28 March 2023
EMA/PRAC/135553/2023
Human Medicines Division

Pharmacovigilance Risk Assessment Committee (PRAC)

Minutes of the meeting on 28 November-01 December 2022

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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Table of contents

1. Introduction

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

The Chair opened the meeting by welcoming all participants. Due to the current coronavirus (COVID-19) pandemic, and the associated EMA Business Continuity Plan (BCP), the meeting was held in-person with some members connected remotely (hybrid setting).

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

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

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

1.2. Agenda of the meeting on 28 November – 01 December 2022

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 24-27 October 2022

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 24-27 October 2022 will be published on the EMA website.

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

2.1. Newly triggered procedures

None

2.2. Ongoing procedures

None

2.3. Procedures for finalisation

2.3.1. Pholcodine (NAP); pholcodine, biclotymol, chlorphenamine (NAP); pholcodine, chlorphenamine (NAP); pholcodine, chlorphenamine, ephedrine (NAP); pholcodine, diphenhydramine (NAP); pholcodine, dextromethorphan, paracetamol (NAP); pholcodine, diphenhydramine, paracetamol, pseudoephedrine (NAP); pholcodine, guaiacol (NAP); pholcodine, paracetamol, pseudoephedrine (NAP) - EMEA/H/A-107i/1521

Applicant(s): various

PRAC Rapporteur: Željana Margan Koletić; PRAC Co-rapporteur: Lina Seibokiene

Scope: Review of the benefit-risk balance following notification by France of a referral under Article 107i of Directive 2001/83/EC, based on pharmacovigilance data

Background

A referral procedure under Article 107i of Directive 2001/83/EC for pholcodine-containing products is to be concluded. The review was initiated following the preliminary results of ALPHO[1], a post-authorisation safety study (PASS) imposed as a condition to the marketing authorisations of pholcodine-containing products suggesting a significant link between exposure to pholcodine during the 12 months preceding surgery and a risk of peri-anaesthetic anaphylactic reaction related to neuromuscular blocking agents (NMBA). For further background, see PRAC minutes September 2022[2]. A final assessment of the data submitted was produced by the Rapporteurs according to the agreed timetable.

Discussion

PRAC discussed the conclusion reached by the Rapporteurs.

PRAC reviewed the totality of the data available for pholcodine-containing products in relation to the risk of perianaesthetic anaphylactic reaction related to NMBAs, in writing and in an oral explanation. This included the results of observational studies including the ALPHO[1] study, literature data, post-marketing case reports as well as responses submitted by the MAHs and the submissions by the stakeholders.

PRAC considered that the data reviewed confirm an association between the use of pholcodine and the risk of perianaesthetic anaphylactic reaction to NMBAs, an unpredictable and potentially life-threatening situation.

No specific characteristics for perianesthetic anaphylactic reaction to NMBA could be identified in patients who have been treated with pholcodine, and therefore all these patients are considered at risk. In addition, PRAC could not identify risk minimisation measures that would be effective at reducing the risk of perianaesthetic anaphylactic reaction related to NMBAs in patients who have been treated with pholcodine-containing products.

Therefore, PRAC concluded that the risk of perianaesthetic anaphylactic reaction related to NMBAs outweighs the benefit of pholcodine in the treatment of non-productive cough, a symptomatic indication considered acute and not serious.

Further, PRAC could not identify conditions which if fulfilled would demonstrate a positive benefit-risk balance for pholcodine-containing products in a defined patient population.

[1] Neuromuscular blocking agent anaphylaxis and pholcodine exposure – A case-control study, Central Hospital - Nancy, France, Principal investigator: Pierre Gillet
[2] Held on 29 August – 01 September 2022

As a consequence, PRAC considered that the benefit-risk balance of pholcodine-containing products is no longer favourable.

Summary of recommendation(s)/conclusions

- PRAC adopted a recommendation, by majority, to revoke the marketing authorisation(s) for pholcodine-containing products to be considered by CMDh for a position – see EMA Press Release (EMA/906150/2022) entitled 'EMA recommends withdrawal of pholcodine medicines from EU market' published on 02 December 2022.
- PRAC agreed on the distribution of a direct healthcare professional communication (DHPC) together with a communication plan.

Thirty-two members voted in favour of the recommendation whilst two members[3] had divergent views. The Icelandic and Norwegian PRAC members agreed with the recommendation.

Post-meeting note 1: the press release entitled 'EMA recommends withdrawal of pholcodine medicines from EU market' (EMA/906150/2022) representing the position adopted by CMDh was published on the EMA website on 16 December 2022. The press release (EMA/126062/2023) reflecting the date of the European Commission's final legally binding decision applicable in all EU Member States was published on the EMA website on 29 March 2023.

Post-meeting note 2: the PRAC assessment report (EMA/950036/2022) was published on the EMA website on 22 March 2023.

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

3.1. Newly triggered procedures

None

3.2. Ongoing procedures

3.2.1. Topiramate (NAP); topiramate, phentermine (NAP) - EMEA/H/A-31/1520

Applicant(s): various

PRAC Rapporteur: Ulla Wändel Liminga; PRAC Co-rapporteur: Martin Huber

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

Background

A referral procedure under Article 31 of Directive 2001/83/EC is ongoing for topiramate- and topiramate/phentermine-containing medicines following the publication by *Bjørk et al.*[4] in which the authors concluded on a statistically significant increase of neurodevelopmental disorders, in particular autism spectrum disorders and intellectual disability, in children with

[3] John Joseph Borg, Nikica Mirošević Skvrce
[4] Bjørk M, Zoega H, Leinonen MK, et al. Association of prenatal exposure to antiseizure medication with risk of autism and intellectual disability. JAMA Neurol. Published online May 31, 2022. doi:10.1001/jamaneurol.2022.1269

prenatal exposure to topiramate. Given the potential increased risk of neurodevelopmental disorders highlighted in this study with in utero exposure to topiramate and the known risk of congenital malformations, the matter was referred to PRAC for further evaluation. For further background, see PRAC minutes September 2022[5].

Summary of recommendation(s)/conclusions

- PRAC discussed the assessment reports issued by the Rapporteurs.
- PRAC adopted a list of outstanding issues (LoOI) to be addressed by the MAHs in accordance with a revised timetable (EMA/PRAC/702489/2022 rev.1).

3.3. Procedures for finalisation

None

3.4. Re-examination procedures[6]

None

3.5. Others

None

4. Signals assessment and prioritisation[7]

4.1. New signals detected from EU spontaneous reporting systems

See also Annex 14.1.

4.1.1. Coronavirus (COVID-19) vaccine (ChAdOx1-S [recombinant]) - VAXZEVRIA (CAP)

Applicant: AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

Scope: Signal of pemphigus and pemphigoid

EPITT 19858 – New signal

Lead Member State(s): BE

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.

[5] Held on 29 August – 01 September 2022
[6] Re-examination of PRAC recommendation under Article 32 of Directive 2001/83/EC
[7] 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

During routine signal detection activities, a signal of pemphigus and pemphigoid was identified by EMA, based on 98 cases retrieved from EudraVigilance and 18 cases identified in the literature.

The Rapporteur confirmed that the signal needed initial analysis and prioritisation by PRAC.

Discussion

Having considered the available evidence in EudraVigilance and the literature, PRAC agreed that further evaluation on the signal of pemphigus and pemphigoid with Vaxzevria (coronavirus (COVID-19) vaccine (ChAdOx1-S [recombinant]) is warranted.

Summary of recommendation(s)

- The MAH for Vaxzevria (coronavirus (COVID-19) vaccine (ChAdOx1-S [recombinant]) should submit to EMA, within 60 days, a cumulative review of cases of pemphigus and pemphigoid from all sources, including available data from clinical trials, scientific literature and post marketing exposure. The MAH should also perform a causality assessment and discuss the plausibility and possible mechanism(s) of action for the occurrence of pemphigus or pemphigoid following administration of the vaccine. In addition, the MAH should provide a cumulative review of cases of dermatitis bullous and bullous condition. The MAH should also provide an observed versus expected (O/E) analysis for all cases. Finally, the MAH should propose to update the product information and/or RMP as warranted.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.1.2. Elasomeran – SPIKEVAX (CAP)

Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Signal of pemphigus and pemphigoid

EPITT 19860 – New signal

Lead Member State(s): DK

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 pemphigus and pemphigoid was identified by EMA, based on 107 cases retrieved from EudraVigilance.

The Rapporteur confirmed that the signal needed initial analysis and prioritisation by PRAC.

Discussion

Having considered the available evidence in EudraVigilance and the literature, PRAC agreed that further evaluation on the signal of pemphigus and pemphigoid with Spikevax (elasomeran) is warranted.

Summary of recommendation(s)

- The MAH for Spikevax (elasomeran) should submit to EMA, within 60 days, a cumulative review of cases of pemphigus and pemphigoid from all sources, including available data from clinical trials, scientific literature and post marketing exposure. The MAH should also perform a causality assessment and discuss the plausibility and possible mechanism(s) of action for the occurrence of pemphigus or pemphigoid following administration of the vaccine. In addition, the MAH should provide a cumulative review of cases of dermatitis bullous and bullous condition. The MAH should also provide an observed versus expected (O/E) analysis for all cases. Finally, the MAH should propose to update the product information and/or RMP as warranted.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.1.3. Tozinameran – COMIRNATY (CAP)

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Signal of pemphigus and pemphigoid

EPITT 19859 – New signal

Lead Member State(s): 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 pemphigus and pemphigoid was identified by EMA, based on 206 cases retrieved from EudraVigilance and 63 case reports from the literature.

The Rapporteur confirmed that the signal needed initial analysis and prioritisation by PRAC.

Discussion

Having considered the available evidence in EudraVigilance and the literature, PRAC agreed that further evaluation on the signal of pemphigus and pemphigoid with Comirnaty (tozinameran) is warranted.

Summary of recommendation(s)

- The MAH for Comirnaty (tozinameran) should submit to EMA, within 60 days, a cumulative review of cases of pemphigus and pemphigoid from all sources, including available data from clinical trials, scientific literature and post marketing exposure. The MAH should also perform a causality assessment and discuss the plausibility and possible mechanism(s) of action for the occurrence of pemphigus or pemphigoid following administration of the vaccine. In addition, the MAH should provide a cumulative review of cases of dermatitis bullous and bullous condition. The MAH should also provide an observed versus expected (O/E) analysis for all cases. Finally, the MAH should propose to update the product information and/or RMP as warranted.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.2. New signals detected from other sources

None

4.3. Signals follow-up and prioritisation

4.3.1. Cetuximab – ERBITUX (CAP) - EMEA/H/C/000558/SDA/054

Applicant: Merck Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of nephrotic syndrome

EPITT 19819 – Follow-up to July 2022

Background

For background information, see PRAC minutes July 2022.

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

Discussion

Having considered the available evidence from case reports in the literature and EudraVigilance, the MAH's responses and the Rapporteur's assessment, PRAC concluded that there is insufficient evidence to establish a causal relationship between cetuximab and nephrotic syndrome at present.

Summary of recommendation(s)

- The MAH for Erbitux (cetuximab) should continue to closely monitor any new cases of nephrotic syndrome and related disorders as part of routine safety surveillance.

4.3.2. Diphtheria, tetanus, pertussis (acellular, component), poliomyelitis (inactivated) vaccine (adsorbed) (NAP); diphtheria, tetanus, pertussis (acellular, component), poliomyelitis (inactivated) vaccine (adsorbed, reduced antigen(s) content) (NAP)

Applicant(s): various

PRAC Rapporteur: Anette Kirstine Stark

Scope: Signal of immune thrombocytopenia

EPITT: 19831 – Follow-up to July 2022

Background

For background information, see PRAC minutes July 2022.

