred terms (PTs) hepatic function abnormal, hypertransaminasaemia, hepatitis cholestatic, hepatic failure, cholangitis and cholangitis acute. In addition, the MAHs for naproxen-containing medicines for systemic formulations should provide a cumulative review of cases of reporting events of venous thromboembolism with use of naproxen and hormonal contraceptives and provide a discussion on the impact of the available evidence on the benefit/risk of systemic naproxen. Finally, the MAHs for naproxen-containing medicines for systemic

³⁵ Update of SmPC sections 4.3, 4.4, 4.6 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position.

formulations should also discuss the need for any potential amendments to the product information and a proposal for additional risk minimisation measures, as warranted.

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

6.3.7. Permethrin (NAP) - PSUSA/00002355/202308

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

Permethrin is a pyrethroid insecticide indicated for the treatment of treatment of head lice (*Pediculus capitis*), of scabies (caused by *Sarcoptes scabiei*) and of crab lice (caused by *Pthirus pubis*).

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing permethrin 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 permethrin-containing medicinal products in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAHs should continue to address the important identified risks of hypersensitivity and anaphylaxis, and neurotoxicity, the important potential risks development of resistance, pregnancy and lactation, Parkinson's disease and carcinogenic/mutagenic potential, as well as the missing information related to the use in newborns and infants up to the age of 2 months and the use in infants aged 2 to 23 (36) months. In addition, the MAHs should address the topic of autism including all relevant MedDRA preferred terms (PTs).

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. Trimetazidine (NAP) - PSUSA/00003043/202308

Applicant(s): various

PRAC Lead: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

Background

Trimetazidine is a metabolic agent acting on the myocardial cells, indicated as add-on therapy for the symptomatic treatment of patients with stable angina pectoris who are inadequately controlled by, or intolerant to, first-line antianginal therapies.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing trimetazidine 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 trimetazidine-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add drug reaction with eosinophilia and systemic symptoms (DRESS) as a warning and add DRESS and paraesthesia as undesirable effects with frequency 'not known' and 'uncommon' respectively. Therefore, the current terms of the marketing authorisation(s) should be varied³⁶.
- In the next PSUR, the MAHs should continue to closely monitor events of dyspnoea through internal signal detection process providing also a literature review, as well as of syncope and hyperhidrosis.

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.

6.3.9. Vincristine (NAP) - PSUSA/00003121/202308

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

Vincristine is a vinca alkaloid with antineoplastic effect, indicated for the treatment of several malignancies like primarily as a component of various chemotherapeutic regimens for the treatment of acute leukaemias, as well as in conjunction with other oncology drugs in the treatment of Hodgkin's Disease, all forms of lymphoma, Wilm's tumour, sarcomas and tumours of the breast, brain and lung.

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

³⁶ 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.

- Nevertheless, the product information should be updated to add (an) interaction(s) with azole antifungals and also add it as warning. Therefore, the current terms of the marketing authorisation(s) should be varied³⁷.
- In the next PSUR, the MAHs should provide a cumulative review of interstitial lung disease, and discuss the need to update the product information as warranted. In addition, the MAHs should discuss administration error (intrathecal injection) as important identified 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.

6.3.10. Zolpidem (NAP) - PSUSA/00003151/202308

Applicant(s): various

PRAC Lead: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

Background

Zolpidem is a benzodiazepine-like hypnotic agent, indicated for the short-term treatment of insomnia in adults in situations where the insomnia is debilitating or is causing severe distress for the patient.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing zolpidem 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 zolpidem-containing medicinal products in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAHs should add drug abuse and dependence as important identified risk and continue to monitor cases of psychiatric and paradoxical reactions, long QT syndrome, dementia/dementia Alzheimer type, abuse/dependence and illicit use/chemical submission.

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

6.4. Follow-up to PSUR/PSUSA procedures

See Annex I 16.3.1.

³⁷ Update of SmPC sections 4.4 and 4.5. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position.

6.5. Variation procedure(s) resulting from PSUSA evaluation

See Annex I 16.4.1.

6.6. Expedited summary safety reviews³⁸

None

7. Post-authorisation safety studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)³⁹

See Annex I 17.1.

7.2. Protocols of PASS non-imposed in the marketing authorisation(s)⁴⁰

See Annex I 17.1.1.

7.3. Results of PASS imposed in the marketing authorisation(s)⁴¹

See Annex I 17.2.1.

7.4. Results of PASS non-imposed in the marketing authorisation(s)⁴²

See also Annex I 17.3.1.

7.4.1. Belimumab - BENLYSTA (CAP) - EMEA/H/C/002015/II/0116

Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Mari Thorn

Scope: Submission of the final report for the Belimumab Pregnancy registry (BEL114256) listed as a category 3 study in the RMP. This is a non-interventional study to evaluate pregnancy and infant outcomes for pregnancies in women with systemic lupus erythematosus (SLE) exposed to commercially supplied belimumab within the 4 months preconception and/or during pregnancy. In addition, the BPR protocol planned to collect pregnancy and infant outcomes for pregnancies in women with systemic lupus erythematosus (SLE) and safety and effectiveness of belimumab in systemic lupus erythematosus (SABLE) protocol who were not exposed to belimumab and enrolled in BPR. The RMP version 45.0 has also been submitted

Background

³⁸ 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

³⁹ In accordance with Article 107n of Directive 2001/83/EC

⁴⁰ 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

⁴¹ In accordance with Article 107p-q of Directive 2001/83/EC

⁴² In accordance with Article 61a (6) of Regulation (EC) No 726/2004, in line with the revised variations regulation for any submission as of 4 August 2013

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

As stated in the [RMP](#) of Benlysta (belimumab), the MAH conducted a non-imposed non-interventional PASS (BEL114256) to evaluate pregnancy and infant outcomes following Benlysta (belimumab) exposure and health status of live born infants. The Rapporteur assessed the MAH's final study report in addition to the MAH's answers to the request for supplementary information (RSI). For further background, see [PRAC minutes November 2023](#).

Summary of advice

- Based on the available data, the MAH's responses to the RSI and the Rapporteur's review, PRAC considered that the ongoing variation assessing the final study report could be recommended for approval.
- PRAC considered that the product information (PI) should be updated to reflect the presently available data on pregnancy exposure in woman exposed to belimumab. However, the current data are too limited to confirm a causal relationship between belimumab and birth defects, and thus the current recommendation in the PI that 'Benlysta should not be used during pregnancy unless the potential benefit justifies the potential risk to the foetus' remains appropriate.

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

See Annex I 17.4.1.

7.6. Others

None

7.7. New Scientific Advice

None

7.8. Ongoing Scientific Advice

None

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

None

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

8.1. Annual reassessments of the marketing authorisation

See Annex I 18.1.

8.2. Conditional renewals of the marketing authorisation

See Annex I 18.1.1.

8.3. Renewals of the marketing authorisation

See Annex I 18.2.1.

9. Product related pharmacovigilance inspections

9.1. List of planned pharmacovigilance inspections

None

9.2. Ongoing or concluded pharmacovigilance inspections

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

9.3. Others

None

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

10.1. Safety related variations of the marketing authorisation

10.1.1. Semaglutide – RYBELSUS (CAP) - EMEA/H/C/4953/X/0038

Applicant: Novo Nordisk A/S

PRAC Rapporteur (for product): Mari Thorn

PRAC Rapporteur (for procedure): Bianca Mulder

Scope: Consultation of PRAC on a DHPC and communication plan in the framework of a line extension to introduce new strengths of tablets for Rybelsus (semaglutide)

Background

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

A line extension proposing to introduce new strengths of tablets for Rybelsus (semaglutide) is under evaluation at CHMP. PRAC was requested to provide advice on this variation.

Summary of advice

- Based on the review of the available information, PRAC agreed with CHMP that, in case of a positive CHMP opinion of this line extension, there is a need for a direct healthcare

professional communication (DHPC) which should be circulated to target healthcare professionals (HCPs) to inform them on the new formulation and the associated measures put in place to avoid the risk of medication errors due to formulation mix-ups once the new formulation will be placed in the EU Member States and during the temporary period of time during which the current and new formulations will co-exist in the EU market. PRAC reviewed and agreed with the content of the DHPC and the communication plan highlighting that the message that 'Rybelsus should always be used as one tablet per day' should be included prominently in the DHPC. Moreover, it was also discussed and agreed that pharmacists should be included as recipients for the DHPC, as well as prescribing HCPs.

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. Ibuprofen; ibuprofen lysine; ibuprofen, caffeine; ibuprofen, pseudoephedrine hydrochloride; ibuprofen, drotaverine hydrochloride (NAP) - CZ/H/XXXX/WS/075

Applicant(s): Opella Healthcare Czech s.r.o

PRAC Lead: Jana Lukacisinova

Scope: PRAC consultation on work sharing variation to update the product information of ibuprofen-containing products in order to add a risk of renal tubular acidosis and hypokalaemia and overdose based on the MHRA review, on request of Czech Republic

Background

Ibuprofen and ibuprofen lysine are non-steroidal anti-inflammatory drugs (NSAID) used as an anti-inflammatory and analgesic product for a variety of indications and specifically for pain of various origin and nature (headache, toothache, neuralgia, osteoarticular and muscular pain, menstrual pain) and as an adjuvant in common cold or influenza for the symptomatic relief of pain and fever, as well as for inflammatory forms of rheumatism such as rheumatoid arthritis, ankylosing spondylitis and Still's disease, subject to certain conditions.

In the context of the evaluation of a work sharing variation to update the product information of ibuprofen-containing products in order to add a risk of renal tubular acidosis and hypokalaemia and overdose based on the MHRA review, Czech Republic requested PRAC advice on its assessment.

Summary of advice

- Based on the review of the available information, PRAC agreed with the evaluation of the reference member state (RMS) with few suggestions, recommending amendments to the product information (PI) of ibuprofen, ibuprofen lysine, ibuprofen/caffeine, ibuprofen/pseudoephedrine hydrochloride and ibuprofen/drotaverine hydrochloride (SmPC section 4.9 and PL section 3) in order to add information related to the prolonged use at higher than recommended doses or overdose which may result in renal tubular acidosis and hypokalaemia. PRAC also agreed that the data and PI amendments in the framework of variation CZ/H/XXXX/WS/075 may be relevant for other systemic ibuprofen-containing products.

11.2. Other requests

None

12. Organisational, regulatory and methodological matters

12.1. Mandate and organisation of PRAC

12.1.1. Mandate of PRAC Chairperson and Vice-Chairperson – call for nominations

The mandate of the PRAC Chair, Sabine Strauss, will expire on 2 September 2024 and that of the PRAC Vice-Chair, Martin Huber on 30 September 2024.

The elections of a new PRAC Chair will take place at the July 2024 PRAC meeting and that of the new Vice-Chair at the September 2024 PRAC meeting.

Expressions of interest should be sent to the Agency, to the PRAC secretariat. Candidates are kindly asked to submit a brief CV in support of their candidature together with a cover letter highlighting their expertise.

12.1.2. PRAC membership

None

12.1.3. Vote by proxy

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

12.2. Coordination with EMA Scientific Committees or CMDh-v

None

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

None

12.4. Cooperation within the EU regulatory network

12.4.1. EMA review of seasonal influenza vaccines enhanced safety surveillance systems - interim guidance

PRAC leads: Jean Michel Dogné, Nathalie Gault, Gabriele Mauer, Maria del Pilar Rayon, David Olsen

During the PRAC plenary meeting in April 2024, PRAC agreed to waive the requirement to submit enhanced safety surveillance data for all seasonal influenza vaccines (both national and centrally approved) while the 'Interim guidance on enhanced safety surveillance for seasonal influenza vaccines in the EU' ([EMA/PRAC/222346/2014](#)) is under review.

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

12.4.3. PRAC strategic review and learning meeting (SRLM) under the Belgium presidency of the European Union (EU) Council – Hulpe, Belgium, 27 - 29 May 2024 - agenda

PRAC lead: Jean-Michel Dogné, Jo Robays

PRAC was informed on the final agenda for the 'PRAC strategic review and learning meeting (SRLM)', to be held on 27-29 May 2024 in Hulpe, Belgium, under the Belgian presidency of the Council of the European Union (EU). The topics to be discussed cover Artificial Intelligence in Pharmacovigilance activities, pharmacovigilance in pregnancy and additional risk minimisation measures, as well as different perspectives of pharmacovigilance at EU level during crisis and normal times.

12.5. Cooperation with International Regulators

None

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

12.6.1. PRAC and WHO pharmacovigilance team enhanced engagement and collaboration in Article 58 procedures

PRAC lead: Sabine Straus

Following discussions that started in June 2022 during the PRAC SRLM meeting in Paris, France, PRAC has included in the 2024 workplan an objective to enhance engagement and collaboration between PRAC and WHO pharmacovigilance team for EUM4all procedures (also referred to as Article 58 procedures). At the organisational, regulatory and methodological matters (ORGAM) meeting on 25 April 2024, the EMA Secretariat presented the current processes in place at CHMP level for involving WHO appointed National Regulatory Agencies (NRA) experts in initial applications for EUM4all procedures, including the roles and the responsibilities of the functions involved. In order to optimize the process at the level of

PRAC, a pilot will be initiated in the following months in the context of an initial marketing authorisation application. Importantly, nominations of pharmacovigilance experts at NRA levels are required to start the pilot. The timelines and the milestones were presented to the Committee. PRAC welcomed the initiative and flagged the importance of the training and knowledge sharing with the NRA experts.