The MAHs GSK, Sanofi and AJ Vaccines A/S replied to the request for information on the signal of immune thrombocytopenia and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence from spontaneous cases, case reports in the literature, clinical, mechanistic and epidemiological studies as well as the MAHs' responses and the Rapporteur's assessment, PRAC concluded that there is insufficient evidence to

confirm a causal association between administration of diphtheria, tetanus, pertussis (acellular, component), poliomyelitis (inactivated) vaccine (adsorbed) and diphtheria, tetanus, pertussis (acellular, component), poliomyelitis (inactivated) vaccine (adsorbed, reduced antigen(s) content) and the occurrence of immune thrombocytopenia at present.

Summary of recommendation(s)

- The MAHs for diphtheria, tetanus, pertussis (acellular, component), poliomyelitis (inactivated) vaccines (adsorbed) and MAHs for diphtheria, tetanus, pertussis (acellular, component), poliomyelitis (inactivated) vaccines (adsorbed, reduced antigen(s) content) should continue to closely monitor any new cases of immune thrombocytopenia as part of routine safety surveillance.

4.4. Variation procedure(s) resulting from signal evaluation

None

5. Risk management plans (RMPs)

5.1. Medicines in the pre-authorisation phase

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

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

See also Annex 15.1.

5.1.1. Eculizumab - EMEA/H/C/005652

Scope: Treatment of paroxysmal nocturnal haemoglobinuria

5.1.2. Ivosidenib - EMEA/H/C/005936, Orphan

Applicant: Les Laboratoires Servier

Scope : Treatment of acute myeloid leukaemia and treatment of metastatic cholangiocarcinoma

5.1.3. Ivosidenib - TIDHESCO (CAP MAA) - EMEA/H/C/006174, Orphan

Applicant: Les Laboratoires Servier

Scope: Treatment of acute myeloid leukaemia

5.1.4. Lenadogene nolparvovec - EMEA/H/C/005047, Orphan

Applicant: GenSight Biologics S.A., ATMP[8]

[8] Advanced therapy medicinal product

Scope: Treatment of vision loss due to Leber Hereditary Optic Neuropathy (LHON)

5.1.5. Niraparib, abiraterone acetate - EMEA/H/C/005932

Scope: Treatment of adult patients with prostate cancer

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

See Annex 15.2.

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

See also Annex 15.3.

5.3.1. Emicizumab - HEMLIBRA (CAP) - EMEA/H/C/004406/II/0027

Applicant: Roche Registration GmbH

PRAC Rapporteur: Amelia Cupelli

Scope: Extension of indication to include treatment of adult and paediatric patients with haemophilia A without factor VIII (FVIII) inhibitors who have mild or moderate disease for whom prophylaxis is clinically indicated. Consequently, sections 4.1, 4.8, 5.1 and 5.2 of the SmPC are updated. In addition, section 4.2 of the SmPC is updated to make clearer that the maintenance dose for Hemlibra (emicizumab) applies from week 5 of dosing. The package leaflet and the RMP (version 4.0) are updated accordingly

Background

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

CHMP is evaluating an extension of the therapeutic indication for Hemlibra, a centrally authorised product containing emicizumab, to include treatment of adult and paediatric patients with haemophilia A without factor VIII (FVIII) inhibitors who have mild or moderate disease for whom prophylaxis is clinically indicated. PRAC is responsible for providing advice to CHMP on the necessary updates to the RMP to support this extension of indication. For further background, see PRAC minutes January 2022, PRAC minutes May 2022 and PRAC minutes October 2022[9].

Summary of advice

- The RMP for Hemlibra (emicizumab) in the context of the variation under evaluation by CHMP could be considered acceptable provided that an update to RMP version 4.5 is submitted along with satisfactory responses to the request for supplementary information (RSI).
- PRAC considered acceptable at this stage the proposed observational study to characterise 'thromboembolic events (not associated with activated prothrombin complex concentrate (aPCC) exposure)' as an important potential risk and the information on the long-term safety of emicizumab treatment in patients with moderate

[9] Held on 26-29 September 2022

haemophilia A and severe bleeding phenotype. However, PRAC acknowledged that several details are lacking and require to be further evaluated at the time of the full protocol evaluation. In this context, PRAC considered that the MAH should provide clarifications on the availability of appropriate outcome measures, the possibility of including additional variables, the quality of data and on the possibility of accessing individual patient-level data. The MAH should also discuss the adequateness of data source(s) in collecting data suitable for the scope of the investigation.

5.3.2. Riociguat - ADEMPAS (CAP) - EMEA/H/C/002737/II/0037

Applicant: Bayer AG

PRAC Rapporteur: Kimmo Jaakkola

Scope: Extension of indication to include treatment of pulmonary arterial hypertension (PAH) in paediatric patients aged 6 to less than 18 years of age with WHO Functional Class (FC) I to III in combination with endothelin receptor antagonists with or without prostanoids for Adempas (riociguat), based on results from pivotal study PATENT-CHILD (Study 15681); this is a Phase III, Open-label, individual dose titration study to evaluate safety, tolerability and pharmacokinetics of riociguat in children from 6 to less than 18 years of age with PAH; As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5.1, 5.2 and 5.3 of the SmPC are updated. The package Leaflet is updated in accordance. Version 8.1 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the package leaflet

Background

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

CHMP is evaluating an extension of the therapeutic indication for Adempas, a centrally authorised product containing riociguat, to include treatment of pulmonary arterial hypertension (PAH) in paediatric patients aged 6 to less than 18 years of age with WHO[10] functional class (FC) I to III in combination with endothelin receptor antagonists with or without prostanoids for Adempas (riociguat), based on the results from pivotal study 15681 (PATENT-CHILD). PRAC is responsible for providing advice to CHMP on the necessary updates to the RMP to support this extension of indication.

Summary of advice

- The RMP for Adempas (riociguat) in the context of the variation under evaluation by CHMP could be considered acceptable provided that an update to RMP version 8.1 is submitted along with satisfactory responses to the request for supplementary information (RSI).
- In light of the proposed paediatric indication and taking into account the limited evidence of bone safety in the paediatric population, PRAC considered that a safety concern regarding bone safety should be re-introduced in the list of safety concerns and that the ongoing paediatric PATENT-CHILD LTE study should be included as an additional pharmacovigilance activity listed as a category 3 study in the RMP. In addition, PRAC requested the MAH to explore additional pharmacovigilance activities to follow paediatric

[10] World Health Organization

bone safety, namely the use of data from registries of patients with pulmonary arterial hypertension.

6. Periodic safety update reports (PSURs)

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

See also Annex 16.1.

6.1.1. Atezolizumab - TECENTRIQ (CAP) - PSUSA/00010644/202205

Applicant: Roche Registration GmbH

PRAC Rapporteur: Inês Ribeiro-Vaz

Scope: Evaluation of a PSUSA procedure

Background

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

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Tecentriq, a centrally authorised medicine containing atezolizumab 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 Tecentriq (atezolizumab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add haemophagocytic lymphohistiocytosis (HLH) as a warning and as an undesirable effect with a frequency 'rare', as well as to add a warning regarding the risk of gastrointestinal perforation associated with colitis. Therefore, the current terms of the marketing authorisation(s) should be varied[11].
- In the next PSUR, the MAH should provide cumulative reviews of cases of cholangitis sclerosing and scleroderma, as well as of cases of ileus, myelitis and myelitis transverse. The MAH should also review the publication by *Han et al*[12] investigating the safety and efficacy of immune checkpoint inhibitors (ICIs) in patients with cancer and autoimmune disease (AID) and any new available information on the matter, and discuss the possible mechanism(s) of action. The MAH should propose an update of the product information and the RMP as warranted. Finally, the MAH should closely monitor cases of gastrointestinal perforation, ulceration, haemorrhage or obstruction.

[11] Update of SmPC sections 4.2, 4.4, 4.8 and Annex II-D. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion.
[12] Han CY, Fitzgerald C, Lee M, Valero C, Gönen M, Shoushtari A, Morris LGT. Association Between Toxic Effects and Survival in Patients With Cancer and Autoimmune Disease Treated With Checkpoint Inhibitor Immunotherapy. JAMA Oncol. 2022 Sep 1;8(9):1352-1354. doi: 10.1001/jamaoncol.2022.2081. PMID: 35797031; PMCID: PMC9264212.

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. Pemigatinib - PEMAZYRE (CAP) - PSUSA/00010923/202204

Applicant: Incyte Biosciences Distribution B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

Background

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

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Pemazyre, a centrally authorised medicine containing pemigatinib 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 Pemazyre (pemigatinib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the existing warning on hyperphosphatemia to include non-uraemic calciphylaxis as a possible outcome of (untreated) hyperphosphatemia. Therefore, the current terms of the marketing authorisation(s) should be varied[13].
- In the next PSUR, the MAH should provide a cumulative review of cases of soft tissue mineralisation. The MAH should propose an update of the product information as warranted. The MAH should also provide a review of cases of exposure during pregnancy and should monitor any adverse events in patients with a prior history of mild to moderate hepatic impairment.

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

6.1.3. Ripretinib - QINLOCK (CAP) - PSUSA/00010962/202205 (with RMP)

Applicant: Deciphera Pharmaceuticals (Netherlands) B.V.

PRAC Rapporteur: Željana Margan Koletić

Scope: Evaluation of a PSUSA procedure

Background

[13] 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.

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

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Qinlock, a centrally authorised medicine containing ripretinib 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 Qinlock (ripretinib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add malignant melanoma as a warning and as an undesirable effect with a frequency 'uncommon'. Therefore, the current terms of the marketing authorisation(s) should be varied[14]. As a consequence, the MAH should remove 'malignant melanoma' as a potential risk and 'squamous cell carcinoma of skin' as an important identified risk from the list of safety concerns in the RMP.
- In the next PSUR, the MAH should provide a cumulative review of cases of gastrointestinal (GI) perforation, including data from clinical trials and literature, as well as a discussion on whether the mechanism(s) through which tyrosine kinase inhibitors already associated with GI perforation could be applicable to ripretinib.

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. Sacituzumab govitecan - TRODELVY (CAP) - PSUSA/00010959/202204

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

Background

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

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Trodelvy, a centrally authorised medicine containing sacituzumab govitecan 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 Trodelvy (sacituzumab govitecan) in the approved indication(s) remains unchanged.

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

- Nevertheless, the product information should be updated to add pneumonia as an undesirable effect with a frequency 'common'. Therefore, the current terms of the marketing authorisation(s) should be varied[15].

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. Tafamidis - VYNDAQEL (CAP) - PSUSA/00002842/202205

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

Background

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

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Vyndaqel, a centrally authorised medicine containing tafamidis 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 Vyndaqel (tafamidis) in the approved indication(s) remains unchanged.
- Nevertheless, the product information of Vyndaqel (tafamidis) 61 mg should be updated to add diarrhoea as well as rash and pruritus as undesirable effects with a frequency 'common'. Therefore, the current terms of the marketing authorisation(s) should be varied[16].
- In the next PSUR, the MAH should continue to closely monitor cases of cardiac failure, upper abdominal pain, urinary tract infections (UTI) (including urosepsis) or exacerbation of UTI, hepatotoxicity and hypersensitivity reactions. The MAH should propose to update the product information as warranted. The MAH should also provide cumulative reviews of cases of hypothyroidism and hyperthyroidism, and of cases of rash and/or pruritus.

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. Tocilizumab - ROACTEMRA (CAP) - PSUSA/00002980/202204

Applicant: Roche Registration GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

[15] 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.
[16] Update of SmPC section 4.8 for Vyndaqel (tafamidis) 61 mg. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion.

Scope: Evaluation of a PSUSA procedure

Background

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

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Roactemra, a centrally authorised medicine containing tocilizumab 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 Roactemra (tocilizumab) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- The MAH should submit to EMA, within 60 days, cumulative reviews of cases of psychiatric disorders including depression and related disorders, ulcerative keratitis, and pyoderma gangrenosum. The MAH should include a discussion on the potential patho-mechanisms, together with a proposal 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.

6.1.7. Tucatinib - TUKYSA (CAP) - PSUSA/00010918/202204

Applicant: Seagen B.V.