12.7. PRAC work plan

None

12.8. Planning and reporting

12.8.1. Marketing authorisation applications (MAA) forecast for 2024 – planning update dated Q1 2024

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

12.8.2. MAAs 3-year forecast report for March 2024 - December 2026

At the organisational, regulatory and methodological matters (ORGAM) meeting on 25 April 2024, the EMA Secretariat presented the 3-year forecast report on marketing authorisation applications planned for submission (the business 'pipeline') in the period 2024-2026 for information to PRAC. PRAC noted the information.

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

None

12.10.3. PSURs repository

None

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

In line with the criteria for plenary presentation of updates to the EURD List adopted by PRAC in December 2021, PRAC endorsed the draft revised EURD list, version April 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 April 2024, the updated EURD list was adopted by CHMP and CMDh at their April 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

None

12.12. Adverse drug reactions reporting and additional monitoring

12.12.1. Management and reporting of adverse reactions to medicinal products

None

12.12.2. Additional monitoring

None

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

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

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

12.13. EudraVigilance database

12.13.1. Activities related to the confirmation of full functionality

None

12.14. Risk management plans and effectiveness of risk minimisations

12.14.1. Risk management systems

None

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

None

12.15. Post-authorisation safety studies (PASS)

12.15.1. Post-authorisation Safety Studies – imposed PASS

None

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

None

12.16. Community procedures

12.16.1. Referral procedures for safety reasons

None

12.17. Renewals, conditional renewals, annual reassessments

None

12.18. Risk communication and transparency

12.18.1. Public participation in pharmacovigilance

None

12.18.2. Safety communication

None

12.19. Continuous pharmacovigilance

12.19.1. Incident management

None

12.20. Impact of pharmacovigilance activities

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

PRAC lead: Sabine Straus

The EMA Secretariat presented to PRAC the final draft of the Good pharmacovigilance practice (GVP) module XVI on 'Risk minimisation measures: selection of tools and effectiveness indicators' – revision 3. The EMA Secretariat summarised the comments received during the public consultation in 2021 and highlighted the main areas of clarifications needed based on the comments received. The document has been revised for clarity, underpinned by clarified terminology and guidance, with a clearer document structure overall. The PRAC members are invited to provide their comments in writing by 23 May 2024. The target date for publication of the GVP module XVI revision 3 is August 2024.

12.21. Others

12.21.1. EU NTC training webinar on the regulatory/Health Technology Assessment (HTA) interface under the HTA Regulation

PRAC was informed about the EU NTC webinar on the regulatory/HTA interface under the HTA Regulation that will be held virtually on 2nd May 2024. The agenda will cover an overview of the new HTA Regulation, outline of collaboration between regulators and HTAs under the new legal framework, followed by mutual learning about the respective assessment scopes. PRAC noted the information.

12.21.2. Guideline on risk assessment of medicinal products on human reproduction and lactation: from data to labelling – concept paper on revision of the guideline

PRAC lead: Ulla Wändel Liminga

The EMA Secretariat presented to PRAC an update on the joint CHMP-PRAC activity regarding drafting the concept paper on revision of the Guideline on Risk Assessment of Medicinal Products on Human Reproduction and Lactation: from Data to Labelling. The objective of this activity, presented in both CHMP and PRAC workplans for 2024, is to strengthen systematic generation of information on the benefits and risks of medicines in pregnancy and breastfeeding, considering the developments in the non-clinical field and post-authorisation data, among others, and ensuring alignment with other relevant guidelines. The EMA Secretariat presented the activity of the drafting group, timelines, including past and future milestones. PRAC noted the information and agreed proceeding with the next steps, i.e. public consultation. PRAC will be updated in due course with the outcome of the public consultation.

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

PRAC lead: Liana Martirosyan

At the organisational, regulatory and methodological matters (ORGAM) meeting on 25 April 2024, the PRAC Lead presented to PRAC the report on the activity of the drafting group on the risks of dependence and addiction of opioids, including the feedback received from PRAC members following the discussion at PRAC ORGAM in January 2024. For background, see [PRAC minutes January 2024](#). The feedback showed that there is a clear wish to contain opioid use disorder (OUD) risks at EU level. PRAC highlighted the importance of the work done by the drafting group and the valuable knowledge and information collected since the start of this initiative, including feedback from various stakeholders. PRAC considered that further discussions are needed in order to decide what would be the most appropriate way to move forward. PRAC will be updated on further developments.

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

The EMA Secretariat presented to PRAC a summary of the activity of DARWIN EU® in the past 2 years, including a summary of completed, ongoing and planned studies. Following the previous discussions and recommendations from the 2023 RWD study report, where the need to explore possibilities for early identification of RWE needs and to accelerate RWD generation was highlighted, the EMA Secretariat presented to PRAC a proposal to take this forward as a pilot in the context of the PSUSA procedures. PRAC noted that further discussions are needed mainly related to the process, including timelines, roles and responsibilities, additional workload related to the review of study protocols and results, as well as to the appropriate regulatory framework to address particular cases such as class effects or multiple active substances. PRAC agreed to move forward with the proposal. The EMA Secretariat will revisit the process once more experience is gained and will report back to PRAC in case further adjustments are needed.

13. Any other business

Next meeting on: 13-16 May 2024

14. Annex I – Signals assessment and prioritisation⁴³

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 timetables⁴⁴.

⁴³ 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

⁴⁴ Either MAH(s)'s submission within 60 days followed by a 60 day-timetable assessment or MAH's submission cumulative review within an ongoing or upcoming PSUR/PSUSA procedure (if the DLP is within 90 days), and no disagreement has been raised before the meeting

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

14.1.1. Anakinra – KINERET (CAP)

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Karin Erneholm

Scope: Signal of amyloidosis

EPITT 20073 – New signal

Lead Member State(s): DK

14.1.2. Apalutamide – ERLEADA (CAP)

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Tiphaine Vaillant

Scope: Signal of lichenoid keratosis

EPITT 20060 – New signal

Lead Member State(s): FR

14.1.3. Pirfenidone – ESBRIET (CAP), Pirfenidone axunio (CAP); Pirfenidone Viatris (CAP); NAP

Applicant: Roche Registration GmbH, various

PRAC Rapporteur: Rhea Fitzgerald

Scope: Signal of lichenoid drug eruption

EPITT 20069 – New signal

Lead Member State(s): IE

14.1.4. Posaconazole - NOXAFIL (CAP), Posaconazole Accord (CAP), Posaconazole AHCL (CAP); NAP

Applicant: Merck Sharp & Dohme B.V. (Noxafil), Accord Healthcare S.L.U. (Posaconazole Accord, Posaconazole AHCL), various

PRAC Rapporteur: Nathalie Gault

Scope: Signal of photosensitivity reaction

EPITT 20076 – New signal

Lead Member State(s): FR

14.2. Signals follow-up and prioritisation

None

14.3. Variation procedure(s) resulting from signal evaluation

14.3.1. Dabrafenib - FINLEE (CAP) - EMEA/H/C/005885/WS2670/0004; Trametinib - SPEXOTRAS (CAP) - EMEA/H/C/005886/WS2670/0003

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: To include into the product information for dabrafenib and trametinib the signal 'peripheral neuropathy' in line with the PRAC recommended wording from EMA/PRAC/289010/2023, EPITT No. 19947

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. Dasatinib - (CAP MAA) - EMEA/H/C/006251

Scope (pre D-180 phase): Treatment of adult patients with advanced renal cell carcinoma (RCC)

15.1.2. Enzalutamide - (CAP MAA) - EMEA/H/C/006299

Scope (pre D-180 phase): Treatment of prostate cancer

15.1.3. Nilotinib - (CAP MAA) - EMEA/H/C/006315

Scope (pre D-180 phase): Treatment of Philadelphia chromosome positive chronic myelogenous leukaemia (CML)

15.1.4. Pomalidomide - (CAP MAA) - EMEA/H/C/006273

Scope (pre D-180 phase): Treatment of adult patients with multiple myeloma

15.1.5. Pomalidomide - (CAP MAA) - EMEA/H/C/006314

Scope (pre D-180 phase): Treatment of multiple myeloma

15.1.6. Pomalidomide - (CAP MAA) - EMEA/H/C/006294

Scope (pre D-180 phase): Treatment of adults with multiple myeloma

15.1.7. [Sotatercept - \(CAP MAA\) - EMEA/H/C/005647, PRIME, Orphan](#)

Applicant: Merck Sharp & Dohme B.V.

Scope (pre D-180 phase): Treatment of pulmonary arterial hypertension in adults

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

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

15.2.1. [Afamelanotide - SCENESSE \(CAP\) - EMEA/H/C/002548/II/0049, Orphan](#)

Applicant: Clinuvel Europe Limited

PRAC Rapporteur: Martin Huber

Scope: Termination of 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

15.2.2. [Avelumab - BAVENCIO \(CAP\) - EMEA/H/C/004338/II/0044/G](#)

Applicant: Merck Europe B.V.

PRAC Rapporteur: Karin Erneholm

Scope: Grouped application comprising four variations as follows:

Type II (C.I.11.b): To update Annex II and the RMP version 7.1 for Bavencio to change the classification of 'safety in patients with autoimmune disease' to the important identified risk 'other immune mediated adverse reactions' along with removal of the patient information brochure from the educational material, following the PRAC assessment report PSUSA/00010635/202303.

Type IA (A.6): To change ATC level name from 'Other antineoplastic agents, monoclonal antibodies' to 'Antineoplastic agents, monoclonal antibodies, PD-1/PDL-1 (Programmed cell death protein 1/death ligand 1) inhibitors' in Section 5.1 of the Summary of Product Characteristics (SmPC). The ATC code remains unchanged.

Type IA (C.I.z): To update the statement for 'infusion-related reactions' in section 4.4 of the SmPC and to align terminology with the RMP for the term 'immune-related' versus 'immune-mediated'.

Type IAIN (C.I.12): To remove from the product information the black symbol and explanatory statements for medicinal products subject to additional monitoring.

In addition, the MAH took this opportunity to introduce editorial changes and to bring the PI in line with the latest QRD template version 10.3

15.2.3. [Coronavirus \(COVID-19\) vaccine \(recombinant, adjuvanted\) - NUVAXOVID \(CAP\) - EMEA/H/C/005808/II/0060](#)

Applicant: Novavax CZ, a.s.

PRAC Rapporteur: Gabriele Maurer

Scope: Submission of an updated RMP version 4.2 after approval of adapted COVID-19 vaccine by new strain, Omicron XBB.1.5

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

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Marie Louise Schougaard Christiansen

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

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

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

15.3.1. Afamelanotide - SCENESSE (CAP) - EMEA/H/C/002548/II/0044, Orphan

Applicant: Clinuvel Europe Limited

PRAC Rapporteur: Martin Huber

Scope: Extension of indication for the prevention of phototoxicity in adolescent patients (12 to under 18 years of age) with erythropoietic protoporphyria (EPP), based on the analysis of the safety and efficacy data available. As a consequence, sections 4.1, 4.2 and 4.4 of the SmPC are updated. The package leaflet is updated in accordance. Version 9.4 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce a minor editorial correction to the product information

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

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Gabriele Maurer

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

requests an extension of the market protection by one additional year

15.3.3. Brexucabtagene autoleucl - TECARTUS (CAP) - EMEA/H/C/005102/WS2632/0041; Axicabtagene ciloleucl - YESCARTA (CAP) - EMEA/H/C/004480/WS2632/0072

Applicant: Kite Pharma EU B.V., ATMP

PRAC Rapporteur: Karin Erneholm

Scope: Update of sections 4.2 and 5.1 of the SmPC in order to update the safety monitoring timelines based on data from clinical studies, postmarketing studies, and literature. The package leaflet is updated accordingly. In addition, the MAH took the opportunity to implement editorial changes to sections 2.2, 6.3 and 6.6 and to update sections 4.4 and 4.5 of the SmPC to align the language across both products

15.3.4. 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

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

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Liana Martirosyan

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

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

Applicant: STADA Arzneimittel AG

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Extension of indication to slow kidney function decline in adults with primary immunoglobulin A (IgA) nephropathy (IgAN) for KINPEYGO, based on Part B of study NefIgArd (NEF-301), listed as the final specific obligation in the Annex II; this is a Phase 3, randomised, double-blind, placebo-controlled, multicentre study to evaluate the efficacy,

safety, and tolerability of oral Nefecon compared to matching placebo in patients with primary IgAN on a background of optimised renin-angiotensin system (RAS) inhibitor therapy. As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The package leaflet is updated in accordance. Version 1.1 of the RMP has also been submitted

15.3.7. [Canagliflozin - INVOKANA \(CAP\) - EMEA/H/C/002649/WS2619/0066/G;](#) [Canagliflozin, metformin - VOKANAMET \(CAP\) - EMEA/H/C/002656/WS2619/0073/G](#)

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Martin Huber

Scope: A grouped application consisting of two Type II variations, as follows:

C.I.4: Update of section 4.4 of the SmPC in order to amend an existing warning on diabetic ketoacidosis based on literature. The package leaflet is updated accordingly.