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

Background

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

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Tukysa, a centrally authorised medicine containing tucatinib 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 Tukysa (tucatinib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add a warning on the persistence of concomitant grade 2 diarrhoea with concomitant grade ≥2 nausea and/or vomiting. Therefore, the current terms of the marketing authorisation(s) should be varied[17].

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

- In the next PSUR, the MAH should discuss the value of antidiarrheal prophylaxis with the approved combination treatment (tucatinib in combination with trastuzumab and capecitabine) and should continue to closely monitor the risk of infections including urinary tract infection and pneumonia as well as the risks of nausea and vomiting.

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. Zanubrutinib - BRUKINSA (CAP) - PSUSA/00010960/202205

Applicant: BeiGene Ireland Ltd

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

Background

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

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Brukinsa, a centrally authorised medicine containing zanubrutinib 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 Brukinsa (zanubrutinib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add febrile neutropenia as an undesirable effect with a frequency 'common' and dermatitis exfoliative generalised with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[18].
- In the next PSUR, the MAH should continue to closely monitor cases of severe cutaneous adverse reactions (SCARs). In addition, the MAH should provide cumulative reviews of cases of cryptococcosis and all other identified pathogen specified infections, sepsis and septic shock, and of nausea. Moreover, the MAH should include a detailed analysis of cases of cardiac failure with a discussion on the potential mechanism of action. The MAH should propose an update of the product information as warranted.

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

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

See also Annex 16.2.

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

6.2.1. Pramipexole - MIRAPEXIN (CAP); SIFROL (CAP); NAP - PSUSA/00002491/202204

Applicants: Boehringer Ingelheim International GmbH (Mirapexin, Sifrol), various

PRAC Rapporteur: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

Background

Pramipexole is a dopamine agonist indicated in adults for the treatment of the signs and symptoms of idiopathic Parkinson's disease, alone or in combination with levodopa, and for the symptomatic treatment of moderate to severe idiopathic restless legs syndrome (RLS). For further background information on substance(s) and indication(s) of centrally authorised product(s) identified as 'CAP', see Human medicine European public assessment report (EPAR) on the EMA website.

Based on the assessment of the PSURs, PRAC reviewed the benefit-risk balance of Mirapexin and Sifrol, centrally authorised medicines containing pramipexole, and nationally authorised medicine(s) containing pramipexole and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of pramipexole-containing products in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisations should be maintained.
- In the next PSUR, the MAHs for pramipexole-containing products should include 'suicide-related behaviour' as important potential risk in the list of safety concerns. In addition, all MAHs should provide a cumulative review of cases of parasomnia/sleep walking and of cases of augmentation (earlier onset of symptoms in the evening (or even the afternoon), increase in symptoms, and spread of symptoms to involve other extremities), including a review of the literature and clinical trials. The MAHs should propose to update the product information as warranted.

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

6.2.2. Zonisamide - ZONEGRAN (CAP); NAP - PSUSA/00003152/202203

Applicants: Amdipharm Limited (Zonegran), various

PRAC Rapporteur: Ronan Grimes

Scope: Evaluation of a PSUSA procedure

Background

Zonisamide is a sulphonamide indicated as adjunctive therapy for partial seizures with or without secondary generalisation and for the treatment of adults with newly diagnosed epilepsy. For further background information on substance(s) and indication(s) of centrally authorised product(s) identified as 'CAP', see Human medicine European public assessment report (EPAR) on the EMA website

Based on the assessment of the PSURs, PRAC reviewed the benefit-risk balance of Zonegran, a centrally authorised medicine containing zonisamide, and nationally authorised medicine(s) containing zonisamide and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of zonisamide-containing products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add information regarding risks associated with the use of zonisamide in women of childbearing potential and during pregnancy. Therefore, the current terms of the marketing authorisations should be varied[19].
- In the next PSUR, the MAH Advanz Pharma should continue to monitor cases of cardiac conduction disorders and provide an updated review of available data including any additional data that may be available from in vitro studies. In addition, the MAH Advanz Pharma should continue to monitor cases of disordered body temperature and dehydration, and provide an updated review of available data including cases of anhidrosis, hypohidrosis, heat stroke, heat exhaustion, heat illness, dehydration, hyperthermia, body temperature fluctuation, body temperature increased, temperature regulation disorder and feeling hot.

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

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

See also Annex 16.3.

6.3.1. Bleomycin (NAP) - PSUSA/00000422/202203

Applicant(s): various

PRAC Lead: Marie Louise Schougaard Christiansen

Scope: Evaluation of a PSUSA procedure

Background

Bleomycin is an antineoplastic antibiotic indicated for the treatment of malignant neoplasms.

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

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

- Nevertheless, the product information should be updated to add a warning regarding the risk of acute myeloid leukaemia and myelodysplastic syndrome after treatment with bleomycin used concomitantly with other antineoplastic agents. Therefore, the current terms of the marketing authorisation(s) should be varied[20].
- In the next PSUR, the MAH(s) of bleomycin-containing products should include ototoxicity as an important potential risk in the PSUR list of safety concerns.

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. Cefuroxime axetil (NAP) - PSUSA/00009099/202204

Applicant(s): various

PRAC Lead: Maia Uusküla

Scope: Evaluation of a PSUSA procedure

Background

Cefuroxime axetil is a second-generation cephalosporin antibiotic indicated for the treatment of bacterial infections caused by susceptible pathogens, and for the treatment of early Lyme disease and subsequent prevention of late Lyme disease.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing cefuroxime axetil 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 cefuroxime axetil-containing product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add Kounis syndrome as a warning and as an undesirable effect with a frequency 'not known'. In addition, severe cutaneous adverse reactions (SCARs) should be added as a warning and syndrome and drug reaction with eosinophilia and systemic symptoms (DRESS) as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[21].

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. Cefuroxime sodium[22] (NAP) - PSUSA/00000615/202204

Applicant(s): various

[20] Update of SmPC section 4.4. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position.
[21] Update of SmPC section 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.
[22] All routes of administration except intracameral use

PRAC Lead: Maia Uusküla

Scope: Evaluation of a PSUSA procedure

Background

Cefuroxime sodium is a second-generation cephalosporin antibiotic. Cefuroxime sodium–containing products[22] are indicated for the treatment of community acquired pneumonia, acute exacerbations of chronic bronchitis, complicated urinary tract infections, soft-tissue infections, intra-abdominal infections and as prophylaxis against infection in gastrointestinal, orthopaedic, cardiovascular and gynaecological surgery.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing cefuroxime sodium 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 cefuroxime sodium-containing product(s) [22] in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add Kounis syndrome as a warning and as an undesirable effect with a frequency 'not known'. In addition, severe cutaneous adverse reactions (SCARs) should be added as a warning and syndrome and drug reaction with eosinophilia and systemic symptoms (DRESS) as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[23].
- In the next PSUR, the MAH(s) should provide an update review on off-label intracameral use.

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. Ethinylestradiol, levonorgestrel (NAP) - PSUSA/00001309/202204

Applicant(s): various

PRAC Lead: Marie Louise Schougaard Christiansen

Scope: Evaluation of a PSUSA procedure

Background

Ethinylestradiol is an estrogen and levonorgestrel a progestin. In combination, ethinylestradiol/levonorgestrel is indicated as a combined oral contraceptive (COC) for the prevention of pregnancy.

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

Summary of recommendation(s) and conclusions

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

- Based on the review of the data on safety and efficacy, the benefit-risk balance of ethinylestradiol/levonorgestrel-containing product(s) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAHs for ethinylestradiol/levonorgestrel-containing product(s) should provide cumulative reviews of cases of hypothyroidism associated with use of oral contraceptives and discuss whether an update of the product information is warranted.

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

6.3.5. Etoricoxib (NAP) - PSUSA/00001334/202203

Applicant(s): various

PRAC Lead: Inês Ribeiro-Vaz

Scope: Evaluation of a PSUSA procedure

Background

Etoricoxib is a highly selective inhibitor of cyclooxygenase-II (COX-II) indicated for adults and adolescents over 16 years of age for the treatment of acute and chronic signs and symptoms of osteoarthritis (OA) and rheumatoid arthritis (RA), ankylosing spondylitis (AS), acute gouty arthritis, primary dysmenorrhea, moderate to severe acute post-operative pain associated with dental surgery, moderate to severe acute post-operative pain associated with abdominal gynaecological surgery, and for the relief of acute and chronic pain.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing etoricoxib 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 etoricoxib-containing product(s) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAHs for etoricoxib-containing product(s) should provide reviews of cases of dermatitis exfoliative generalised and drug reaction with eosinophilia and systemic syndromes (DRESS), as well as of cases of pulmonary embolism, deep vein thrombosis and intracranial haemorrhage. These reviews should include data from clinical trials and the literature. The MAHs should propose an update of the product information as warranted.

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

6.3.6. Fentanyl [24] [25] (NAP) - PSUSA/00001370/202204

Applicant(s): various

PRAC Lead: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

Background

Fentanyl is a phenylpiperidine opioid. It is indicated, as transdermal patches, in adults for the management of severe chronic pain that requires continuous long-term opioid administration and for long-term management of severe chronic pain in children from 2 years of age who are receiving opioid therapy. It is also indicated, as solution for injection, in adults and paediatric patients as an opioid analgesic supplement in general or regional anaesthesia, as an anaesthetic premedication, for induction of anaesthesia, as an adjunct in maintenance of general and regional anaesthesia as well as an anaesthetic agent with oxygen in selected high-risk patients undergoing major surgery.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s)[26] containing fentanyl 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 fentany[26,27]l-containing product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information of fentanyl-containing transdermal patches should be updated in order to further minimise the risk of opioid use disorder (OUD). In addition, the product information of fentanyl-containing transdermal patches and solution for injection should be updated to add toxic leukoencephalopathy as a possible symptom of fentanyl overdose. Also, the labelling of the outer and immediate packaging (where possible) of fentanyl-containing transdermal patches should be updated to add a warning regarding accidental use and ingestion. Therefore, the current terms of the marketing authorisation(s) should be varied[26].
- In the next PSUR, the MAH Janssen should provide a detailed review of cases of oesophageal dysfunction, including literature data on long-term fentanyl use and oesophageal dysfunction, together with a discussion on the underlying mechanism. The MAHs of fentanyl transdermal patches (Janssen, Sandoz, Hexal, Lek Pharmaceuticals, 1a Pharma) should continue to provide analysis (over a 5-year period) of the events of dependence, abuse and overdose, as well as of accidental exposure. The MAHs of fentanyl transdermal patches should continue to monitor skeletal muscle rigidity in relation to respiratory depression. Based on this data, the MAHs should discuss the need for an update of the product information and assess the implementation of new risk minimisation measures and their effectiveness.

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

[24] Transdermal patches and solution for injection only
[25] Nationally authorised product(s) only
[26] Update of SmPC sections 4.2, 4.4, 4.8 and 4.9. The package leaflet and the outer and immediate packaging are updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position.

6.3.7. Ivermectin[27] (NAP) - PSUSA/00010377/202204

Applicant(s): various

PRAC Lead: Nathalie Gault

Scope: Evaluation of a PSUSA procedure

Background

Ivermectin is a semi-synthetic antiparasitic derivative of avermectins macrocyclic lactones indicated[28] for the treatment of onchocerciasis, intestinal strongyloidiasis, proven or suspected microfilaremia in patients with lymphatic filariasis caused by *Wuchereria bancrofti*. Ivermectin is also indicated for the treatment of human sarcoptic scabies, subject to certain conditions.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of ivermectin-containing product(s) for systemic use in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add a warning regarding severe cutaneous adverse reactions. Therefore, the current terms of the marketing authorisation(s) should be varied[29].
- In the next PSUR, the MAH(s) should provide an in-depth analysis of medication errors and propose risk minimisation measures as relevant. In addition, the MAH(s) should provide and discuss the narratives of cases of headache, respiratory failure and hepatic cytolysis. Moreover, the MAH(s) should provide a cumulative review of cases of a potential interaction between warfarin and ivermectin, including literature data, together with a discussion on the possible mechanism of action, as well as a discussion on a possible effect of ivermectin on coagulation and prothrombin time prolongation. The MAH(s) should propose 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.