C.I.4: Update of sections 4.6 and 5.3 of the SmPC in order to update information on pregnancy based on literature. The RMP version 11.1 has also been submitted

15.3.8. [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

15.3.9. [Ceftazidime, avibactam - ZAVICEFTA \(CAP\) - EMEA/H/C/004027/II/0035](#)

Applicant: Pfizer Ireland Pharmaceuticals

PRAC Rapporteur: Rugile Pilviniene

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

opportunity to introduce minor editorial changes to the product information

15.3.10. Coronavirus (COVID-19) vaccine (Ad26.COVID-S, recombinant) - JCOVDEN (CAP) - EMEA/H/C/005737/II/0076

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of sections 4.5, 4.8 and 5.1 of the SmPC in order to update information regarding the co-administration of JCOVDEN with influenza vaccine based on the final report from study VAC31518COV3005 listed as a category 3 study in the RMP; this is a randomised, double-blind, phase 3 study to evaluate safety, reactogenicity, and immunogenicity of co-administration of Ad26.COVID.S and influenza vaccines in healthy adults 18 years of age and older. The package leaflet is updated accordingly. Version 8.1 of the RMP has also been submitted

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

Applicant: Hipra Human Health S.L.

PRAC Rapporteur: Zane Neikena

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

15.3.12. Decitabine, cedazuridine - INAQOVI (CAP) - EMEA/H/C/005823/II/0002

Applicant: Otsuka Pharmaceutical Netherlands B.V.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Grouped application consisting of based on final results from studies ASTX727-01, ASTX727-02, ASTX727-04, E7727-01, and E7727-02: C.I.6: Extension of indication to include treatment of adult patients with myelodysplastic syndromes (MDS) for INAQOVI and C.I.6: Extension of indication to include treatment of adult patients with chronic myelomonocytic leukaemia (CMML) for INAQOVI. 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 1.1 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 a 1-year extension of the market protection

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

Applicant: AstraZeneca AB

PRAC Rapporteur: Amelia Cupelli

Scope: Extension of indication for Lynparza in combination with Imfinzi for the maintenance

treatment of adult patients with newly diagnosed advanced or recurrent endometrial cancer following treatment with Imfinzi and platinum-based chemotherapy, based on results from pivotal phase III study, D9311C00001 (DUO-E). This was a phase III, randomised, double-blind, placebo-controlled, multicentre study evaluating the efficacy and safety of durvalumab in combination with platinum-based chemotherapy (paclitaxel + carboplatin) followed by maintenance durvalumab with or without olaparib for patients with newly diagnosed advanced or recurrent endometrial cancer. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet is updated in accordance. Version 30 of the RMP has also been submitted

15.3.14. Elasmomeran - SPIKEVAX (CAP) - EMEA/H/C/005791/II/0120

Applicant: Moderna Biotech Spain S.L.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Submission of the final report from study mRNA-1273-P301 (phase 3, randomised, stratified, observer-blind, placebo-controlled study to evaluate the efficacy, safety, and immunogenicity of mRNA-1273 SARS-CoV-2 vaccine in adults aged 18 years and older) listed as a category 3 study in the RMP. The RMP version 8.2 has also been submitted

15.3.15. Eliglustat - CERDELGA (CAP) - EMEA/H/C/003724/X/0036/G, Orphan

Applicant: Sanofi B.V.

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Extension application to introduce a new strength (21 mg capsule, hard) grouped with an extension of indication (C.I.6.a) to include treatment of paediatric patients with GD1 who are 6 years and older with a minimum body weight of 15 kg, who have been previously treated with enzyme replacement therapy (ERT), and who are CYP2D6 poor metabolisers (PMs), intermediate metabolisers (IMs) or extensive metabolisers (EMs) for Cerdelga, based on interim results from study EFC13738 (Open label, two cohort (with and without imiglucerase), multicentre study to evaluate pharmacokinetics, safety, and efficacy of eliglustat in pediatric patients with Gaucher disease type 1 and type 3). 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. The RMP version 8.0 has also been submitted. In addition, the MAH took this opportunity to introduce editorial changes to the product information

15.3.16. Enfortumab vedotin - PADCEV (CAP) - EMEA/H/C/005392/II/0013

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Eva Jirsová

Scope: Extension of indication to include in combination with pembrolizumab, the first-line treatment of adult patients with locally advanced or metastatic urothelial cancer who are eligible for platinum-containing chemotherapy for PADCEV, based on the final results from study KEYNOTE-A39/EV-302: 'An open label, randomised, controlled phase 3 study of enfortumab vedotin in combination with pembrolizumab versus chemotherapy alone in previously untreated locally advanced (LA) or metastatic urothelial cancer (mUC)'; As a consequence, sections 4.1, 4.2, 4.4, 4.6, 4.8, 5.1, 5.2, 5.3 and 6.6 of the SmPC are updated. The package leaflet is updated in accordance. Version 3.0 of the RMP has also

been submitted. As part of the application the MAH is requesting a 1-year extension of the market protection

15.3.17. 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

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

Applicant: Argenx

PRAC Rapporteur: Rhea Fitzgerald

Scope: Update of section 4.4 of the SmPC in order to amend an existing warning on infusion reactions and hypersensitivity reactions, and update of section 5.1 of the SmPC to update the mechanism of action of efgartigimod in relation to albumin; based on final results from study ARGX-113-1705 listed a category 3 study in the RMP. This is a long-

term, single-arm, open-label, multicentre, phase 3 follow-on study of ARGX-113-1704 to evaluate the safety and tolerability of ARGX-113 in patients with myasthenia gravis having generalised muscle weakness. The RMP version 2.2 has also been submitted

15.3.19. Fedratinib - INREBIC (CAP) - EMEA/H/C/005026/II/0020, Orphan

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Sonja Hrabcik

Scope: Update of sections 4.2, 4.4 and 4.8 of the SmPC in order to update information regarding thiamine levels based on a review of the primary results of the study FEDR-MF-002. This is a Phase 3, multicentre, open-label, randomised study to evaluate the efficacy and safety of fedratinib compared with BAT in subjects with DIPSS intermediate-2 or high-risk primary MF, post-PV MF, or post-ET MF and previously treated with ruxolitinib. The RMP version 3 has also been submitted

15.3.20. Ganaxolone - ZTALMY (CAP) - EMEA/H/C/005825/II/0004/G, Orphan

Applicant: Marinus Pharmaceuticals Emerald Limited

PRAC Rapporteur: Adam Przybylkowski

Scope: A grouped application comprised of 8 Type II variations as follows:

1 Type II (C.I.4): Update of section 5.2 of the SmPC in order to update ganaxolone metabolite pattern at steady state based on re-analysis of 1042-TQT-1001 listed as a category 3 study in the RMP to evaluate the ganaxolone steady-state metabolite.

7 Type II (C.I.13): Submission of the final non-clinical study reports for the in vitro drug-drug interaction (DDI) potential and in vivo pharmacokinetics (PK) of the metabolite M17 listed as category 3 studies in the RMP.

The RMP version 1.2 has also been submitted. In addition, the MAH took the opportunity to introduce updates to the product information that reflect clarifications and typographical corrections, including to sections 4.2 and 4.4 of the SmPC

15.3.21. Ganaxolone - ZTALMY (CAP) - EMEA/H/C/005825/II/0006, Orphan

Applicant: Marinus Pharmaceuticals Emerald Limited

PRAC Rapporteur: Adam Przybylkowski

Scope: Update of section 5.1 of the SmPC in order to update open-label data based on the final report from study 1042-CDD-3001 OLE listed as a category 3 study in the RMP. This was the open-label portion of the pivotal study 1042-CDD-3001; a double-blind, randomised, placebo-controlled trial of adjunctive ganaxolone treatment in children and young adults with cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD) followed by long-term open-label treatment. The RMP version 1.4 has also been submitted

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

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Kimmo Jaakkola

Scope: Submission of the final report from study ORION-8 - a long-term extension trial of

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

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

Applicant: Basilea Pharmaceutica Deutschland GmbH

PRAC Rapporteur: Adam Przybylkowski

Scope: Extension application to add a new strength of 40 mg hard capsule to be used in paediatric patients 6 years and older grouped with a type II variation (C.I.6.a) in order to extend the indication to include treatment of paediatric patients aged 1 year and older for CRESEMBA 200 mg powder, based on final results from studies 9766-CL-0107 and 9766-CL-0046. Study 9766-CL-0046 is a phase 1, open-label, multicentre study to evaluate the PK, safety and tolerability of intravenous and oral isavuconazonium sulfate in paediatric patients. This study was conducted in two sequential parts: Part 1 with three intravenous dosing cohorts, and Part 2 with two oral dosing cohorts. Study 9766-CL-0107 is a phase 2, open-label, non-comparative, multicentre study to evaluate the safety and tolerability, efficacy, and PK of isavuconazole for the treatment of invasive aspergillosis or mucormycosis in paediatric patients aged 1 to < 18 years. As a consequence, sections 4.1, 4.2, 4.5, 4.8, 5.1, 5.2, and 6.6 of the SmPC are updated. The package leaflet is updated in accordance. Version 9.1 of the RMP has also been submitted

15.3.24. Lanadelumab - TAKHZYRO (CAP) - EMEA/H/C/004806/II/0040, Orphan

Applicant: Takeda Pharmaceuticals International AG Ireland Branch

PRAC Rapporteur: Kirsti Villikka

Scope: Update of section 4.4 of the SmPC in order to remove the information related to non-availability of clinical data on the use of lanadelumab in hereditary angioedema (HAE) patients with normal C1 Inhibitor (C1-INH) activity, based on results from studies CASPIAN (SHP643-303) and CASPIAN OLE (TAK-743-3001). CASPIAN (SHP643-303) is a phase 3, multicentre, randomised, placebo-controlled, double-blind study to evaluate the efficacy and safety of lanadelumab for prevention against acute attacks of nonhistaminergic angioedema with C1-INH; and CASPIAN OLE (TAK-743-3001) is an open-label study to evaluate the long-term safety and efficacy of lanadelumab for prevention against acute attacks of nonhistaminergic Angioedema with C1-INH. The RMP version 4.0 has also been submitted. In addition, the MAH took the opportunity to implement editorial changes to the SmPC and the package leaflet

15.3.25. Maralixibat - LIVMARLI (CAP) - EMEA/H/C/005857/II/0003/G, Orphan

Applicant: Mirum Pharmaceuticals International B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Grouped variation consisting of: 1) Extension of indication to include treatment of Progressive Familial Intrahepatic Cholestasis (PFIC) in patients 2 months of age and older for LIVMARLI, based on results from studies MRX-502, LUM001-501, MRX-503, MRX-800 and MRX-801; MRX-502 is an international, multicenter, randomised, double-blind, placebo-controlled, parallel group Phase 3 study that evaluated the efficacy and safety of

maralixibat in PFIC participants aged >12 months to <18 years on a proposed dosage of up to 600 µg/kg BID over 6 months. 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 Annex II are updated in accordance. Version 2.0 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to introduce minor editorial changes; 2) B.I.b.1.b. In addition, further editorial changes are made in module 3 which are consequential to the extension of indication and the higher maximum daily dose

15.3.26. [Meningococcal Group A, C, W and Y conjugate vaccine - MENQUADFI \(CAP\) - EMEA/H/C/005084/II/0027](#)

Applicant: Sanofi Pasteur

PRAC Rapporteur: Jean-Michel Dogné

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

15.3.27. [Midazolam - BUCCOLAM \(CAP\) - EMEA/H/C/002267/II/0061](#)

Applicant: Neuraxpharm Pharmaceuticals S.L.

PRAC Rapporteur: Liana Martirosyan

Scope: Extension of indication to include treatment of adults to Buccolam 10 mg, based on the results from study 2023-504903-10-00; this is an interventional study, relative bioavailability to investigate the pharmacokinetics of a single dose of midazolam oromucosal solution (Buccolam) compared to midazolam solution for intramuscular injection (Hypnovel) in healthy volunteers under fasting conditions. As a consequence, sections 4.1, 4.2, 4.8, 5.1, 5.2, 6.5 and 6.6 of the SmPC are updated. The package leaflet and labelling are updated in accordance. Version 8.1 of the RMP has also been submitted

15.3.28. [Nivolumab - OPDIVO \(CAP\) - EMEA/H/C/003985/II/0140](#)

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Martin Huber

Scope: Extension of indication to include Opdivo for the treatment of patients with resectable stage II-IIIB non-small cell lung cancer, based on results from study CA209977T; a phase 3, randomised, double-blind study of neoadjuvant chemotherapy plus nivolumab versus neoadjuvant chemotherapy plus placebo, followed by surgical resection and adjuvant treatment with nivolumab or placebo for participants with resectable stage II-IIIB non-small cell lung cancer. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The package leaflet is updated in accordance. Version 36.0 of the RMP has also been submitted

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

Applicant: Roche Registration GmbH

PRAC Rapporteur: Gabriele Maurer

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

15.3.30. Osimertinib - TAGRISSO (CAP) - EMEA/H/C/004124/II/0053

Applicant: AstraZeneca AB

PRAC Rapporteur: Bianca Mulder

Scope: Extension of indication to include TAGRISSO in combination with pemetrexed and platinum-based chemotherapy for the first-line treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating epidermal growth factor receptor (EGFR) mutations, based on final results from study FLAURA2 (D5169C00001); this is a Phase III, open-label, randomised study of osimertinib with or without platinum plus pemetrexed chemotherapy, multicentre study to assess the efficacy and safety of TAGRISSO as first-line treatment in patients with EGFR mutation-positive, locally advanced or metastatic NSCLC. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.3 of the SmPC are updated. The package leaflet is updated in accordance. Version 16 of the RMP has also been submitted

15.3.31. Pembrolizumab - KEYTRUDA (CAP) - EMEA/H/C/003820/II/0150

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Bianca Mulder

Scope: Extension of indication to include in combination with enfortumab vedotin, the first-line treatment of locally advanced or metastatic urothelial carcinoma in adults, based on the final results from KEYNOTE-A39/EV-302: 'an open label, randomised, controlled phase 3 study of enfortumab vedotin in combination with pembrolizumab versus chemotherapy alone in previously untreated locally advanced (LA) or metastatic urothelial cancer (mUC)'; 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 45.1 of the RMP has also been submitted

15.3.32. Pemigatinib - PEMAZYRE (CAP) - EMEA/H/C/005266/II/0015, Orphan

Applicant: Incyte Biosciences Distribution B.V.

PRAC Rapporteur: Bianca Mulder

Scope: Extension of indication to include treatment of adults with myeloid/lymphoid neoplasms (MLNs) with Fibroblast Growth Factor Receptor1 (FGFR1) rearrangement for Pemazyre, based on final results from study INCB 54828-203 (FIGHT-203); this is a phase 2, open-label, monotherapy, multicentre study to evaluate the efficacy and safety of INCB054828 in subjects with myeloid/lymphoid neoplasms with FGFR1 rearrangement. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8 and 5.1 of the SmPC are updated. The package leaflet is updated in accordance. Version 3.0 of the RMP has also been submitted.

In addition, the MAH took the opportunity to introduce minor changes to the product information. As part of the application, the MAH is requesting a 1-year extension of the market protection

15.3.33. Pertuzumab, trastuzumab - PHESGO (CAP) - EMEA/H/C/005386/II/0023/G

Applicant: Roche Registration GmbH

PRAC Rapporteur: Gabriele Maurer

Scope: A grouped application comprised of 2 Type II variations and 1 Type IA variation, as follows:

Type II variation (C.I.4): Update of sections 4.8 and 5.1 of the SmPC in order to update efficacy and safety information, based on the final report from study WO40324 (FeDeriCa) listed as a category 3 study in the RMP. This is a phase 3, randomised, multicentre, open-label, two-arm study to evaluate the pharmacokinetics, efficacy, and safety of subcutaneous administration of the fixed-dose combination of pertuzumab and trastuzumab in combination with chemotherapy in patients with HER2-positive early breast cancer.

Type II variation (C.I.4): Update of section 4.8 of the SmPC in order to only present specific Phesgo safety data by updating the summary of safety profile and the tabulated list of adverse reactions to reflect this information. The package leaflet is updated accordingly.

Type IA variation (A.6): To change the ATC code of pertuzumab and trastuzumab from L01XY02 to L01FY01. The RMP version 3.0 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

15.3.34. Pneumococcal polysaccharide conjugate vaccine (20-valent, adsorbed) - PREVENAR 20 (CAP) - EMEA/H/C/005451/II/0023

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Jean-Michel Dogné

Scope: Submission of the final current B7471015 study protocol, the Statistical Analysis Plan (SAP) and the final country feasibility assessment report for Apexxnar. The RMP (version 5.0) is updated accordingly

15.3.35. Respiratory syncytial virus, glycoprotein F, recombinant, stabilised in the pre-fusion conformation, adjuvanted with AS01E - AREXVY (CAP) - EMEA/H/C/006054/II/0008

Applicant: GlaxoSmithkline Biologicals S.A.

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Extension of indication to include treatment of adults 50-59 years of age who are at increased risk for respiratory syncytial virus (RSV) disease for Arexvy, based on results from study 219238 (RSV OA=ADJ-018); this is a phase 3, observer-blind, placebo-controlled, randomised, multi-country, multi-centre, non-inferiority study with 2 cohorts to evaluate immunogenicity, reactogenicity and safety of a single dose of RSVPreF3 OA in adults 50-59 years of age. As a consequence, sections 4.1, 4.6, 4.8 and 5.1 of the SmPC are updated. The package leaflet is updated in accordance. Version 1.1 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the product information, to bring it in line with the latest QRD template version

10.3, and to update the list of local representatives in the package leaflet. As part of the application, the MAH is requesting a 1-year extension of the market protection

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

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Liana Martirosyan

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

15.3.37. Ruxolitinib - JAKAVI (CAP) - EMEA/H/C/002464/X/0070/G

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension application to introduce a new pharmaceutical form associated with a new strength (5 mg/ml oral solution) and a new route of administration (gastric use), indicated for the treatment of graft versus host disease (GvHD) in patients aged 28 days or older.

The above line extension is grouped with a type II variation:

- C.I.6.a - To include treatment of paediatric patients aged 28 days to less than 18 years old in acute and chronic Graft versus Host Disease for JAKAVI, based on final results from studies REACH4 (CINC424F12201) and REACH5 (Study CINC424G12201). REACH4 is a phase I/II open-label, single-arm, multi-centre study of ruxolitinib added to corticosteroids in paediatric patients with grade II-IV acute graft vs. host disease after allogeneic hematopoietic stem cell transplantation; while REACH5 is a phase II open-label, single-arm, multi-centre study of ruxolitinib added to corticosteroids in paediatric subjects with moderate and severe chronic graft vs. host disease after allogeneic stem cell transplantation (both for oral solution and already approved tablets presentations). 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. The RMP (version 16) is updated in accordance. In addition, the MAH took the opportunity to implement editorial changes to Annex II

15.3.38. Sarilumab - KEVZARA (CAP) - EMEA/H/C/004254/X/0043/G

Applicant: Sanofi Winthrop Industrie

PRAC Rapporteur: Monica Martinez Redondo

Scope: Extension application to add a new strength of 175 mg/ml solution for injection in vial, grouped with an extension of indication to include treatment of active polyarticular-course juvenile idiopathic arthritis (pcJIA) in patients 2 years of age and older for KEVZARA, based on results from study DRI13925; this is a multinational, multi-centre, open-label, 2 phase, 3 portions study to describe the pharmacokinetics (PK) profile as well as safety and efficacy of sarilumab. 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 3.0 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the product information

15.3.39. Teclistamab - TECVAYLI (CAP) - EMEA/H/C/005865/II/0009

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Jana Lukacisinova

Scope: Update of section 4.4 of the SmPC in order to update the warning on progressive multifocal leukoencephalopathy (PML) based on a cumulative safety review. The package leaflet is updated accordingly. The RMP version 4.1 has also been submitted. In addition, the MAH took the opportunity to introduce minor updates to the PI and to update the list of local representatives in the package leaflet

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

Applicant: Almirall S.A

PRAC Rapporteur: Adam Przybylkowski

Scope: Type II (B.IV.1.c) - to add the 200 mg solution for injection in pre-filled pen which is an integrated part of the primary packaging of the medicinal product

15.3.41. Tislelizumab - TEVIMBRA (CAP) - EMEA/H/C/005919/II/0003

Applicant: Beigene Ireland Limited

PRAC Rapporteur: Bianca Mulder

Scope: Extension of indication to include in combination with platinum-based chemotherapy the first-line treatment of adult patients with unresectable, locally advanced or metastatic oesophageal squamous cell carcinoma (OSCC) for Temvimbra, based on results from study BGB-A317-306; this is a multi-regional, randomised, placebo-controlled, double-blind phase 3 study evaluating the efficacy and safety of tislelizumab in combination with chemotherapy compared to placebo in combination with chemotherapy as first-line treatment in patients with unresectable or locally advanced recurrent or metastatic OSCC. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.6, 4.8 and 5.1 of the SmPC are updated. The package leaflet is updated in accordance. Version 1.1 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the product information

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

Applicant: Takeda Pharmaceuticals International AG Ireland Branch

PRAC Rapporteur: Martin Huber

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

15.3.43. Voclosporin - LUPKYNIS (CAP) - EMEA/H/C/005256/II/0013

Applicant: Otsuka Pharmaceutical Netherlands B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Update of section 4.6 of the SmPC in order to update breast-feeding information based on final results from study AUR-VCS-2021-04. This study is a single-centre, open-label, phase 1, lactation study to investigate the amount of voclosporin excreted in breast milk following a single oral dose of 23.7 mg voclosporin in healthy, lactating, female volunteers. The package leaflet is updated accordingly. The updated RMP version 5.0 has also been submitted

16. Annex I - Periodic safety update reports (PSURs)

Based on the assessment of the following PSURs, PRAC concluded that the benefit-risk balance of the medicine(s) mentioned below remains favourable in the approved indication(s) and adopted a recommendation to maintain the current terms of the marketing authorisation(s) together with the assessment report. As per the agreed criteria, the procedures listed below were finalised at the PRAC level without further plenary discussion.

The next PSURs should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal, unless changes apply as stated in the outcome of the relevant PSUR/PSUSA procedure(s).

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

16.1.1. Abrocitinib - CIBINQO (CAP) - PSUSA/00010976/202309

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Petar Mas

Scope: Evaluation of a PSUSA procedure

16.1.2. Amikacin⁴⁵ - ARIKAYCE LIPOSOMAL (CAP) - PSUSA/00010882/202309

Applicant: Insmmed Netherlands B.V.

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

⁴⁵ For centrally authorised product(s) only

16.1.3. Bedaquiline - SIRTURO (CAP) - PSUSA/00010074/202309

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.4. Cenobamate - ONTOZRY (CAP) - PSUSA/00010921/202309

Applicant: Angelini S.p.A.

PRAC Rapporteur: Jo Robays

Scope: Evaluation of a PSUSA procedure

16.1.5. Cholic acid⁴⁶ - ORPHACOL (CAP) - PSUSA/00010208/202309

Applicant: Theravia

PRAC Rapporteur: Sofia Trantza

Scope: Evaluation of a PSUSA procedure

16.1.6. Ciltacabtagene autoleucl - CARVYKTI (CAP) - PSUSA/00011000/202308

Applicant: Janssen-Cilag International NV, ATMP

PRAC Rapporteur: Jo Robays

Scope: Evaluation of a PSUSA procedure

16.1.7. Cipaglucosidase alfa - POMBILITI (CAP) - PSUSA/00011047/202309

Applicant: Amicus Therapeutics Europe Limited

PRAC Rapporteur: Mari Thorn

Scope: Evaluation of a PSUSA procedure

16.1.8. Cobicistat - TYBOST (CAP) - PSUSA/00010081/202308

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.1.9. Cobimetinib - COTELLIC (CAP) - PSUSA/00010450/202308

Applicant: Roche Registration GmbH

PRAC Rapporteur: Bianca Mulder

Scope: Evaluation of a PSUSA procedure

⁴⁶ For oxosteroid-reductase or hydroxy-steroid dehydrogenase deficiency indication only

16.1.10. Crizotinib - XALKORI (CAP) - PSUSA/00010042/202308

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

16.1.11. Damoctocog alfa pegol - JIVI (CAP) - PSUSA/00010732/202308

Applicant: Bayer AG

PRAC Rapporteur: Bianca Mulder

Scope: Evaluation of a PSUSA procedure

16.1.12. Darvadstrocel - ALOFISEL (CAP) - PSUSA/00010676/202309

Applicant: Takeda Pharma A/S, ATMP

PRAC Rapporteur: Gabriele Maurer

Scope: Evaluation of a PSUSA procedure

16.1.13. Deucravacitinib - SOTYKTU (CAP) - PSUSA/00011046/202309

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Liana Martirosyan

Scope: Evaluation of a PSUSA procedure

16.1.14. Duvelisib - COPIKTRA (CAP) - PSUSA/00010939/202309

Applicant: Secura Bio Limited

PRAC Rapporteur: Petar Mas

Scope: Evaluation of a PSUSA procedure

16.1.15. Filgotinib - JYSELECA (CAP) - PSUSA/00010879/202309

Applicant: Galapagos N.V.