6.3.8. Lamivudine, tenofovir disoproxil (NAP) - PSUSA/00010751/202203

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

[27] Systemic use only
[28] Systemic use only
[29] Update of SmPC section 4.4. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position.

Lamivudine/tenofovir disoproxil is an antiretroviral combination, indicated as part of antiretroviral combination therapy for the treatment of human immunodeficiency virus 1 (HIV-1) infected adults over 18 years of age and are taken orally once daily with food.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing lamivudine/tenofovir disoproxil 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 lamivudine/tenofovir disoproxil-containing product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add bone density decreased as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[30].
- In the next PSUR, the MAHs for lamivudine/tenofovir disoproxil-containing product(s) should update the PSUR list of safety concerns in order to include pancreatitis, liver disorder/exacerbation of hepatitis, renal toxicity and bone events due to proximal renal tubulopathy/loss of bone mineral density as important identified risks; off-label use in hepatitis B virus (HBV) mono-infected patients, HIV-1/HBV coinfected patients and in paediatric patients as important potential risks; as well as safety in children (including long-term safety), safety in elderly patients, safety in pregnancy and lactation, and safety in patients with renal impairment as missing information.

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

6.3.9. Methoxyflurane (NAP) - PSUSA/00010484/202205

Applicant(s): various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

Background

Methoxyflurane is a volatile fluorinated hydrocarbon anaesthetic with analgesic properties at subanaesthetic doses, indicated for the treatment of emergency relief of pain in conscious patients with trauma and associated pain, and for the relief of pain in conscious patients who require analgesia for surgical procedures.

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

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

- Nevertheless, the product information should be updated to add respiratory depression as a warning and as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[31].
- In the next PSUR, the MAH(s) for methoxyflurane-containing product(s) should discuss the publication by *Pyle et al*[32] and assess whether an update of the product information on pregnancy exposure is warranted.

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

6.3.10. Omeprazole (NAP) - PSUSA/00002215/202204

Applicant(s): various

PRAC Lead: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

Background

Omeprazole is a proton-pump inhibitor (PPI) indicated for various medical disorders of the gastrointestinal tract related to excess of gastric acid secretion, subject to certain conditions.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing omeprazole 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 omeprazole-containing product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add tubulointerstitial nephritis (TIN) as a warning and as an undesirable effect with a frequency 'rare'. Therefore, the current terms of the marketing authorisation(s) should be varied[33].
- In the next PSUR, the MAH(s) for omeprazole-containing product(s) should monitor cases of nephrotoxicity, as it is now included as important identified risk in the PSUR list of safety concerns. The MAH(s) for omeprazole-containing product(s) should provide detailed reviews of cases of gastric neoplasms malignant, of drug-drug interaction (DDI) between omeprazole and immune checkpoint inhibitors (ICIs), and between levothyroxine-based medicines and PPIs. The MAH(s) should propose 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.

[31] 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.
[32] Pyle, A., et al., Prevalence and perinatal outcomes following in utero exposure to prehospital emergency methoxyflurane: a 17-year retrospective cohort study. Paediatr Drugs, 2022. 24(5): p. 547-554
[33] Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position.

6.3.11. Triptorelin (NAP) - PSUSA/00003048/202203

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

Triptorelin is a synthetic analogue of the natural gonadotropin releasing hormone (GnRH), indicated for the treatment of prostate cancer, breast cancer, female infertility, central precocious puberty (CPP), endometriosis, uterine myoma and paraphilia subject to certain conditions.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing triptorelin 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 triptorelin-containing product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information for the treatment of paediatric patients should be updated to add idiopathic intracranial hypertension as a warning and as an undesirable effect with a frequency 'not known'. In addition, the product information of triptorelin-containing product(s) indicated for the treatment of male patients should be updated to add fatty liver to the existing warning on metabolic changes. Therefore, the current terms of the marketing authorisation(s) should be varied[34].
- In the next PSUR, the MAH(s) for triptorelin-containing product(s) should provide a cumulative review of cases of cerebrovascular events in women, as well as discussions on cases of metabolic syndrome (including hypertension, dyslipidaemia, insulin resistance, abnormal glucose tolerance) and non-alcoholic fatty liver disease in women.

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

6.3.12. Vinorelbine (NAP) - PSUSA/00003124/202204

Applicant(s): various

PRAC Lead: Eva Jirsová

Scope: Evaluation of a PSUSA procedure

Background

Vinorelbine is an antineoplastic compound and immuno-modulating agent indicated, as mono-and/or polychemotherapy in advanced non-small-cell lung cancer (NSCLC) as monotherapy or in combination with other chemotherapy (CHT), as adjuvant treatment of NSCLC in combination with platinum-based CHT, and advanced breast cancer (ABC) as

[34] 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.

monotherapy or in combination with other agents (intravenous use). Vinorelbine as soft capsules is indicated for the treatment of NSCLC and ABC.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing vinorelbine 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 vinorelbine-containing product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add pulmonary embolism, posterior reversible encephalopathy syndrome and skin hyperpigmentation (serpentine supravenous hyperpigmentation) as undesirable effects with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[35].

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

6.4. Follow-up to PSUR/PSUSA procedures

See also Annex **Error! Reference source not found.**

6.4.1. Methotrexate - NORDIMET (CAP) - EMEA/H/C/003983/LEG 005

Applicant: Nordic Group B.V.

PRAC Rapporteur: Martin Huber

Scope: Comprehensive reviews of available evidence in relation to the mechanism of genotoxicity of methotrexate, as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00002014/202110) concluded in June 2022

Background

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

Following the evaluation of the most recently submitted PSUR(s) for the above-mentioned medicine(s), the MAH was requested to submit further data on the mechanism of genotoxicity of methotrexate. For background, see PRAC minutes June 2022. The responses were assessed by the Rapporteur for further PRAC advice.

Summary of advice/conclusion(s)

- Based on the available data and the Rapporteur's assessment, and considering the safety working party (SWP) response on questions from CMDh on 'recommendations on the duration of contraception following the end of treatment with a genotoxic drug', PRAC agreed that the product information should be amended to reduce the duration of

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

contraception following end of treatment with methotrexate for male from six to three months, the same applying in case of semen donation.

- The MAH should submit to EMA, within 60 days, a variation to update[36] the product information accordingly.

6.4.2. Methotrexate - JYLAMVO (CAP) - EMEA/H/C/003756/LEG 004

Applicant: Therakind (Europe) Limited

PRAC Rapporteur: Martin Huber

Scope: Comprehensive reviews of available evidence in relation to the mechanism of genotoxicity of methotrexate, as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00002014/202110) concluded in June 2022

Background

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

Following the evaluation of the most recently submitted PSUR(s) for the above-mentioned medicine(s), the MAH was requested to submit further data on the mechanism of genotoxicity of methotrexate. For background, see PRAC minutes June 2022. The responses were assessed by the Rapporteur for further PRAC advice.

Summary of advice/conclusion(s)

- Based on the available data and the Rapporteur's assessment, and considering the safety working party (SWP) response on questions from CMDh on 'recommendations on the duration of contraception following the end of treatment with a genotoxic drug', PRAC agreed that the product information should be amended to reduce the duration of contraception following end of treatment with methotrexate for male from six to three months, the same applying in case of semen donation.
- The MAH should submit to EMA, within 60 days, a variation to update[37] the product information accordingly.

6.5. Variation procedure(s) resulting from PSUSA evaluation

See Annex **Error! Reference source not found.**

6.6. Expedited summary safety reviews[38]

See Annex 16.6.

[36] Update of SmPC sections 4.4 and 4.6. The package leaflet is to be updated accordingly
[37] Update of SmPC sections 4.4 and 4.6. The package leaflet is to be updated accordingly
[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

7. Post-authorisation safety studies (PASS)

7.1. Protocols of PASS non-imposed in the marketing authorisation(s)[39]

See also Annex 17.1.

7.1.1. Lisocabtagene maraleucel - BREYANZI (CAP) - EMEA/H/C/PSP/S/0098.1

Applicant: Bristol-Myers Squibb Pharma EEIG, ATMP[40]

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: MAH's response to PSP/0098 [Submission of a non-interventional PASS of patients treated with commercially available liso-cel (lisocabtagene maraleucel) for relapsed/refractory diffuse large B-cell lymphoma, primary mediastinal B-cell lymphoma, and follicular lymphoma Grade 3B after 2 or more lines of systemic therapy in the postmarketing setting to characterise the incidence and severity of selected adverse drug reactions (ADRs), as outlined in the SmPC, and to monitor for potential clinically important adverse events (AEs) that have not yet been identified as part of the liso-cel safety profile] as per the request to supplementary information (RSI) adopted in July 2022

Background

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

In order to fulfil the specific obligation to conduct a PASS imposed in the marketing authorisation(s) of Breyanzi (lisocabtagene maraleucel), the MAH Bristol-Myers Squibb Pharma EEIG submitted to EMA protocol JCAR017-BCM-005 for a study entitled: 'a non-interventional, PASS of patients treated with commercially available liso-cel (lisocabtagene maraleucel) for relapsed/refractory diffuse large B-cell lymphoma, primary mediastinal B-cell lymphoma, and follicular lymphoma grade 3B after 2 or more lines of systemic therapy in the post-marketing setting' for review by PRAC. PRAC is responsible for evaluating the PASS protocol. For background information, see PRAC minutes July 2022.

Summary of advice

- Having considered the draft protocol JCAR017-BCM-005 in accordance with Article 107n of Directive 2001/83/EC, PRAC agreed that the PASS is non-interventional and endorsed the protocol.
- In addition, PRAC discussed the requirements for other chimeric antigen receptors (CAR-T) cell products and considered that, although at this stage, it is not entirely clear whether national registries in the EU (e.g. DESCAR-T[41]) will be able to provide the data to meet the PASS objectives, the MAHs should further explore additional options for safety and efficacy follow-up of patients treated with CAR-T cell products.

[39] 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
[40] Advanced therapy medicinal product
[41] A French nationwide registry for patients treated by CAR-T cells

7.2. Results of PASS imposed in the marketing authorisation(s)[42]

See Annex 17.2.

7.3. Results of PASS non-imposed in the marketing authorisation(s)[43]

None

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

See Annex 17.4.

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

See Annex 17.5.

7.6. Others

See Annex 17.6.

7.7. New Scientific Advice

None

7.8. Ongoing Scientific Advice

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

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

None

7.10. Conditional renewals of the marketing authorisation

None

7.11. Renewals of the marketing authorisation

None

[42] In accordance with Article 107p-q of Directive 2001/83/EC
[43] 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

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

8.1. Annual reassessments of the marketing authorisation

See Annex 18.1.

8.2. Conditional renewals of the marketing authorisation

See Annex 18.2.

8.3. Renewals of the marketing authorisation

See Annex 18.3.

9. Product related pharmacovigilance inspections

9.1. List of planned pharmacovigilance inspections

None

9.2. Ongoing or concluded pharmacovigilance inspections

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

9.3. Others

None

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

10.1. Safety related variations of the marketing authorisation

None

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

None

10.3. Other requests

None

10.4. Scientific Advice

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

contain commercially confidential information.

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

11.1. Safety related variations of the marketing authorisation

11.1.1. Methotrexate (NAP) - DE/H/PSUFU/00002014/202110

Applicant (s): various

PRAC Lead: Martin Huber

Scope: PRAC consultation on a PSUR follow-up (PSU FU) procedure evaluating comprehensive reviews of available evidence in relation to the mechanism of genotoxicity of methotrexate, as discussed at PRAC and agreed by CMDh following the conclusion of the PSUR single assessment (PSUSA) procedure (PSUSA/00002014/202110) concluded in June 2022, on request of Germany

Background

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

Based on the assessment of the recent PSUSA procedure for methotrexate (PSUSA/00002014/202110) concluded in June 2022, PRAC considered that reviews of available evidence in relation to the mechanism of genotoxicity of methotrexate should be further assessed. For further background, see to PRAC minutes June 2022.

On request of CMDh, MAH(s) for nationally approved methotrexate-containing product(s) submitted the requested safety reviews for evaluation within a periodic safety update follow-up (PSU FU) procedure. In the context of the ongoing evaluation of the PSU FU procedure (DE/H/PSUFU/00002014/202110), Germany, as lead Member State (LMS), requested PRAC advice on its assessment.

Summary of advice

- Based on the review of the available information and evidence, PRAC supported the Lead Member State (LMS) assessment that the product information should be updated to reflect the duration of contraception for male patients to last 3 months at least after the end of treatment with methotrexate and that the same recommendations should apply for semen donation. PRAC also agreed that the recommendations for duration of contraception for female patients should remain unchanged (i.e. at last 6 months following discontinuation of treatment with methotrexate).

11.2. Other requests

None

12. Organisational, regulatory and methodological matters

12.1. Mandate and organisation of the PRAC

12.1.1. PRAC membership

The Chair welcomed Inês Ribeiro Vaz as the new alternate for Portugal (mandate started on 08 November 2022), replacing Marcia Sofia Sanches de Castro Lopes Silva.

12.1.2. Vote by proxy

None

12.2. Coordination with EMA Scientific Committees or CMDh-v

None

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

None

12.4. Cooperation within the EU regulatory network

12.4.1. Coronavirus (COVID-19) pandemic - update

The EMA Secretariat updated PRAC on the activities of the COVID-19 EMA pandemic Task Force (ETF), including an overview of the ongoing clinical trials to evaluate the safety and efficacy of medicines in development as potential treatments for COVID-19, as well as study results on effectiveness of COVID-19 mRNA vaccines' (booster dose and adapted mRNA bivalent vaccines) against the new Omicron subvariants. The EMA Secretariat also provided to PRAC an update on the Ebola Sudan outbreak and the candidate vaccines to be included in the upcoming clinical trials.

12.5. Cooperation with International Regulators

12.5.1. International Conference on Harmonisation (ICH) E2D(R1) - Post-approval safety data management: definitions and standards for expedited reporting

PRAC lead: Željana Margan Koletić

The EMA Secretariat together with the EU designated experts presented to PRAC a summary of the activities conducted in 2022 by the Expert Working Group on the revision of the ICH E2D guideline 'Post-approval safety data management: definitions and standards for expedited reporting', as well as an update on the outcome of the meeting of the Expert Working Group that took place in Incheon, South-Korea, in November 2022. PRAC noted the information.

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

None

12.7. PRAC work plan

None

12.8. Planning and reporting

None

12.9. Pharmacovigilance audits and inspections

12.9.1. Pharmacovigilance systems and their quality systems

None

12.9.2. Pharmacovigilance inspections

None

12.9.3. Pharmacovigilance audits

None

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

12.10.1. Periodic safety update reports

None

12.10.2. Granularity and Periodicity Advisory Group (GPAG)

None

12.10.3. PSURs repository

None

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

PRAC endorsed the draft revised EURD list, version December 2022, reflecting PRAC's comments impacting on the data lock point (DLP) and PSUR submission frequencies of the substances/combinations. PRAC endorsed the newly allocated Rapporteurs for upcoming PSUSAs in accordance with the principles previously endorsed by PRAC (see PRAC minutes April 2013).

Post-meeting note: following the PRAC meeting of December 2022, the updated EURD list

was adopted by CHMP and CMDh at their December 2022 meetings and published on the EMA website, see: Home> Human Regulatory>Post-authorisation>Pharmacovigilance>Periodic safety update reports>EURD list> 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 reporting

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

The PRAC was informed of 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 reason

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. Strategy on measuring the impact of pharmacovigilance – PRAC interest group (IG) Impact – PRAC stakeholder engagement regarding risk minimisation

PRAC lead: Liana Gross-Martirosyan

The EMA Secretariat presented to PRAC an update on the progress on enhancing PRAC engagement with patient and healthcare professional stakeholders for risk minimisation measures (RMM), focusing on the establishment of a process taking this forward as one of the main deliverables of the PRAC Impact Strategy. Building on conceptional work and studies on past EMA engagement for pharmacovigilance achieved in 2019 to 2021, a pilot process was agreed by PRAC (see PRAC minutes April 2022) and started in July 2022 with the first meeting of the PRAC Risk Minimisation Alliance (PRISMA). The EMA Secretariat presented the membership composition of PRISMA, as well as the group objectives and

planned activities for 2023. A further update on PRISMA activities will be provided in due course.

12.20.2. Strategy on measuring the impact of pharmacovigilance – PRAC interest group (IG) Impact - review of effectiveness PASS assessed by PRAC between 2016-2021 – final report

The EMA Secretariat, together with the EU designated experts, presented to PRAC a review of industry-sponsored risk minimisation measure (RMM) effectiveness post-authorisation safety studies (PASS) conducted by Utrecht University, The Netherlands and assessed by PRAC between 2016 and 2021. This review is a deliverable of the PRAC IG Impact work plan investigating factors associated with effective and ineffective RMM, with the aim to provide a better understanding of study limitations and other factors that may prevent a conclusion on RMM effectiveness based on a quantitative and qualitative analysis of study reports and assessment reports. PRAC members were invited to provide written comments on the report by 16 January 2023.

12.21. Others

12.21.1. EMA pregnancy strategy

The EMA Secretariat presented to PRAC an overview of the EMA strategy on medicines used in pregnant and breastfeeding individuals. The presentation included a summary of the current guidelines for capturing safety information related to pregnancy and breastfeeding, but also the EU and global ongoing initiatives in order to address the need for a more consistent information on the impact of the use of medicinal products on pregnancy, breastfeeding and children to be collected throughout the life cycle of a medicinal product. PRAC noted the information.

12.21.2. Good Pharmacovigilance Practice (GVP) Guideline on product or population specific considerations III: pregnancy and breastfeeding

The EMA Secretariat informed PRAC on the ongoing activities on the GVP chapter III on 'Pregnant and breastfeeding women'. An overview of the comments received from the public consultation was given and the next steps on the finalisation of the document were proposed.

12.21.3. IRIS for core regulatory procedures - update

IRIS is an online platform for handling product-related scientific and regulatory procedures with EMA. The EMA Secretariat provided PRAC with an update on how core regulatory procedures will be further implemented in IRIS and highlighted open opportunities for National competent Authorities (NCAs) experts to contribute to the ongoing work. PRAC noted the information.

13. Any other business

None

14. Annex I – Signals assessment and prioritisation[44]

14.1. New signals detected from EU spontaneous reporting systems

As per the agreed criteria for new signal(s), PRAC adopted without further plenary discussion the recommendation of the Rapporteur to request MAH(s) to submit a cumulative review following standard timetables[45].

14.1.1. Evolocumab – REPATHA (CAP)

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Kimmo Jaakkola

Scope: Signal of weight increase and abnormal weight gain

EPITT 19867 – New signal

Lead Member State(s): FI

14.2. New signals detected from other sources

None

14.3. Signals follow-up and prioritisation

None

15. Annex I – Risk management plans

15.1. Medicines in the pre-authorisation phase

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

15.1.1. Molnupiravir –EMEA/H/C/005789

Scope: Treatment of coronavirus disease 2019 (COVID-19)

15.1.2. Raltegravir potassium - EMEA/H/C/005813

Scope: Treatment of human immunodeficiency virus (HIV-1)

[44] 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

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

15.1.3. Trastuzumab - EMEA/H/C/005769

Scope: Treatment of metastatic and early breast cancer and metastatic gastric cancer (MGC)

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. Aripiprazole - ARIPIPRAZOLE MYLAN PHARMA (CAP); NAP - EMEA/H/C/003803/WS2306/0020

Applicant(s): Mylan Pharmaceuticals Limited

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Submission of an updated RMP (version 6.0) to align the safety concerns in the RMP with the reference product. In addition, nationally authorised products have been included in the RMP for the company

15.2.2. Coronavirus (COVID-19) vaccine (Ad26.COV2-S, recombinant) - JCOVDEN (CAP) - EMEA/H/C/005737/II/0065

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of an updated RMP version 5.1 in order to update the clinical exposure and risk sections

15.2.3. Coronavirus (COVID-19) vaccine (recombinant, adjuvanted) - NUVAXOVID (CAP) - EMEA/H/C/005808/II/0028

Applicant: Novavax CZ, a.s.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Submission of an updated RMP version 2.1 due to reclassification of myocarditis and/or pericarditis from important potential risk to important identified risk

15.2.4. Estrogens conjugated, bazedoxifene - DUAVIVE (CAP) - EMEA/H/C/002314/II/0032

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Martin Huber

Scope: Submission of an updated RMP version 3.2 in order to reflect the updated study milestones and completion of the PASS of CE/BZA in the United States (US PASS, Study B2311060) previously assessed as part of II/0030 (MEA 002.15), as well as to update the post marketing data with the data lock point of 31 October 2021

15.2.5. Filgrastim - FILGRASTIM HEXAL (CAP) - EMEA/H/C/000918/WS2369/0066; ZARZIO (CAP) - EMEA/H/C/000917/WS2369/0067

Applicant: Sandoz GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Submission of an updated RMP version 13.0 to reduce the list of safety concerns and remove risks which are well characterised and already included in the product information, following PSUR single assessment (PSUSA) procedure (PSUSA/00001391/202109) concluded in May 2022. Additionally, the due date of the final study report EP06-501 (MEA007) has been updated

15.2.6. Micafungin - MYCAMINE (CAP) - EMEA/H/C/000734/II/0047

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Martin Huber

Scope: Update of Annex II and the RMP to version 23.0 to include the results of the non-interventional PASS 9463-PV-0002: effectiveness check of the prescriber checklist for Mycamine (micafungin)

15.2.7. Palivizumab - SYNAGIS (CAP) - EMEA/H/C/000257/II/0131

Applicant: AstraZeneca AB

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Submission of an updated RMP version 2.0 in order to remove from the list of safety concerns "Anaphylaxis, Anaphylactic shock, and Hypersensitivity" and "Medication error of mixing lyophilised and liquid palivizumab before injection". In addition, the MAH took the opportunity to apply the revised template

15.2.8. Ropeginterferon alfa-2b - BESREMI (CAP) - EMEA/H/C/004128/II/0025

Applicant: AOP Orphan Pharmaceuticals GmbH

PRAC Rapporteur: Inês Ribeiro-Vaz

Scope: Submission of an updated RMP version 1.1 for Besremi to revise safety concerns according to GVP Module V Rev.2

15.2.9. Tobramycin - TOBI PODHALER (CAP) - EMEA/H/C/002155/II/0053, Orphan

Applicant: Mylan IRE Healthcare Limited

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Submission of an updated RMP version 8.0 following PSUR single assessment (PSUSA) procedure (PSUSA/00009315/202106) concluded in February 2022 in order to update it based on the guidance provided in the GVP and to remove the safety concerns as well as to reflect the finalisation of study CTBM100C2407 and the transfer of ownership

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 medicine(s) mentioned below.