PRAC Rapporteur: Petar Mas

Scope: Evaluation of a PSUSA procedure

16.1.16. Fosdenopterin - NULIBRY (CAP) - PSUSA/00011017/202308

Applicant: TMC Pharma (EU) Limited

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.17. [Fremanezumab - AJOVY \(CAP\) - PSUSA/00010758/202309](#)

Applicant: TEVA GmbH

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

16.1.18. [Galcanezumab - EMGALITY \(CAP\) - PSUSA/00010733/202309](#)

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

16.1.19. [Ganaxolone - ZTALMY \(CAP\) - PSUSA/00000093/202309](#)

Applicant: Marinus Pharmaceuticals Emerald Limited

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.20. [Gilteritinib - XOSPATA \(CAP\) - PSUSA/00010832/202309](#)

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.21. [Glofitamab - COLUMVI \(CAP\) - PSUSA/00000067/202309](#)

Applicant: Roche Registration GmbH

PRAC Rapporteur: Jana Lukacisinova

Scope: Evaluation of a PSUSA procedure

16.1.22. [Gozetotide - LOCAMETZ \(CAP\) - PSUSA/00011030/202309](#)

Applicant: Novartis Europharm Limited

PRAC Rapporteur: John Joseph Borg

Scope: Evaluation of a PSUSA procedure

16.1.23. [Idebenone⁴⁷ - RAXONE \(CAP\) - PSUSA/00010412/202309](#)

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

⁴⁷ For centrally authorised product(s) only

16.1.24. Imlifidase - IDEFIRIX (CAP) - PSUSA/00010870/202308

Applicant: Hansa Biopharma AB

PRAC Rapporteur: Bianca Mulder

Scope: Evaluation of a PSUSA procedure

16.1.25. Influenza vaccine (intranasal, live attenuated) - FLUENZ TETRA (CAP) - PSUSA/00001742/202308

Applicant: AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

16.1.26. Linaclotide - CONSTELLA (CAP) - PSUSA/00010025/202308

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.27. Lonapegsomatropin - SKYTROFA (CAP) - PSUSA/00010969/202308

Applicant: Ascendis Pharma Endocrinology Division A/S

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.28. Lorlatinib - LORVIQUA (CAP) - PSUSA/00010760/202309

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Barbara Kovacic Bytyqi

Scope: Evaluation of a PSUSA procedure

16.1.29. Lusutrombopag - MULPLEO (CAP) - PSUSA/00010755/202309

Applicant: Shionogi B.V.

PRAC Rapporteur: Mari Thorn

Scope: Evaluation of a PSUSA procedure

16.1.30. Lutetium (¹⁷⁷Lu) vipivotide tetraxetan - PLUVICTO (CAP) - PSUSA/00011031/202309

Applicant: Novartis Europharm Limited

PRAC Rapporteur: John Joseph Borg

Scope: Evaluation of a PSUSA procedure

16.1.31. Mecasermin - INCRELEX (CAP) - PSUSA/00001942/202308

Applicant: Ipsen Pharma

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

16.1.32. Meropenem, vaborbactam - VABOREM (CAP) - PSUSA/00010727/202308

Applicant: Menarini International Operations Luxembourg S.A.

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

16.1.33. Miglustat⁴⁸ - OPFOLDA (CAP) - PSUSA/00000077/202309

Applicant: Amicus Therapeutics Europe Limited

PRAC Rapporteur: Mari Thorn

Scope: Evaluation of a PSUSA procedure

16.1.34. Mirikizumab - OMVOH (CAP) - PSUSA/00000049/202309

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Sonja Hrabcik

Scope: Evaluation of a PSUSA procedure

16.1.35. Naloxegol - MOVENTIG (CAP) - PSUSA/00010317/202309

Applicant: Kyowa Kirin Holdings B.V.

PRAC Rapporteur: Eamon O'Murchu

Scope: Evaluation of a PSUSA procedure

16.1.36. Naltrexone, bupropion - MYSIMBA (CAP) - PSUSA/00010366/202309

Applicant: Orexigen Therapeutics Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.37. Nivolumab, relatlimab - OPDUALAG (CAP) - PSUSA/00011018/202309

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

⁴⁸ For treatment of Pompe disease only

16.1.38. Olipudase alfa - XENPOZYME (CAP) - PSUSA/00011003/202309

Applicant: Sanofi B.V.

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.39. Pembrolizumab - KEYTRUDA (CAP) - PSUSA/00010403/202309

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Bianca Mulder

Scope: Evaluation of a PSUSA procedure

16.1.40. Pralsetinib - GAVRETO (CAP) - PSUSA/00010961/202309

Applicant: Roche Registration GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.41. Pyronaridine. artesunate - PYRAMAX (Art 58⁴⁹) - EMEA/H/W/002319/PSUV/0035

Applicant: Shin Poong Pharmaceutical Co., Ltd.

PRAC Rapporteur: Nathalie Gault

Scope: Evaluation of a PSUR procedure

16.1.42. Raltegravir - ISENTRESS (CAP) - PSUSA/00010373/202309

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Nathalie Gault

Scope: Evaluation of a PSUSA procedure

16.1.43. Rimegepant - VYDURA (CAP) - PSUSA/00010997/202308

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Karin Erneholm

Scope: Evaluation of a PSUSA procedure

16.1.44. Ruxolitinib⁵⁰ - OPZELURA (CAP) - PSUSA/00011052/202309

Applicant: Incyte Biosciences Distribution B.V.

PRAC Rapporteur: Adam Przybylkowski

⁴⁹ Article 58 of Regulation (EC) No 726/2004 allows the Committee for Medicinal Products for Human Use (CHMP) to give opinions, in co-operation with the World Health Organisation (WHO) on medicinal products for human use that are intended exclusively for markets outside of the European Union (EU)

⁵⁰ For non-segmental vitiligo indication only

Scope: Evaluation of a PSUSA procedure

16.1.45. Sodium thiosulfate - PEDMARQSI (CAP) - PSUSA/00000066/202309

Applicant: Fennec Pharmaceuticals (EU) Limited

PRAC Rapporteur: Karin Erneholm

Scope: Evaluation of a PSUSA procedure

16.1.46. Somapacitan - SOGROYA (CAP) - PSUSA/00010920/202308

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.47. Spesolimab - SPEVIGO (CAP) - PSUSA/00011033/202309

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Nathalie Gault

Scope: Evaluation of a PSUSA procedure

16.1.48. Teduglutide - REVESTIVE (CAP) - PSUSA/00009305/202308

Applicant: Takeda Pharmaceuticals International AG Ireland Branch

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Evaluation of a PSUSA procedure

16.1.49. Tepotinib - TEPMETKO (CAP) - PSUSA/00010979/202309

Applicant: Merck Europe B.V.

PRAC Rapporteur: Bianca Mulder

Scope: Evaluation of a PSUSA procedure

16.1.50. Valoctocogene roxaparvovec - ROCTAVIAN (CAP) - PSUSA/00011009/202308

Applicant: BioMarin International Limited, ATMP

PRAC Rapporteur: Bianca Mulder

Scope: Evaluation of a PSUSA procedure

16.1.51. Zoledronic acid⁵¹ - ACLASTA (CAP) - PSUSA/00009334/202308

Applicant: Sandoz Pharmaceuticals d.d.

PRAC Rapporteur: Mari Thorn

⁵¹ For osteoporosis indication only

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. Azilsartan medoxomil, chlortalidone - EDARBI (CAP); NAP - PSUSA/00000280/202308

Applicant: Takeda Pharma A/S (Edarbi), various

PRAC Rapporteur: Bianca Mulder

Scope: Evaluation of a PSUSA procedure

16.2.2. Glycopyrronium⁵² - SIALANAR (CAP); NAP - PSUSA/00010529/202309

Applicant: Proveca Pharma Limited (Sialanar), various

PRAC Rapporteur: Zane Neikena

Scope: Evaluation of a PSUSA procedure

16.2.3. Sitagliptin - JANUVIA (CAP); RISTABEN (CAP); TESAVEL (CAP); XELEVIA (CAP); NAP; metformin hydrochloride, sitagliptin - EFFICIB (CAP); JANUMET (CAP); RISTFOR (CAP); VELMETIA (CAP); NAP - PSUSA/00010673/202308

Applicant: Merck Sharp & Dohme B.V., various

PRAC Rapporteur: Bianca Mulder

Scope: Evaluation of a PSUSA procedure

16.2.4. Trientine - CUFENCE (CAP); CUPRIOR (CAP); NAP - PSUSA/00010637/202309

Applicant: Univar Solutions BV (Cufence), Orphalan (Cuprior), various

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

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

16.3.1. Aztreonam⁵³ (NAP) - PSUSA/00010178/202308

Applicant(s): various

PRAC Lead: Marie Louise Schougaard Christiansen

Scope: Evaluation of a PSUSA procedure

⁵² For severe sialorrhoea indication only

⁵³ For parenteral use only

16.3.2. Dexamfetamine (NAP) – PSUSA/00000986/202309

Applicant(s): various

PRAC Lead: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.3.3. Finasteride (NAP) - PSUSA/00001392/202308

Applicant(s): various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.3.4. Fluocinolone acetonide⁵⁴ (NAP) - PSUSA/00010224/202308

Applicant(s): various

PRAC Lead: Carla Torre

Scope: Evaluation of a PSUSA procedure

16.3.5. Human plasma protease C1 inhibitor (NAP) - PSUSA/00010163/202308

Applicant(s): various

PRAC Lead: Gabriele Maurer

Scope: Evaluation of a PSUSA procedure

16.3.6. Ipratropium, xylometazoline (NAP) - PSUSA/00009201/202308

Applicant(s): various

PRAC Lead: Petar Mas

Scope: Evaluation of a PSUSA procedure

16.3.7. Mirtazapine (NAP) - PSUSA/00002068/202308

Applicant(s): various

PRAC Lead: Liana Martirosyan

Scope: Evaluation of a PSUSA procedure

16.3.8. Modafinil (NAP) - PSUSA/00010242/202308

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

⁵⁴ Intravitreal implant in applicator

16.3.9. Pefloxacin (NAP) - PSUSA/00002322/202308

Applicant(s): various

PRAC Lead: Polona Golmajer

Scope: Evaluation of a PSUSA procedure

16.3.10. Phenytoin (NAP) - PSUSA/00002392/202308

Applicant(s): various

PRAC Lead: Eamon O'Murchu

Scope: Evaluation of a PSUSA procedure

16.3.11. Prednisolone (NAP) - PSUSA/00002506/202308

Applicant(s): various

PRAC Lead: Polona Golmajer

Scope: Evaluation of a PSUSA procedure

16.3.12. Ramipril (NAP) - PSUSA/00002607/202308

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.3.13. Rosuvastatin, perindopril, indapamide (NAP) - PSUSA/00010752/202308

Applicant(s): various

PRAC Lead: Polona Golmajer

Scope: Evaluation of a PSUSA procedure

16.3.14. Suxamethonium (NAP) - PSUSA/00002834/202308

Applicant(s): various

PRAC Lead: Barbara Kovacic Bytyqi

Scope: Evaluation of a PSUSA procedure

16.3.15. Trazodone (NAP) - PSUSA/00003012/202308

Applicant(s): various

PRAC Lead: Rugile Pilviniene

Scope: Evaluation of a PSUSA procedure

16.3.16. Typhoid polysaccharide vaccine (NAP) - PSUSA/00003065/202308

Applicant(s): various

PRAC Lead: Gabriele Maurer

Scope: Evaluation of a PSUSA procedure

16.4. Follow-up to PSUR/PSUSA procedures

16.4.1. Dolutegravir - TIVICAY (CAP) - EMEA/H/C/002753/LEG 015.4

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Martin Huber

Scope: Second annual report for the submission of the available data from the RESPOND study – LEG requested after the procedure EMEA/H/C/PSUSA/00010075/202101 which concerns dolutegravir (Tivicay), dolutegravir/abacavir/lamivudine (Triumeq) and dolutegravir/lamivudine (Dovato)

16.4.2. Dolutegravir, abacavir, lamivudine - TRIUMEQ (CAP) - EMEA/H/C/002754/LEG 010.4

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Martin Huber

Scope: Second annual report for the submission of the available data from the RESPOND study – LEG requested after the procedure EMEA/H/C/PSUSA/00010075/202101 which concerns dolutegravir (Tivicay), dolutegravir/abacavir/lamivudine (Triumeq) and dolutegravir/lamivudine (Dovato)

16.4.3. Dolutegravir, lamivudine - DOVATO (CAP) - EMEA/H/C/004909/LEG 005.4

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: David Olsen

Scope: Second annual report for the submission of the available data from the RESPOND study – LEG requested after the procedure EMEA/H/C/PSUSA/00010075/202101 which concerns dolutegravir (Tivicay), dolutegravir/abacavir/lamivudine (Triumeq) and dolutegravir/lamivudine (Dovato)

16.4.4. Meningococcal group A, C, W135 and Y conjugate vaccine - NIMENRIX (CAP) - EMEA/H/C/002226/LEG 058

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: David Olsen

Scope: From PSUSA/20044/202304: cumulative review of cases of hypersensitivity/allergic reaction (including anaphylaxis)

16.5. Variation procedure(s) resulting from PSUSA evaluation

16.5.1. Etanercept - ENBREL (CAP) - EMEA/H/C/000262/II/0254

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Monica Martinez Redondo

Scope: Update of section 4.8 of the SmPC in order to update the frequency of Adverse Drug Reaction (ADR) 'glomerulonephritis' from 'not known' to 'rare' following PSUSA/00010795/202302 procedure, based on available evidence from clinical trials, literature, and post-marketing data. The package leaflet is updated accordingly

16.5.2. Ioflupane (¹²³I) - DATSCAN (CAP) - EMEA/H/C/000266/II/0067

Applicant: GE Healthcare B.V.

PRAC Rapporteur: Tiphaine Vaillant

Scope: To update sections 4.4 and 4.5 of the SmPC and section 2 of the package leaflet to implement the recommendation of the PRAC following the PSUSA procedure (EMEA/H/C/PSUSA/00001767/202207). In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet

16.5.3. Isatuximab - SARCLISA (CAP) - EMEA/H/C/004977/II/0027

Applicant: Sanofi Winthrop Industrie

PRAC Rapporteur: Monica Martinez Redondo

Scope: Update of section 4.8 of the SmPC in order to add 'thrombocytopenia' and 'anaemia' to the list of adverse drug reactions (ADRs) and to amend the frequency of all remaining ADRs with their appropriate frequencies, following PRAC request in the outcome of the PSUSA procedure PSUSA/00010851/202303

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

Applicant: Sanofi Pasteur

PRAC Rapporteur: Jean-Michel Dogné

Scope: Update of section 4.8 of the SmPC in order to add 'hypersensitivity including anaphylaxis' to the list of adverse drug reactions (ADRs) with frequency not known, based on a cumulative review of cases of hypersensitivity/allergic reaction (including anaphylaxis) following the request by PRAC in the Assessment Report for PSUSA/00010044/202304. The package leaflet is updated accordingly

16.6. Expedited summary safety reviews⁵⁵

None

⁵⁵ 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

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)⁵⁶

17.1.1. Alemtuzumab - LEMTRADA (CAP) - EMEA/H/C/PSA/S/0107.1

Applicant: Sanofi Belgium

PRAC Rapporteur: Karin Ernehalm

Scope: Substantial amendment to a non-interventional PASS to investigate drug utilisation and safety monitoring patterns for Lemtrada (alemtuzumab) [MAH's response to PSA/S/0107]

17.1.2. Ketoconazole - KETOCONAZOLE HRA (CAP) - EMEA/H/C/PSA/S/0109.1

Applicant: HRA Pharma Rare Diseases

PRAC Rapporteur: Petar Mas

Scope: Substantial amendment to a prospective, multi-country, observational registry to collect clinical information on patients with endogenous Cushing's syndrome exposed to Ketoconazole (using the existing European Registry on Cushing's Syndrome (ERCUSYN)), to assess drug utilisation pattern and to document the safety (e.g. hepatotoxicity, QT prolongation) and effectiveness of Ketoconazole [MAH's response to PSA/S/0109]

17.2. Protocols of PASS non-imposed in the marketing authorisation(s)⁵⁷

17.2.1. Avatrombopag - DOPTLET (CAP) - EMEA/H/C/004722/MEA 003.5

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Monica Martinez Redondo

Scope: MAH's response to MEA 003.4 and revised protocol for a study to further characterise the long-term safety profile of avatrombopag in patients with primary chronic immune thrombocytopenia in European patient registers and electronic healthcare databases as requested in the conclusions of variation II/0004/G finalised in December 2020 as per the request for supplementary information (RSI) adopted November 2023

17.2.2. Bimekizumab - BIMZELX (CAP) - EMEA/H/C/005316/MEA 003.3

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Liana Martirosyan

⁵⁶ In accordance with Article 107n of Directive 2001/83/EC

⁵⁷ 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

Scope: Submission of a revised protocol for study PS0036: bimekizumab pregnancy exposure and outcome registry - an OTIS autoimmune diseases in pregnancy study

17.2.3. Bimekizumab - BIMZELX (CAP) - EMEA/H/C/005316/MEA 004.3

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Liana Martirosyan

Scope: MAH's response to MEA 004.2 [Protocol amendment v 2.0 for Study No. PS0037: an observational cohort study to evaluate bimekizumab exposure during pregnancy, to monitor the safety of bimekizumab use in pregnancy] as per the request for supplementary information (RSI) adopted in December 2023

17.2.4. Coronavirus (COVID-19) vaccine (recombinant protein receptor binding domain fusion heterodimer) - BIMERVAX (CAP) - EMEA/H/C/006058/MEA 008.1

Applicant: Hipra Human Health S.L.

PRAC Rapporteur: Zane Neikena

Scope: Amended Protocol and MAH's responses to MEA 008 [PASS VAC4EU: non-imposed, non-interventional, category 3 post authorisation observational study to assess the safety of Bimervax using electronic health record (EHR) databases in Europe] as per the request for supplementary information (RSI) adopted in October 2023

17.2.5. Deucravacitinib - SOTYKTU (CAP) - EMEA/H/C/005755/MEA 001.1

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Liana Martirosyan

Scope: Revised Protocol / MAH's responses to MEA 001 [PASS IM011194 (non-imposed/non-interventional/RMP)] as adopted in September 2023. Long-term, observational cohort study of adults with plaque psoriasis, who are new users of deucravacitinib, non-TNFi (tumor necrosis factor inhibitor) biologics, TNFi biologics, or non-biologic systemic therapy in the real-world clinical setting (IM011194). To evaluate the long-term safety of deucravacitinib in patients with psoriasis in the real-world setting

17.2.6. Diroximel fumarate - VUMERITY (CAP) - EMEA/H/C/005437/MEA 001.2

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Martin Huber

Scope: Interim report for PASS 272MS401 (non-imposed/non-interventional/Cat. 3): a prospective observational pregnancy exposure registry to characterise how DRF may affect pregnancy and infant outcomes. An updated protocol was also submitted

17.2.7. Elasmomeran - SPIKEVAX (CAP) - EMEA/H/C/005791/MEA 065.4

Applicant: Moderna Biotech Spain S.L.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Third interim report and revised protocol for study mRNA-1273-P910: clinical course, outcomes and risk factors of myocarditis and pericarditis following administration of Moderna vaccines targeting SARS-CoV-2

17.2.8. Ivosidenib - TIBSOVO (CAP) - EMEA/H/C/005936/MEA 003.1

Applicant: Les Laboratoires Servier

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Revised protocol for a non-imposed/non-interventional, category 3 study in the RMP to evaluate the effectiveness of the Ivosidenib Patient Alert Card (additional Risk Minimisation Measure) for awareness of differentiation syndrome in acute myeloid leukaemia (AML) patients, using process indicators for awareness, receipt of the material, utility and knowledge, as per the request for supplementary information as adopted in November 2023

17.2.9. Mavacamten - CAMZYOS (CAP) - EMEA/H/C/005457/MEA 002.1

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Kimmo Jaakkola

Scope: Revised Protocol for a non-imposed, non-interventional (CV027-1148) meta-analysis of phase 3, placebo-controlled, double-blind, randomised studies of mavacamten in patients with symptomatic hypertrophic cardiomyopathy (HCM), to evaluate the cardiovascular safety profile based on a composite endpoint of time to first occurrence of major cardiovascular event (MACE) meta-analysis event, including three clinical trials in symptomatic obstructive hypertrophic cardiomyopathy (HCM) population (EXPLORER-HCM, VALOR-HCM, China oHCM Phase 3 trial) and one clinical trial in symptomatic non-obstructive HCM population (ODYSSEY-HCM)

17.2.10. Risankizumab - SKYRIZI (CAP) - EMEA/H/C/004759/MEA 001.8

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Liana Martirosyan

Scope: MAH's responses to MEA001.7 [Revised Protocol, Study No. P19-633 a post-marketing registry-based prospective cohort study of long-term safety of risankizumab in real world setting in Denmark and Sweden] as per the request for supplementary information (RSI) adopted in January 2024

17.2.11. Tezepelumab - TEZSPIRE (CAP) - EMEA/H/C/005588/MEA 005.1

Applicant: AstraZeneca AB

PRAC Rapporteur: Eva Jirsová

Scope: Revised protocol for PASS D5180R00024 (TRESPASS) (non-imposed/non-interventional): an observational multi-country PASS to evaluate the risk of serious adverse cardiovascular events in adolescent and adult patients with severe asthma taking tezepelumab

17.2.12. Tozinameran - COMIRNATY (CAP) - EMEA/H/C/005735/MEA 064.2

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Liana Martirosyan

Scope: Protocol Amendment for Study C4591051: a non-interventional post-approval safety study of Pfizer-BioNTech Bivalent COVID-19 vaccine in the United States to ensure comprehensive understanding of real-world safety of the Pfizer-BioNTech COVID-19 bivalent Omicron-modified vaccine in large samples of general US populations

17.2.13. Upadacitinib - RINVOQ (CAP) - EMEA/H/C/004760/MEA 012.5

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Petar Mas

Scope: MAH's responses to MEA 12.4 and revised protocol for Study P21-825 (drug utilization study evaluating the additional risk minimisation measures for upadacitinib in the treatment of atopic dermatitis in Europe) as per the request for supplementary information (RSI) adopted in December 2023

17.3. Results of PASS imposed in the marketing authorisation(s)⁵⁸

17.3.1. Umeclidinium bromide, vilanterol - ANORO ELLIPTA (CAP); LAVENTAIR ELLIPTA (CAP); INCRUSE ELLIPTA (CAP); ROLUFTA ELLIPTA (CAP) - EMEA/H/C/PSR/S/0048

Applicant: GlaxoSmithKline Trading Services Limited

PRAC Rapporteur: Amelia Cupelli

Scope: Final study report for a post-authorisation safety observational cohort study to quantify the incidence and comparative safety of selected cardiovascular and cerebrovascular events in chronic obstructive pulmonary disease (COPD) patients using inhaled umeclidinium/vilanterol (UMEC/VI) combination, or inhaled UMEC versus tiotropium

17.4. Results of PASS non-imposed in the marketing authorisation(s)⁵⁹

17.4.1. Adalimumab - HUMIRA (CAP) - EMEA/H/C/000481/II/0218

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Mari Thorn

Scope: Submission of the final report for study P10-023 listed as a category 3 study in the RMP. This is a 10-year, post marketing, observational registry to assess long term safety of Humira (adalimumab) in adult patients with chronic plaque psoriasis (Ps)

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

Applicant: Amgen Europe B.V.

⁵⁸ In accordance with Article 107p-q of Directive 2001/83/EC

⁵⁹ 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

PRAC Rapporteur: Mari Thorn

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

17.4.3. Etanercept - BENEPALI (CAP) - EMEA/H/C/004007/MEA 003.5

Applicant: Samsung Bioepis NL B.V.

PRAC Rapporteur: Monica Martinez Redondo

Scope: Final study results of a prospective, observational cohort study whose objectives are to evaluate the long-term effectiveness, safety, and costs associated with tumour necrosis factor-inhibitor therapies in the treatment of rheumatoid arthritis (RA) and to compare this to a cohort of RA patients who are treated with non-biologic DMARDs (RABBIT-RA)

17.4.4. Fremanezumab - AJOVY (CAP) - EMEA/H/C/004833/II/0047

Applicant: TEVA GmbH

PRAC Rapporteur: Kirsti Villikka

Scope: Submission of the final report from the PASS study TV48125-MH-50039 listed as a category 3 study in the RMP. This is a long-term, prospective, observational study to evaluate the safety, including cardiovascular safety, of fremanezumab in patients with migraine in routine clinical practice. The RMP version 6.0 has also been submitted

17.4.5. Infliximab - FLIXABI (CAP) - EMEA/H/C/004020/II/0084/G

Applicant: Samsung Bioepis NL B.V.