15.3.1. Atidarsagene autotemcel - LIBMELDY (CAP) - EMEA/H/C/005321/II/0011/G, Orphan

Applicant: Orchard Therapeutics (Netherlands) B.V., ATMP[46]

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Grouped variations consisting of: 1) update of sections 4.2, 4.4, 4.5, 4.8, and 5.1 of the SmPC in order to remove the option of using bone marrow (BM) as a cellular source for the manufacture of Libmeldy, as a result of an evolution of clinical practices and also to rationalise the manufacture of this highly complex medicinal product; the package leaflet and Labelling are updated accordingly. In addition, the MAH took the opportunity to remove ANX/002 from the Annex II and to introduce minor editorial changes to the product information. The RMP version 1.3 has also been submitted; 2) other quality related variations

15.3.2. Baricitinib - OLUMIANT (CAP) - EMEA/H/C/004085/II/0028

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Extension of indication to include treatment of coronavirus disease 2019 (COVID-19) in hospitalised adult and paediatric patients aged 10 years and older who require low-flow oxygen or non-invasive ventilation/high flow oxygen. As a consequence, sections 4.1, 4.2, 4.4, 4.6, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated. Annex II, the package leaflet and the RMP (version 11.1) are updated in accordance

15.3.3. Bimekizumab - BIMZELX (CAP) - EMEA/H/C/005316/II/0010

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Extension of indication to include treatment of adults with active axial spondyloarthritis (axSpA), including non-radiographic axial spondyloarthritis (nr-axSpA) and ankylosing spondylitis (AS, radiographic axial spondyloarthritis), based on interim results from two interventional and controlled phase III clinical studies: AS0010 (BE MOBILE 1) and AS0011 (BE MOBILE 2), which provide evidence of the efficacy and safety of bimekizumab in axSpA (nr-axSpA and AS), both compared to placebo treatment. Further supportive data is provided by the results of a phase 2a exploratory study (AS0013), a phase 2b, dose-ranging study (AS0008) and its ongoing follow-on phase 2b open-label extension (OLE) study (AS0009). As a consequence, sections 4.1, 4.2, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet is updated in accordance. Version 1.2 of the RMP has also been submitted. Furthermore, the product information is brought in line with the latest QRD template version 10.2 rev.1

[46] Advanced therapy medicinal product

15.3.4. Bimekizumab - BIMZELX (CAP) - EMEA/H/C/005316/II/0011

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Extension of indication to include treatment of active psoriatic arthritis in adults patients who have had an inadequate response or who have been intolerant to one or more DMARDs for Bimzelx (bimekizumab), based on interim results of a Phase III study in biological DMARD naïve study participants (PA0010; BE OPTIMAL) and the final results of the Phase III study in study participants who are inadequate responders (inadequate response or intolerant) to ≤2 prior TNF inhibitors (PA0011; BE COMPLETE). Both Phase III studies are interventional studies aimed to evaluate the efficacy and safety of bimekizumab. For PA0010, the Initial Treatment Period was placebo- and no inferential active reference (adalimumab)-controlled, while PA0011 was placebo-controlled. Further supportive data comprise the results of a Phase 1 study (PA0007), a Phase 2b dose-finding study (PA0008) and a Phase 2 open label extension study (PA0009). A Phase 3 open-label extension study is currently ongoing (PA0012). As a consequence, sections 4.1, 4.2, 4.5, 4.8, 5.1 and 5.2 to the SmPC have been 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 10.2 rev.1. As part of the application the MAH is requesting a 1-year extension of the market protection

15.3.5. Caplacizumab - CABLIVI (CAP) - EMEA/H/C/004426/II/0040, Orphan

Applicant: Ablynx NV

PRAC Rapporteur: Jan Neuhauser

Scope: Update of sections 4.2, 4.4, 4.5, 4.8 and 5.1 of the SmPC in order to update information on long-term efficacy and safety based on final results from study ALX0681-C302/LTS16371 - Prospective Follow-up Study for Patients who Completed Study ALX0681-C301 (HERCULES) to Evaluate Long-term Safety and Efficacy of Caplacizumab (Post-HERCULES), listed as a category 3 study in the RMP. The Post-HERCULES study was a Phase III, 36-month follow-up study from HERCULES (parent study) to evaluate the long-term outcomes as well as the safety and efficacy of repeat use of caplacizumab in patients who experienced a recurrence of acquired thrombotic thrombocytopenic purpura *(*aTTP). The RMP version 3.0 has also been submitted

15.3.6. Ciltacabtagene autoleucel - CARVYKTI (CAP) - EMEA/H/C/005095/II/0003, Orphan

Applicant: Janssen-Cilag International NV, ATMP[47]

PRAC Rapporteur: Jo Robays

Scope: Update of sections 4.4 and 4.8 of the SmPC in order to update the existing warnings on cytokine release syndrome (CRS), neurologic toxicities and grading of related events and to update the list of adverse drug reactions (ADRs) based on previously reviewed data from studies MMY2001 and MMY2003, and an additional internal characterisation of neurotoxicity risk. The package leaflet is updated accordingly. The RMP version 2.1 has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes

[47] Advanced therapy medicinal product

to the product information

15.3.7. Ciltacabtagene autoleucel - CARVYKTI (CAP) - EMEA/H/C/005095/II/0004/G, Orphan

Applicant: Janssen-Cilag International NV, ATMP[48]

PRAC Rapporteur: Jo Robays

Scope: Grouped variations consisting of: 1) update of section 4.4 of the SmPC in order to add a new warning on increased risk of severe/fatal COVID-19 infections following Covid-19 signal evaluation from the ongoing study 68284528MMY3002 (CARTITUDE-4) based on a cumulative review of all clinical trials, registries and literature; 2) update of section 4.4 of the SmPC in order to add a new warning on risk of severe bleeding in the context of hemophagocytic lymphohistiocytosis syndrome (HLH) following a signal evaluation from the ongoing study 68284528MMY3002 (CARTITUDE-4) based on cumulative review of all clinical trials, registries and literature. The package leaflet is updated accordingly. The RMP version 2.2 has also been submitted

15.3.8. Concentrate of proteolytic enzymes enriched in bromelain - NEXOBRID (CAP) - EMEA/H/C/002246/II/0058, Orphan

Applicant: MediWound Germany GmbH

PRAC Rapporteur: Martin Huber

Scope: Extension of current indication for removal of eschar in adults with deep partial- and full-thickness thermal burns to the paediatric population for NexoBrid based on interim results from study MW2012-01-01 (CIDS study), listed as Study MW2012-01-01 is a 3-stage, multi-centre, multi-national, randomised, controlled, open label, 2-arm study aiming to demonstrate the superiority of NexoBrid treatment over SOC treatment in paediatric patients (aged 0 to 18 years) with deep partial thickness (DPT) and full thickness (FT) thermal burns of 1% to 30% of total body surface area (TBSA). As a consequence, sections 4.1, 4.2, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The package leaflet is updated accordingly. Version 9 of the RMP has also been submitted

15.3.9. Darolutamide - NUBEQA (CAP) - EMEA/H/C/004790/II/0009

Applicant: Bayer AG

PRAC Rapporteur: Jan Neuhauser

Scope: Extension of indication to include treatment of adult men with metastatic hormone-sensitive prostate cancer (mHSPC) in combination with docetaxel, based on final results from study 17777 (ARASENS): a randomised, double-blind, placebo-controlled phase 3 study designed to demonstrate the superiority of darolutamide in combination with docetaxel over placebo in combination with docetaxel in overall survival (OS) in patients with metastatic hormone-sensitive prostate cancer (mHSPC). As a consequence, sections 4.1, 4.2, 4.5, 4.8 and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 2.1) are updated in accordance. The MAH also requested one additional year of market protection

[48] Advanced therapy medicinal product

15.3.10. Darolutamide - NUBEQA (CAP) - EMEA/H/C/004790/II/0012

Applicant: Bayer AG

PRAC Rapporteur: Jan Neuhauser

Scope: Submission of the final report of carcinogenicity study T104877-7 listed as a category 3 study in the RMP. This is a non-clinical study to assess the carcinogenic potential in mice. The study evaluates the effects of daily oral administration of darolutamide for a period of 6 months in tg-rasH2 transgenic mouse model. The updated RMP version 3.1 has also been submitted

15.3.11. Dolutegravir, abacavir, amivudine - TRIUMEQ (CAP) - EMEA/H/C/002754/X/0101/G

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Martin Huber

Scope: Grouped application consisting of: 1) extension application to introduce a new pharmaceutical form associated with a new strength (5 mg/60 mg/30 mg dispersible tablet). The new presentation is indicated for the treatment of human immunodeficiency virus (HIV) infected children weighing at least 14 kg to less than 25 kg; 2) extension of indication to include treatment of human immunodeficiency virus (HIV) infected children weighing at least 25 kg for the already approved film-coated tablets. As a consequence, sections 4.1, 4.2, 5.1 and 5.2 of the SmPC are updated. The package leaflet and labelling are updated in accordance. The RMP (version 19) is updated in accordance

15.3.12. Dostarlimab - JEMPERLI (CAP) - EMEA/H/C/005204/II/0013

Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Inês Ribeiro-Vaz

Scope: Update of section 5.1 of the SmPC in order to update efficacy and safety information based on interim results from study 4010-01-001 (GARNET) listed as a specific obligation in the Annex II; this is a single-arm, open-label, phase I trial of intravenous dostarlimab in advanced solid tumours. In addition, the MAH took the opportunity to update section E of Annex II. The RMP version 1.2 has also been submitted

15.3.13. Durvalumab - IMFINZI (CAP) - EMEA/H/C/004771/II/0041

Applicant: AstraZeneca AB

PRAC Rapporteur: David Olsen

Scope: Extension of indication to include first-line treatment, with durvalumab in combination with tremelimumab and platinum-based chemotherapy, of adults with metastatic non-small-cell lung carcinoma (NSCLC) with no sensitizing epidermal growth factor receptor (EGFR) mutation or anaplastic lymphoma kinase (ALK) genomic tumour aberrations, based on final results from study D419MC00004 (POSEIDON): a phase 3, randomised, multicentre, open-label, comparative global study to determine the efficacy and safety of tremelimumab and durvalumab or durvalumab in combination with platinum based chemotherapy for first-line treatment in patients with metastatic NSCLC. 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. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet. Furthermore, the product information is brought in line with the latest quality review of documents (QRD) template (version 10.2). The RMP (version 5.1) is updated accordingly

15.3.14. Durvalumab - IMFINZI (CAP) - EMEA/H/C/004771/II/0045

Applicant: AstraZeneca AB

PRAC Rapporteur: David Olsen

Scope: Extension of indication to include IMFINZI in combination with tremelimumab for the treatment of adults with unresectable hepatocellular carcinoma (uHCC), based on final results from Study D419CC00002 (HIMALAYA): a randomised, open-label, multicentre phase III study of durvalumab and tremelimumab as first-line treatment in patients with unresectable hepatocellular carcinoma. 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. In addition, the MAH took the opportunity to implement minor editorial changes in the SmPC and package leaflet. Version 6.1 of the RMP has also been submitted

15.3.15. Evolocumab - REPATHA (CAP) - EMEA/H/C/003766/II/0061

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Kimmo Jaakkola

Scope: Update of sections 4.8 and 5.1 of the SmPC in order to update safety information and include long-term safety and efficacy data based on final results from Study 20130295 and Study 20160250 listed as category 3 studies in the RMP; these are phase 3b, multicentre, open-label extension (OLE) studies designed to assess the long-term safety of evolocumab in subjects who completed the FOURIER study (Study 20110118). The RMP version 8.0 has also been submitted

15.3.16. Granisetron - SANCUSO (CAP) - EMEA/H/C/002296/II/0061

Applicant: Kyowa Kirin Holdings B.V.