PRAC Rapporteur: Mari Thorn

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

C.I.13: Submission of the final report from study CEDUR listed as a category 3 study in the RMP. This is a nationwide German inflammatory bowel disease (IBD) registry to describe the long-term effectiveness of treatment with IBD therapies such as drug survival, effectiveness, side effects of treatment combination, and disease activity achieved

C.I.13: Submission of the final report from study CREDIT listed as a category 3 study in the RMP. This is a Czech Register of IBD Patients on Biological Therapy to monitor effectiveness of total population of IBD patients on biological medication in the Czech Republic and regular analytical evaluation of the effectiveness. The RMP version 13.0 has also been submitted

17.4.6. Lasmiditan - RAYVOW (CAP) - EMEA/H/C/005332/II/0007

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Anna Mareková

Scope: Submission of the final report from study H8H-MC-B005, listed as a category 3 study in the RMP (MEA/003). This is a real-world observational study to assess drug

utilisation patterns in the US among migraine patients treated with lasmiditan. The RMP version 2.1 is submitted alongside the final study report

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

Applicant: Orexigen Therapeutics Ireland Limited

PRAC Rapporteur: Martin Huber

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

17.4.8. [Tacrolimus - ADVAGRAF \(CAP\) - EMEA/H/C/000712/WS2519/0071/G; MODIGRAF \(CAP\) - EMEA/H/C/000954/WS2519/0046/G](#)

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Eamon O'Murchu

Scope: A grouped application consisting of: Type II (C.I.13): Submission of the final report from study F506-PV-0001 listed as a category 3 study in the RMP for Advagraf and Modigraf. This is a non-interventional PASS of outcomes associated with the use of tacrolimus around conception, or during pregnancy or lactation using data from Transplant Pregnancy Registry International (TPRI). The RMP version 5.0 has also been submitted. Type IB (C.I.11.z): To include the feasibility assessment of using alternative secondary-use data sources to replicate the Transplant Pregnancy Registry International (TPRI) study as a category 3 additional pharmacovigilance activity in the RMP, including the milestones for the progress report and the final report of the feasibility assessment, related to EMEA/H/C/000712/MEA/032 and EMEA/H/C/000954/MEA/024

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

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Tiphaine Vaillant

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

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

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

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

17.4.10. [Tozinameran - COMIRNATY \(CAP\) - EMEA/H/C/005735/II/0206/G](#)

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Liana Martirosyan

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

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

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

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

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

17.4.11. [Vonico alfa - VEYVONDI \(CAP\) - EMEA/H/C/004454/II/0033](#)

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Mari Thorn

Scope: Submission of the final report from study TAK-577-4005 listed as a category 3 PASS in the RMP. This is a non-interventional retrospective cohort study that evaluated the safety of VEYVONDI in real-world clinical practice. The RMP version 5.0 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. [Alemtuzumab - LEMTRADA \(CAP\) - EMEA/H/C/003718/ANX 010.9](#)

Applicant: Sanofi Belgium

PRAC Rapporteur: Karin Ernehalm

Scope: Third interim report of Study DUT0008: non-interventional PASS to investigate drug utilisation and safety monitoring patterns for Lemtrada (alemtuzumab)

17.5.2. [Apremilast - OTEZLA \(CAP\) - EMEA/H/C/003746/MEA 008.4](#)

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Monica Martinez Redondo

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

17.5.3. Blinatumomab - BLINCYTO (CAP) - EMEA/H/C/003731/ANX 002.3

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Jana Lukacisinova

Scope: Interim study report for PASS Study 20150136: an observational study of blinatumomab safety and effectiveness, utilisation, and treatment practices

17.5.4. Damoctocog alfa pegol - JIVI (CAP) - EMEA/H/C/004054/MEA 003.5

Applicant: Bayer AG

PRAC Rapporteur: Bianca Mulder

Scope: From Initial MAA: Study 14149: EUHASS Registry (European Haemophilia Safety Surveillance); Quarterly listings, annual reports (1 year after the end of the reporting period (upon receipt from EUHASS))

17.5.5. Etanercept - BENEPALI (CAP) - EMEA/H/C/004007/MEA 002.5

Applicant: Samsung Bioepis NL B.V.

PRAC Rapporteur: Monica Martinez Redondo

Scope: Sixth interim report for an established nationwide register: British Society for Rheumatology Rheumatoid Arthritis Register (BSRBR-RA) for patients with rheumatological disorders treated with biologic agents, designed as a national prospective study whose primary purpose is to assess long-term toxicity from the use of these agents in routine practice [final report expected in 2027]

17.5.6. Etanercept - BENEPALI (CAP) - EMEA/H/C/004007/MEA 004.5

Applicant: Samsung Bioepis NL B.V.

PRAC Rapporteur: Monica Martinez Redondo

Scope: Sixth annual interim report for study from the Anti-Rheumatic Treatment in Sweden (ARTIS) register: a national prospective, observational, uncontrolled cohort study evaluating the risk of selected adverse events (AEs) in rheumatoid arthritis (RA), juvenile idiopathic arthritis, and other rheumatic disease patients treated with etanercept [final report expected in 2027]

17.5.7. Etanercept - BENEPALI (CAP) - EMEA/H/C/004007/MEA 005.5

Applicant: Samsung Bioepis NL B.V.

PRAC Rapporteur: Monica Martinez Redondo

Scope: Sixth annual interim report for study from the British Association of Dermatologists Biologic Interventions Register (BADBIR): a national prospective, observational cohort study of patients with psoriasis, which compares patients treated with biological interventions to a control group not exposed to biologicals [final report expected in 2027]

17.5.8. Infliximab - REMSIMA (CAP) - EMEA/H/C/002576/MEA 020.5

Applicant: Celltrion Healthcare Hungary Kft.

PRAC Rapporteur: Kimmo Jaakkola

Scope: Annual Recruitment Status Report for study CT-P13 4.8: an observational, prospective cohort study to evaluate safety of Remsima SC in patients with rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and psoriasis

17.5.9. Inotersen - TEGSEDI (CAP) - EMEA/H/C/004782/MEA 001.10

Applicant: Akcea Therapeutics Ireland Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Interim report covering the period of 18 September 2022 to 19 September 2023 for study TEG4001: a prospective, non-interventional, long-term, multinational cohort safety study of patients with hereditary transthyretin amyloidosis with polyneuropathy (hATTR-PN)

17.5.10. Octocog alfa - KOVALTRY (CAP) - EMEA/H/C/003825/MEA 004.7

Applicant: Bayer AG

PRAC Rapporteur: Gabriele Maurer

Scope: 14th Annual Report for Study 14149 (listed as a category 3 study in the RMP): evaluation of cases with adverse events (AEs) of special interest in the European Haemophilia Safety Surveillance (EUHASS) registry

17.5.11. Plasmodium falciparum and hepatitis B vaccine (recombinant, adjuvanted) - MOSQUIRIX (Art 58⁶⁰) - EMEA/H/W/002300/MEA 015.1

Applicant: GlaxoSmithkline Biologicals SA

PRAC Rapporteur: Jean-Michel Dogné

Scope: From EMEA/H/W/002300/II/0020: Statistical Analysis Plan (SAP) of EPI-MAL-010 (205071) interim analysis and associated Tables, Figures and Listings (TFLs)

17.5.12. Rurioctocog alfa pegol - ADYNOVI (CAP) - EMEA/H/C/004195/ANX 002.3

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Bianca Mulder

Scope: Fourth progress report for PASS TAK-660-403 (imposed/non-interventional/cat. 3) to investigate the potential effects of PEG accumulation in the choroid plexus of the brain and other tissues/organs

⁶⁰ Article 58 of Regulation (EC) No 726/2004 allows the Committee for Medicinal Products for Human Use (CHMP) to give opinions, in co-operation with the World Health Organisation (WHO) on medicinal products for human use that are intended exclusively for markets outside of the European Union (EU)

17.5.13. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/MEA 014.7

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Martirosyan

Scope: First interim report for PASS A3921321: a PASS of the utilisation and prescribing patterns of Xeljanz (tofacitinib) in two European countries using administrative claims databases and national registries for assessment

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. Afamelanotide - SCENESSE (CAP) - EMEA/H/C/002548/S/0050 (without RMP)

Applicant: Clinuvel Europe Limited

PRAC Rapporteur: Martin Huber

Scope: Annual reassessment of the marketing authorisation

18.1.2. Histamine dihydrochloride - CEPLENE (CAP) - EMEA/H/C/000796/S/0048 (without RMP)

Applicant: Laboratoires Delbert

PRAC Rapporteur: Eamon O'Murchu

Scope: Annual reassessment of the marketing authorisation

18.1.3. Maralixibat - LIVMARLI (CAP) - EMEA/H/C/005857/S/0012 (without RMP)

Applicant: Mirum Pharmaceuticals International B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Annual reassessment of the marketing authorisation

18.2. Conditional renewals of the marketing authorisation

18.2.1. Budesonide - KINPEYGO (CAP) - EMEA/H/C/005653/R/0010 (without RMP)

Applicant: STADA Arzneimittel AG

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Conditional renewal of the marketing authorisation

18.2.2. Talquetamab - TALVEY (CAP) - EMEA/H/C/005864/R/0005 (without RMP)

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Barbara Kovacic Bytyqi

Scope: Conditional renewal of the marketing authorisation

18.2.3. Teclistamab - TECVAYLI (CAP) - EMEA/H/C/005865/R/0010 (without RMP)

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Jana Lukacisinova

Scope: Conditional renewal of the marketing authorisation

18.3. Renewals of the marketing authorisation

18.3.1. Cannabidiol - EPIDYOLEX (CAP) - EMEA/H/C/004675/R/0031 (with RMP)

Applicant: Jazz Pharmaceuticals Ireland Limited

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: 5-year renewal of the marketing authorisation

18.3.2. Gilteritinib - XOSPATA (CAP) - EMEA/H/C/004752/R/0017 (without RMP)

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Martin Huber

Scope: 5-year renewal of the marketing authorisation

18.3.3. 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

18.3.4. Levodopa - INBRIJA (CAP) - EMEA/H/C/004786/R/0022 (without RMP)

Applicant: Acorda Therapeutics Ireland Limited

PRAC Rapporteur: Barbara Kovacic Bytyqi

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 08-11 April 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	
Jan Neuhauser ^a	Member	Austria	No interests declared	
Sonja Hrabcik ^a	Alternate	Austria	No interests declared	
Jean-Michel Dogné ^{a,b}	Member	Belgium	No interests declared	
Jo Robays ^{a,b}	Alternate	Belgium	No interests declared	
Maria Popova-Kiradjieva ^{a,b}	Member	Bulgaria	No interests declared	
Petar Mas ^{a,b}	Member	Croatia	No interests declared	
Barbara Bytyqi ^{a,b}	Member	Croatia	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Panagiotis Psaras ^{a,b}	Alternate	Cyprus	No interests declared	
Eva Jirsová ^{a,b}	Member	Czechia	No interests declared	
Jana Lukacisinova ^{a,b}	Alternate	Czechia	No interests declared	
Marie Louise Schougaard Christiansen ^{a,b}	Member	Denmark	No interests declared	
Karin Erneholm ^{a,b}	Alternate	Denmark	No interests declared	
Maia Uusküla ^a	Member	Estonia	No interests declared	
Kirsti Villikka ^{a,b}	Member	Finland	No interests declared	
Kimmo Jaakkola ^{a,b}	Alternate	Finland	No interests declared	
Tiphaine Vaillant ^{a,b}	Member	France	No interests declared	
Nathalie Gault ^{a,b}	Alternate	France	No interests declared	
Martin Huber ^{a,b}	Member (Vice-Chair)	Germany	No interests declared	
Gabriele Maurer ^{a,b}	Alternate	Germany	No participation in final deliberations and voting on:	4.2.2. Atezolizumab - TECENTRIQ (CAP) - EMEA/H/C/004143/SDA/025.1; Avelumab - BAVENCIO (CAP) - EMEA/H/C/004338/SDA/011.1; Cemiplimab - LIBTAYO (CAP) - EMEA/H/C/004844/SDA/010.1; Dostarlimab - JEMPERLI (CAP) - EMEA/H/C/005204/SDA/005.1; Durvalumab - IMFINZI (CAP) - EMEA/H/C/004771/SDA/012.1; Ipilimumab - YERVOY (CAP) -

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				<p>EMEA/H/C/002213 /SDA/048.1; Nivolumab - OPDIVO (CAP) - EMEA/H/C/003985 /SDA/056.1; Nivolumab, relatlimab - OPDUALAG (CAP) - EMEA/H/C/005481 /SDA/006.1; Pembrolizumab - KEYTRUDA (CAP) - EMEA/H/C/003820 /SDA/040.1; Tislelizumab - TEVIMBRA (CAP) - EMEA/H/C/005919 /SDA/002.1; Tremelimumab - IMJUDO (CAP) - EMEA/H/C/006016 /SDA/003.1</p> <p>4.2.3 Atezolizumab - TECENTRIQ (CAP) - EMEA/H/C/004143 /SDA/024.1; Avelumab - BAVENCIO (CAP) - EMEA/H/C/004338 /SDA/010.1; Cemiplimab - LIBTAYO (CAP) - EMEA/H/C/004844 /SDA/009.1; Dostarlimab - JEMPERLI (CAP) - EMEA/H/C/005204 /SDA/004.1; Durvalumab - IMFINZI (CAP) - EMEA/H/C/004771 /SDA/011.1; Ipilimumab - YERVOY (CAP) - EMEA/H/C/002213 /SDA/047.1; Nivolumab - OPDIVO (CAP) - EMEA/H/C/003985 /SDA/055.1; Nivolumab, relatlimab - OPDUALAG (CAP) -</p>

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				<p>EMA/H/C/005481 /SDA/005.1; Pembrolizumab - KEYTRUDA (CAP) - EMA/H/C/003820 /SDA/039.1; Tislelizumab - TEVIMBRA (CAP) - EMA/H/C/005919 /SDA/001.1; Tremelimumab - IMJUDO (CAP) - EMA/H/C/006016 /SDA/002.1</p> <p>15.3.28 Nivolumab - OPDIVO (CAP) - EMA/H/C/003985 /II/0140</p> <p>16.1.37 Nivolumab, relatlimab - OPDUALAG (CAP) - PSUSA/00011018/202309</p>
Sofia Trantzsa ^{a,b}	Member	Greece	No interests declared	
Georgia Gkegka ^{a,b}	Alternate*	Greece	No interests declared	
Julia Pallos ^{a,b}	Member	Hungary	No participation in final deliberations and voting on:	<p>4.2.2 Atezolizumab - TECENTRIQ (CAP) - EMA/H/C/004143 /SDA/025.1; Avelumab - BAVENCIO (CAP) - EMA/H/C/004338 /SDA/011.1; Cemiplimab - LIBTAYO (CAP) - EMA/H/C/004844 /SDA/010.1; Dostarlimab - JEMPERLI (CAP) - EMA/H/C/005204 /SDA/005.1; Durvalumab - IMFINZI (CAP) - EMA/H/C/004771 /SDA/012.1; Ipilimumab - YERVOY (CAP) - EMA/H/C/002213</p>