PRAC Rapporteur: Rugile Pilviniene

Scope: Update of sections 4.4, 4.6, 4.7, 4.8, 4.10 and 5.3 of the SmPC in order to add serotonin syndrome and application site reactions to the list of adverse drug reactions (ADRs) with a frequency 'not known' as well as application site irritation with a frequency 'uncommon' based on post-marketing data and literature. The MAH also proposes to update sections 4.4 and 4.5 of the SmPC to add drug-drug interaction information with buprenorphine/opioids and serotonergic medicinal products based on post-marketing data and literature. The package leaflet has been updated accordingly. The RMP version 5 has also been submitted. In addition, the MAH took the opportunity to introduce editorial changes in the SmPC

15.3.17. Ipilimumab - YERVOY (CAP) - EMEA/H/C/002213/II/0100

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication to include in combination with nivolumab the treatment of adolescents (12 years of age and older) for advanced (unresectable or metastatic) melanoma, based on the pivotal study CA209070; this is a multicentre, open-label, single arm, phase 1/2 trial of nivolumab +/- ipilimumab in children, adolescents and young adults with recurrent or refractory solid tumours or lymphomas. 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 38.0 of the RMP has also been submitted

15.3.18. Meningococcal group A, C, W-135 and Y conjugate vaccine - MENQUADFI (CAP) - EMEA/H/C/005084/II/0018/G

Applicant: Sanofi Pasteur

PRAC Rapporteur: Jean-Michel Dogné

Scope: Update of sections 4.2, 4.5, 4.8 and 5.1 of the SmPC in order to add long term antibody persistence at least 3 years after primary vaccination, immunogenicity and safety of a booster dose of MenQuadfi in adolescents, adults, and older adults, as well as co-administration data with meningococcal serogroup B vaccine in adolescents and adults, in order to fulfil ANX/002 and ANX/003 based on final results from studies MET59 and MEQ00066, respectively, listed as specific obligations in the Annex II. MET59 is a phase 3b, open-label, partially randomised, parallel-group, active-controlled, multicentre study evaluating the immunogenicity and safety of a booster dose of an investigational quadrivalent MenACYW conjugate vaccine in adolescents and adults, while MEQ00066 is a phase 3, two-stage, randomised, open-label, multi-center trial evaluating the safety and immunogenicity of a single dose of MenACYW conjugate vaccine at least 3 years following initial vaccination with either Menomune vaccine or MenACYW conjugate vaccine in older adults. The Annex II and package leaflet are updated accordingly. The RMP version 1.1 has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the product information

15.3.19. Nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/II/0125/G

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include adolescent patients aged 12 years and older in treatment of advanced (unresectable or metastatic) melanoma (nivolumab monotherapy), treatment of advanced (unresectable or metastatic) melanoma (nivolumab in combination with ipilimumab) and adjuvant treatment of melanoma (nivolumab monotherapy) for Opdivo, based on results from a nonclinical biomarker study (Expression of PD-L1 (CD274), and characterisation of tumour infiltrating immune cells in tumours of paediatric origin), also based on results from a Phase 1/2 clinical study (CA209070, a phase 1/2 study of Nivolumab (Ind# 124729) in children, adolescents, and young adults with recurrent or refractory solid tumours as a single agent and in combination with Ipilimumab) and a modelling and simulation study. As a consequence, sections 4.1, 4.2, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated. The package leaflet is updated in accordance. Version 30.0 of the RMP has also been submitted

15.3.20. Ocrelizumab - OCREVUS (CAP) - EMEA/H/C/004043/II/0034/G

Applicant: Roche Registration GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Grouped variations consisting of: 1) submission of the final report from study BN29739 (VELOCE) listed as a category 3 study in the RMP. This is a phase 3b, multicentre, randomised, parallel-group, open-label study to evaluate the effectiveness of vaccinations in patients with relapsing forms of multiple sclerosis (RMS) undergoing treatment with ocrelizumab; 2) submission of the final report from studies MA30005 (CASTING) and MN30035 (CHORDS). These are prospective, multicentre, international, interventional, open-label phase 3b studies to assess the efficacy and safety of ocrelizumab in patients with relapsing multiple sclerosis who have a suboptimal response to an adequate course of disease-modifying treatment. The RMP version 8.0 has also been submitted

15.3.21. Olipudase alfa - XENPOZYME (CAP) - EMEA/H/C/004850/II/0001/G, Orphan

Applicant: Genzyme Europe BV

PRAC Rapporteur: Martin Huber

Scope: Grouped variations consisting of: 1) update sections 4.6 of the SmPC in order to include a recommendation to conduct a pregnancy test for women of childbearing potential prior to treatment initiation based on embryo-foetal study in mice (study TER0694). In addition, the MAH proposes an update of section 5.3 of the SmPC based on a re-calculation of exposure margins for the embryo-foetal study. MAH also proposes to align the SmPC with the updated CCDS; 2) update sections 4.6 and 5.3 of the SmPC in order to include data in lactating mice based on final results from study MSSM-1120 - Evaluation of Olipudase alfa Transfer Into Milk of Lactating Mice. The package leaflet is updated accordingly. The RMP version 2.0 has also been submitted

15.3.22. Omalizumab - XOLAIR (CAP) - EMEA/H/C/000606/X/0115/G

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Mari Thorn

Scope: Extension application to add a new strength of 300 mg (150 mg/ml) for Xolair solution for injection grouped with quality type II, IB and IAIN variations. The RMP (version 17.0) is updated in accordance

15.3.23. Oritavancin - TENKASI (CAP) - EMEA/H/C/003785/II/0037

Applicant: Menarini International Operations Luxembourg S.A.

PRAC Rapporteur: Adam Przybylkowski

Scope: Extension of indication to include treatment of paediatric population, aged between 3 months and less than 18 years for Tenkasi (oritavancin) 400 mg based on interim results from study TMC-ORI-11-01; this is a multicentre, open-label, dose-finding study of oritavancin single dose infusion in paediatric subjects less than 18 years of age with suspected or confirmed bacterial infections. The purpose of this Phase 1 study is to evaluate the safety, tolerability and PK of oritavancin in paediatric subjects and determine the

optimal dose for a Phase 2 trial in paediatric subjects with acute bacterial skin structure infections (ABSSSI). As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated. The package leaflet is updated in accordance. Version 5.0 of the RMP has also been submitted. In addition, MAH is also taking this opportunity to update the contact details of the local representatives in the package leaflet. Furthermore, the product information is brought in line with the latest QRD template version 10.2 rev 1

15.3.24. Pneumococcal polysaccharide conjugate vaccine (20-valent, adsorbed) - Acalabrutinib NAR (CAP) - EMEA/H/C/005451/II/0006

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Jean-Michel Dogné

Scope: Update of sections 4.5, 4.8 and 5.1 of the SmPC based on final results from study B7471026 (listed as a category 3 study in the RMP): a phase III, randomised, double-blind trial to describe the safety and immunogenicity of 20-valent pneumococcal conjugate vaccine when co-administered with a booster dose of BNT162b2 in adults 65 years of age and older. The package leaflet is updated accordingly. The RMP (version 2.1) has also been submitted to consolidate 2 RMP versions based on the outcome of current procedure and reflecting the changes in RMP version 2.0 (EMEA/H/C/005451/II/0006) and RMP version 1.1 (EMEA/H/C/005451/II/0002)

15.3.25. Ravulizumab - ULTOMIRIS (CAP) - EMEA/H/C/004954/II/0032

Applicant: Alexion Europe SAS

PRAC Rapporteur: Kimmo Jaakkola

Scope: Extension of indication to include the treatment of adult patients with neuromyelitis optica spectrum disorder (NMOSD) who are anti-aquaporin 4 (AQP4) antibody-positive, based on interim results from study ALXN1210-NMO-307; this is a phase 3, external placebo-controlled, open-label, multicentre study to evaluate the efficacy and safety of ravulizumab in adult patients with NMOSD. 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 6.0 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the PI

15.3.26. Rucaparib - RUBRACA (CAP) - EMEA/H/C/004272/II/0036

Applicant: Clovis Oncology Ireland Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension of indication to include maintenance treatment of adult patients with advanced (FIGO Stages III and IV) epithelial ovarian (EOC), fallopian tube (FTC), or primary peritoneal cancer (PPC) who are in response (complete or partial) to first-line platinum-based chemotherapy for RUBRACA, based on interim results from study CO-338-087 (ATHENA); this is a Phase III, randomised, double-blind, dual placebo controlled study of rucaparib as monotherapy and in combination with nivolumab in patients with newly diagnosed EOC, FTC, or PPC who have responded to their first-line treatment (surgery and platinum-based chemotherapy). 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 6.3 of the

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

15.3.27. Rucaparib - RUBRACA (CAP) - EMEA/H/C/004272/II/0037

Applicant: Clovis Oncology Ireland Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of sections 4.8 and 5.1 of the SmPC in order to update the efficacy and safety information and the list of adverse drug reactions (ADRs) based on the final results from study CO-338-014 (ARIEL 3) listed as a category 1 PAES in the Annex II; this is a phase 3, multicentre, randomised, double-blind, placebo-controlled study of rucaparib as switch maintenance following platinum-based chemotherapy in patients with platinum-sensitive, high grade serous or endometrioid epithelial ovarian, primary peritoneal or fallopian tube cancer. The package leaflet is updated accordingly. The RMP version 6.4 has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the product information (PI)

15.3.28. Secukinumab - COSENTYX (CAP) - EMEA/H/C/003729/II/0090

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Monica Martinez Redondo

Scope: Extension of indication to include treatment of hidradenitis suppurativa (HS) for COSENTYX, based on interim results from two phase III studies CAIN457M2301 (SUNSHINE) and CAIN457M2302 (SUNRISE). These studies are ongoing, multicentre, randomised, double-blind, placebo-controlled, parallel group phase 3 studies conducted to assess the short (16 weeks) and long-term (up to 52 weeks) efficacy and safety of two secukinumab dose regimens (Q2W or Q4W) compared to placebo in adult subjects with moderate to severe HS. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2. of the SmPC are updated. The package leaflet and the RMP (version 11) are updated accordingly

15.3.29. Semaglutide - WEGOVY (CAP) - EMEA/H/C/005422/II/0009

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Mari Thorn

Scope: Extension of indication to include treatment of adolescents for weight management for Wegovy based on final results from study NN9536-4451; this trial was conducted to assess the effect and safety of semaglutide in the paediatric population in order to address the unmet need for treatment of adolescents ages 12 to <18 years with obesity. As a consequence, sections 4.1, 4.2, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet is updated in accordance. Version 8.0 of the RMP has also been submitted. Furthermore, the PI is brought in line with the latest QRD template version 10.2

15.3.30. Somatropin - OMNITROPE (CAP) - EMEA/H/C/000607/II/0073

Applicant: Sandoz GmbH

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Update of section 4.4 of the SmPC in order to add a new warning on scoliosis following in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00002772/202003) based on final results from study EP00-401 listed as a category 3 study in the RMP; this is a prospective, open-label, non-comparative, multicentre, Phase IV study to monitor the long-term safety and efficacy of Omnitrope in short children born small for gestational age (SGA), in particular the diabetogenic potential and immunogenicity of rhGH therapy. The package leaflet is updated accordingly. The RMP version 12.0 has also been submitted. In addition, the MAH took the opportunity to implement editorial changes to the SmPC

15.3.31. Tezepelumab - TEZSPIRE (CAP) - EMEA/H/C/005588/II/0001

Applicant: AstraZeneca AB

PRAC Rapporteur: Eva Jirsová

Scope: Addition of a new autoinjector (AI) presentation as an alternative method of administration, with consequential update to the product information. RMP (version 1.1) has been updated accordingly

15.3.32. Tocilizumab - ROACTEMRA (CAP) - EMEA/H/C/000955/II/0114

Applicant: Roche Registration GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include treatment of new indication for slowing the rate of decline in pulmonary function in adult patients with systemic sclerosis-associated interstitial lung disease (SSc-ILD) for RoActemra, based on final results from the pivotal Phase III Study WA29767 (focuSSced) entitled, "A Phase III, Multicentre, Randomised, Double-Blind, Placebo-Controlled, Parallel-Group Study to Assess the Efficacy and Safety of Tocilizumab Versus Placebo in Patients With Systemic Sclerosis" and the supportive Phase II/III Study WA27788 (faSScinate) entitled, "A Phase II/III, Multicentre, Randomised, Double-blind, Placebo-controlled Study To Assess The Efficacy And Safety Of Tocilizumab Versus Placebo In Patients With Systemic Sclerosis". As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet is updated in accordance. Version 28 of the RMP has also been submitted