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				/SDA/048.1; Nivolumab - OPDIVO (CAP) - EMEA/H/C/003985 /SDA/056.1; Nivolumab, relatlimab - OPDUALAG (CAP) - EMEA/H/C/005481 /SDA/006.1; Pembrolizumab - KEYTRUDA (CAP) - EMEA/H/C/003820 /SDA/040.1; Tislelizumab - TEVIMBRA (CAP) - EMEA/H/C/005919 /SDA/002.1; Tremelimumab - IMJUDO (CAP) - EMEA/H/C/006016 /SDA/003.1 4.2.3 Atezolizumab - TECENTRIQ (CAP) - EMEA/H/C/004143 /SDA/024.1; Avelumab - BAVENCIO (CAP) - EMEA/H/C/004338 /SDA/010.1; Cemiplimab - LIBTAYO (CAP) - EMEA/H/C/004844 /SDA/009.1; Dostarlimab - JEMPERLI (CAP) - EMEA/H/C/005204 /SDA/004.1; Durvalumab - IMFINZI (CAP) - EMEA/H/C/004771 /SDA/011.1; Ipilimumab - YERVOY (CAP) - EMEA/H/C/002213 /SDA/047.1; Nivolumab - OPDIVO (CAP) - EMEA/H/C/003985 /SDA/055.1; Nivolumab, relatlimab - OPDUALAG (CAP) - EMEA/H/C/005481

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				<p>/SDA/005.1; Pembrolizumab - KEYTRUDA (CAP) - EMEA/H/C/003820 /SDA/039.1; Tislelizumab - TEVIMBRA (CAP) - EMEA/H/C/005919 /SDA/001.1; Tremelimumab - IMJUDO (CAP) - EMEA/H/C/006016 /SDA/002.1</p> <p>4.2.4 Axicabtagene ciloleucel – YESCARTA (CAP) - EMEA/H/C/004480 /SDA/015; idecabtagene vicleucel – ABECMA (CAP) - EMEA/H/C/004662 /SDA/020; lisocabtagene maraleucel – BREYANZI (CAP) - EMEA/H/C/004731 /SDA/019; ciltabtagene autoleucel – CARVYKTI (CAP) - EMEA/H/C/005095 /SDA/016; tisagenlecleucel – KYMRIAH (CAP) - EMEA/H/C/004090 /SDA/024; brexucabtagene autoleucel – TECARTUS (CAP) - EMEA/H/C/005102 /SDA/013</p> <p>6.1.9. Idcabtagene vicleucel - ABECMA (CAP) - PSUSA/00010954/202309</p> <p>15.2.4 Dasatinib - SPRYCEL (CAP) - EMEA/H/C/000709 /II/0090</p>

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				<p>15.3.19 Fedratinib - INREBIC (CAP) - EMEA/H/C/005026/II/0020</p> <p>15.3.28. Nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/II/0140</p> <p>16.1.13. Deucravacitinib - SOTYKTU (CAP) - PSUSA/00011046/202309</p> <p>16.1.37. Nivolumab, relatlimab - OPDUALAG (CAP) - PSUSA/00011018/202309</p> <p>16.3.1. Aztreonam (NAP) - PSUSA/00010178/202308</p> <p>17.2.5. Deucravacitinib - SOTYKTU (CAP) - EMEA/H/C/005755/MEA 001.1</p> <p>17.2.9. Mavacamten - CAMZYOS (CAP) - EMEA/H/C/005457/MEA 002.1</p>
Guðrún Stefánsdóttir ^{a,b}	Member	Iceland	No participation in final deliberations and voting on:	<p>17.4.2. Denosumab - PROLIA (CAP) - EMEA/H/C/001120/II/0100</p> <p>17.5.2. Apremilast - OTEZLA (CAP) - EMEA/H/C/003746/MEA 008.4</p> <p>17.5.3. Blinatumomab - BLINCYTO (CAP) - EMEA/H/C/003731/ANX 002.3</p>

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Rhea Fitzgerald ^{a,b}	Member	Ireland	No interests declared	
Eamon O Murchu ^{a,b}	Alternate	Ireland	No interests declared	
Amelia Cupelli ^{a,b}	Member	Italy	No interests declared	
Zane Neikena ^{a,b}	Member	Latvia	No interests declared	
Lina Seibokiene ^{a,b}	Alternate	Lithuania	No restrictions applicable to this meeting	
Nadine Petitpain ^{a,b}	Member	Luxembourg	No restrictions applicable to this meeting	
John Joseph Borg ^a	Member (CHMP member)	Malta	No interests declared	
Liana Martirosyan ^{a,b}	Member	Netherlands	No interests declared	
Bianca Mulder ^{a,b}	Alternate	Netherlands	No interests declared	
David Olsen ^{a,b}	Member	Norway	No participation in final deliberations and voting on:	<p>4.2.5. Chlorhexidine (NAP) and other relevant fixed-dose combinations</p> <p>6.3.3. Dienogest, estradiol (NAP) - PSUSA/00010444/202309</p> <p>6.3.6. Naproxen (NAP) - PSUSA/00002125/202308</p> <p>16.1.11. Damoctocog alfa pegol - JIVI (CAP) - PSUSA/00010732/202308</p> <p>17.5.4. Damoctocog alfa pegol - JIVI (CAP) - EMEA/H/C/004054</p>

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				/MEA 003.5 17.5.10. Octocog alfa - KOVALTRY (CAP) - EMEA/H/C/003825 /MEA 004.7
Pernille Harg ^{a,b}	Alternate	Norway	No interests declared	
Adam Przybylkowski ^a	Member	Poland	No interests declared	
Ana Sofia Diniz Martins ^a	Member	Portugal	No interests declared	
Carla Torre ^a	Alternate	Portugal	No interests declared	
Roxana Dondera ^{a,b}	Member	Romania	No interests declared	
Irina Sandu ^{a,b}	Alternate*	Romania	No interests declared	
Anna Mareková ^{a,b}	Member	Slovakia	No interests declared	
Miroslava Gocova ^a	Alternate*	Slovakia	No interests declared	
Polona Golmajer ^{a,b}	Member	Slovenia	No interests declared	
Marjetka Plementas ^{a,b}	Alternate	Slovenia	No interests declared	
Maria del Pilar Rayon ^{a,b}	Member	Spain	No interests declared	
Monica Martinez Redondo ^{a,b}	Alternate	Spain	No interests declared	
Ulla Wändel Liminga ^{a,b}	Member	Sweden	No interests declared	
Mari Thorn ^{a,b}	Alternate	Sweden	No restrictions applicable to this meeting	
Annalisa Capuano ^a	Member*	Independent scientific expert	No interests declared	
Milou-Daniel Drici ^a	Member	Independent scientific expert	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Teresa Herdeiro ^a	Member	Independent scientific expert	No interests declared	
Patricia McGettigan ^a	Member*	Independent scientific expert	No interests declared	
Tania Schink ^a	Member	Independent scientific expert	No restrictions applicable to this meeting	
Hedvig Marie Egeland Nordeng ^a	Member	Independent scientific expert	No interests declared	
Roberto Frontini ^{a,b}	Member	Healthcare Professionals' Representative	No restrictions applicable to this meeting	
Salvatore Antonio Giuseppe Messina ^a	Alternate	Healthcare Professionals' Representative	No interests declared	
Marko Korenjak ^a	Member	Patients' Organisation Representative	No interests declared	
Michal Rataj ^a	Alternate	Patients' Organisation Representative	No interests declared	
Els Beghein ^b	Expert	Belgium	No interests declared	
Christelle Bizimungu ^a	Expert	Belgium	No restrictions applicable to this meeting	
Evelien De Clercq ^a	Expert	Belgium	No interests declared	
Laurence de Fays ^{a,b}	Expert	Belgium	No interests declared	
Olga Kholmanskikh Van Crieelingen ^a	Expert	Belgium	No interests declared	
Flora Musuamba Tshinanu ^a	Expert	Belgium	No restrictions applicable to this meeting	
Charlotte Selvais ^a	Expert	Belgium	No interests declared	
Françoise Wullaume ^a	Expert	Belgium	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Veronika Descikova ^a	Expert	Czech Republic	No interests declared	
Michaela Dlouha ^a	Expert	Czech Republic	No interests declared	
Lucie Skalova ^a	Expert	Czech Republic	No interests declared	
Nicklas Hasselblad Lundstrøm ^a	Expert	Denmark	No interests declared	
Frederikke Hillebrand Laustsen ^a	Expert	Denmark	No restrictions applicable to this meeting	
Torsten Holm Nielsen ^a	Expert	Denmark	No interests declared	
Mette Knudgaard Hjorslev ^a	Expert	Denmark	No interests declared	
Kristina Laursen ^a	Expert	Denmark	No interests declared	
Moritz Sander ^a	Expert	Denmark	No interests declared	
Per Sindahl ^a	Expert	Denmark	No interests declared	
Ditte Søgaard ^a	Expert	Denmark	No interests declared	
Helene Stenbæk Hansen ^{a,b}	Expert	Denmark	No restrictions applicable to this meeting	
Vincent Gazin	Expert	France	No interests declared	
Marion Perrin ^a	Expert	France	No interests declared	
Emilie Vittaz ^a	Expert	France	No interests declared	
Dennis Lex ^{a,b}	Expert	Germany	No interests declared	
Jan Müller-Berghaus ^a	Expert	Germany	No interests declared	
Barbara Bonamassa ^a	Expert	Italy	No interests declared	
Antonella Isgrò ^a	Expert	Italy	No interests declared	
Ingrid Bijsmans ^a	Expert	Netherlands	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Talip Eroglu ^a	Expert	Netherlands	No interests declared	
Margje Monster-Simons ^a	Expert	Netherlands	No interests declared	
Evelyn Mulder-Olthof ^a	Expert	Netherlands	No interests declared	
Paul ten Berg ^a	Expert	Netherlands	No interests declared	
Patrick Vrijlandt ^a	Expert	Netherlands	No interests declared	
Concetta Quintarelli ^a	Expert	Norway	No restrictions applicable to this meeting	
Eva Cantarero ^a	Expert	Spain	No interests declared	
Natividad Galiana ^a	Expert	Spain	No restrictions applicable to this meeting	
Nuria Garcia Sainz ^a	Expert	Spain	No interests declared	
Maria Martinez Gonzalez ^a	Expert	Spain	No interests declared	
Consuelo Mejías ^a	Expert	Spain	No interests declared	
Per Albertsson ^a	Expert	Sweden	No restrictions applicable to this meeting	
Charlotte Anderberg ^a	Expert	Sweden	No interests declared	
Charlotte Backman ^{a,b}	Expert	Sweden	No interests declared	
Karin Bolin ^a	Expert	Sweden	No interests declared	
Karin Fjordén ^a	Expert	Sweden	No restrictions applicable to this meeting	
Anna Schölin ^a	Expert	Sweden	No interests declared	

A representative from the European Commission attended the meeting

Observers from FDA (USA), Health Canada (Canada) and WHO attended the meeting.

Meeting run with support from relevant EMA staff

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

20. Annex III - List of acronyms and abbreviations

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

[Home>Committees>PRAC>Agendas, minutes and highlights](#)

21. Explanatory notes

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

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

(Items 2 and 3 of the PRAC minutes)

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

Signals assessment and prioritisation

(Item 4 of the PRAC minutes)

A safety signal is information on a new or incompletely documented adverse event that is potentially caused by a medicine and that warrants further investigation. Signals are generated from several sources such as spontaneous reports, clinical studies and the scientific literature. The evaluation of safety signals is a routine part of pharmacovigilance and is essential to ensuring that regulatory authorities have a comprehensive knowledge of a medicine's benefits and risks.

The presence of a safety signal does not mean that a medicine has caused the reported adverse event. The adverse event could be a symptom of another illness or caused by another medicine taken by the patient. The evaluation of safety signals is required to establish whether or not there is a causal relationship between the medicine and the reported adverse event.

The evaluation of safety signals may not necessarily conclude that the medicine caused the adverse event in question. In cases where a causal relationship is confirmed or considered likely, regulatory action may be necessary and this usually takes the form of an update of the summary of product characteristics and the package leaflet.

Risk Management Plans (RMPs)

(Item 5 of the PRAC minutes)

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

Assessment of Periodic Safety Update Reports (PSURs)

(Item 6 of the PRAC minutes)

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

Post-authorisation Safety Studies (PASS)

(Item 7 of the PRAC minutes)

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

Product related pharmacovigilance inspections

(Item 9 of the PRAC minutes)

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

More detailed information on the above terms can be found on the EMA website:

<https://www.ema.europa.eu/en>