15.3.33. Trastuzumab deruxtecan - ENHERTU (CAP) - EMEA/H/C/005124/II/0022

Applicant: Daiichi Sankyo Europe GmbH

PRAC Rapporteur: Inês Ribeiro-Vaz

Scope: Extension of indication to include treatment of unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer who have received a prior systemic therapy in the metastatic setting or developed disease recurrence during or withing 6 months of completing adjuvant chemotherapy. Patients with hormone receptor positive (HR+) breast cancer must additionally have received or be ineligible for endocrine therapy; for ENHERTU, based on final results from study DS8201-A-U303 (DESTINY-Breast04). This is a phase III, multicentre, randomised, open-label, active-controlled trial of Trastuzumab Deruxtecan (T-DXd), an Anti-HER2-antibody Drug Conjugate (ADC), versus treatment of physician's choice for HER2-low, unresectable and/or metastatic breast cancer subjects. As a consequence,

sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 1.4) are updated accordingly. In addition, the MAH took the opportunity to update section 4.4 of the SmPC to update the dosing recommendation for corticosteroid treatment (e.g. prednisolone) with a daily dose

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. Acalabrutinib - CALQUENCE (CAP) - PSUSA/00010887/202204

Applicant: AstraZeneca AB

PRAC Rapporteur: Željana Margan Koletić

Scope: Evaluation of a PSUSA procedure

16.1.2. Andexanet alfa - ONDEXXYA (CAP) - PSUSA/00010764/202204

Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.3. Axicabtagene ciloleucel - YESCARTA (CAP) - PSUSA/00010703/202204

Applicant: Kite Pharma EU B.V., ATMP[49]

PRAC Rapporteur: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

16.1.4. Azacitidine[50] - ONUREG (CAP) - PSUSA/00010935/202205

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

[49] Advanced therapy medicinal product
[50] Oral formulations only

16.1.5. Brigatinib - ALUNBRIG (CAP) - PSUSA/00010728/202204

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Inês Ribeiro-Vaz

Scope: Evaluation of a PSUSA procedure

16.1.6. Bupivacaine[51] - EXPAREL LIPOSOMAL (CAP) - PSUSA/00010889/202204

Applicant: Pacira Ireland Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

16.1.7. Conestat alfa - RUCONEST (CAP) - PSUSA/00000873/202204 (with RMP)

Applicant: Pharming Group N.V

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.1.8. Crizanlizumab - ADAKVEO (CAP) - PSUSA/00010888/202205

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Jo Robays

Scope: Evaluation of a PSUSA procedure

16.1.9. Delamanid - DELTYBA (CAP) - PSUSA/00010213/202204

Applicant: Otsuka Novel Products GmbH

PRAC Rapporteur: Jo Robays

Scope: Evaluation of a PSUSA procedure

16.1.10. Diphtheria, tetanus, pertussis antigens (pertussis toxoid, filamentous haemagglutinin) (acellular, component), hepatitis b (rDNA[52]), poliomyelitis (inactivated), haemophilus type b conjugate vaccines (adsorbed) - HEXACIMA (CAP); HEXYON (CAP) - PSUSA/00010091/202204

Applicant(s): Sanofi Pasteur (Hexacima), Sanofi Pasteur Europe (Hexyon)

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.11. Dolutegravir, rilpivirine - JULUCA (CAP) - PSUSA/00010689/202205

Applicant: ViiV Healthcare B.V.

[51] Liposomal formulations only
[52] Ribosomal deoxyribonucleic acid

PRAC Rapporteur: Nathalie Gault

Scope: Evaluation of a PSUSA procedure

16.1.12. Dostarlimab - JEMPERLI (CAP) - PSUSA/00010931/202204

Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Inês Ribeiro-Vaz

Scope: Evaluation of a PSUSA procedure

16.1.13. Drospirenone, estetrol - DROVELIS (CAP); LYDISILKA (CAP) - PSUSA/00010938/202205

Applicant(s): Chemical Works of Gedeon Richter Plc. (Gedeon Richter Plc.) (Drovelis), Estetra SRL (Lydisilka)

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.14. Durvalumab - IMFINZI (CAP) - PSUSA/00010723/202204

Applicant: AstraZeneca AB

PRAC Rapporteur: David Olsen

Scope: Evaluation of a PSUSA procedure

16.1.15. Empagliflozin - JARDIANCE (CAP); empagliflozin, metformin - SYNJARDY (CAP) - PSUSA/00010388/202204

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

16.1.16. Entecavir - BARACLUDE (CAP) - PSUSA/00001224/202203

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.17. Erenumab - AIMOVIG (CAP) - PSUSA/00010699/202205

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

16.1.18. Febuxostat - ADENURIC (CAP) - PSUSA/00001353/202204

Applicant: Menarini International Operations Luxembourg S.A.

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.1.19. Florbetapir (^{18}F) - AMYVID (CAP) - PSUSA/00010032/202204

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.20. Fostamatinib - TAVLESSE (CAP) - PSUSA/00010819/202204

Applicant: Instituto Grifols, S.A.

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.21. Givosiran - GIVLAARI (CAP) - PSUSA/00010839/202205

Applicant: Alnylam Netherlands B.V.

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.22. Glycopyrronium bromide, formoterol - BEVESPI AEROSPHERE (CAP) - PSUSA/00010739/202204

Applicant: AstraZeneca AB

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.1.23. Hepatitis B surface antigen, CpG 1018 adjuvant - HEPLISAV B (CAP) - PSUSA/00010919/202205

Applicant: Dynavax GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.24. Insulin glargine - ABASAGLAR (CAP); LANTUS (CAP); SEMGLEE (CAP); TOUJEO (CAP) - PSUSA/00001751/202204

Applicant: Eli Lilly Nederland B.V. (Abasaglar), Sanofi-Aventis Deutschland GmbH (Lantus, Toujeo), Viatris Limited (Semglee)

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.25. Ivacaftor, tezacaftor, elexacaftor - KAFTRIO (CAP) - PSUSA/00010868/202204

Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.26. Lumacaftor, ivacaftor - ORKAMBI (CAP) - PSUSA/00010455/202205

Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

16.1.27. Lumasiran - OXLUMO (CAP) - PSUSA/00010884/202205

Applicant: Alnylam Netherlands B.V.

PRAC Rapporteur: Mari Thorn

Scope: Evaluation of a PSUSA procedure

16.1.28. Mannitol[53] - BRONCHITOL (CAP) - PSUSA/00009226/202204

Applicant: Pharmaxis Europe Limited

PRAC Rapporteur: Nathalie Gault

Scope: Evaluation of a PSUSA procedure

16.1.29. Meningococcal group a, c, w135, y conjugate vaccine[54] - MENQUADFI (CAP); NIMENRIX (CAP) - PSUSA/00010044/202204

Applicant(s): Sanofi Pasteur (MenQuadfi), Pfizer Europe MA EEIG (Nimenrix)

PRAC Rapporteur: David Olsen

Scope: Evaluation of a PSUSA procedure

16.1.30. Methylnaltrexone bromide - RELISTOR (CAP) - PSUSA/00002023/202203

Applicant: Bausch Health Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.31. Nintedanib[55] - OFEV (CAP) - PSUSA/00010319/202204

Applicant: Boehringer Ingelheim International GmbH

[53] Indicated in cystic fibrosis
[54] Conjugated to tetanus toxoid carrier protein
[55] Respiratory indication(s) only

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Evaluation of a PSUSA procedure

16.1.32. Oestrogens conjugated, bazedoxifene - DUAVIVE (CAP) - PSUSA/00010321/202204

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.33. Ozanimod - ZEPOSIA (CAP) - PSUSA/00010852/202205

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

16.1.34. Parathyroid hormone - NATPAR (CAP) - PSUSA/00010591/202204

Applicant: Takeda Pharmaceuticals International AG

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

16.1.35. Pegcetacoplan - ASPAVELI (CAP) - PSUSA/00010974/202205

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

16.1.36. Potassium citrate, potassium hydrogen carbonate - SIBNAYAL (CAP) - PSUSA/00010932/202204

Applicant: Advicenne

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.37. Ramucirumab - CYRAMZA (CAP) - PSUSA/00010323/202204

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.38. Recombinant vesicular stomatitis virus - Zaire ebolavirus vaccine (live) - ERVEBO (CAP) - PSUSA/00010834/202205

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.39. Remdesivir - VEKLURY (CAP) - PSUSA/00010840/202205

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Eva Jirsová

Scope: Evaluation of a PSUSA procedure

16.1.40. Selpercatinib - RETSEVMO (CAP) - PSUSA/00010917/202205

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.41. Siltuximab - SYLVANT (CAP) - PSUSA/00010254/202204

Applicant: EUSA Pharma (Netherlands) B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.42. Somatrogon - NGENLA (CAP) - PSUSA/00010982/202204

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

16.1.43. Tixagevimab, cilgavimab - EVUSHELD (CAP) - PSUSA/00010992/202205

Applicant: AstraZeneca AB

PRAC Rapporteur: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

16.1.44. Volanesorsen - WAYLIVRA (CAP) - PSUSA/00010762/202205

Applicant: Akcea Therapeutics Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

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

16.2.1. Cetrorelix - CETROTIDE (CAP); NAP - PSUSA/00000633/202204

Applicants: Merck Europe B.V. (Cetrotide), various

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.2.2. Efavirenz - STOCRIN (CAP); SUSTIVA (CAP); NAP - PSUSA/00001200/202204

Applicants: Bristol-Myers Squibb Pharma EEIG (Sustiva), Merck Sharp & Dohme B.V. (Stocrin), various

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.2.3. Hydrochlorothiazide, telmisartan - KINZALKOMB (CAP); MICARDISPLUS (CAP); PRITORPLUS (CAP); telmisartan - KINZALMONO (CAP); MICARDIS (CAP); PRITOR (CAP); NAP - PSUSA/00002882/202203

Applicants: Bayer AG (Kinzalkomb, Kinzalmono, Pritor, PritorPlus), Boehringer Ingelheim International GmbH (Micardis, MicardisPlus), various

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.2.4. Olanzapine - ZALASTA (CAP); ZYPADHERA (CAP); ZYPREXA (CAP); ZYPREXA VELOTAB (CAP); NAP - PSUSA/00010540/202203

Applicants: Eli Lilly Nederland B.V. (Zypadhera, Zyprexa, Zyprexa Velotab), KRKA, d.d., Novo mesto (Zalasta), various

PRAC Rapporteur: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

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

16.3.1. Amlodipine besilate, hydrochlorothiazide, olmesartan medoxomil (NAP) - PSUSA/00002210/202204

Applicant(s): various

PRAC Lead: Jana Lukačišinová

Scope: Evaluation of a PSUSA procedure

16.3.2. Amlodipine, candesartan (NAP) - PSUSA/00010191/202204

Applicant(s): various

PRAC Lead: Eva Jirsová

Scope: Evaluation of a PSUSA procedure

16.3.3. Amlodipine, olmesartan (NAP) - PSUSA/00002208/202204

Applicant(s): various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.3.4. Candesartan (NAP); candesartan, hydrochlorothiazide (NAP) - PSUSA/00000527/202204

Applicant(s): various

PRAC Lead: Mari Thorn

Scope: Evaluation of a PSUSA procedure

16.3.5. Carvedilol (NAP) - PSUSA/00000575/202204

Applicant(s): various

PRAC Lead: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

16.3.6. Carvedilol, ivabradine (NAP) - PSUSA/00010883/202204

Applicant(s): various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.3.7. Certoparin (NAP) - PSUSA/00000625/202204

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.3.8. Epoprostenol (NAP) - PSUSA/00001242/202203

Applicant(s): various

PRAC Lead: Ronan Grimes

Scope: Evaluation of a PSUSA procedure

16.3.9. Estradiol, norethisterone (NAP) - PSUSA/00001278/202203

Applicant(s): various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.3.10. Gentamicin[56] (NAP) - PSUSA/00010628/202203

Applicant(s): various

PRAC Lead: Valentina Di Giovanni

Scope: Evaluation of a PSUSA procedure

16.3.11. Glucosamine (NAP) - PSUSA/00001539/202203

Applicant(s): various

PRAC Lead: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

16.3.12. Human rabies immunoglobulin (NAP) - PSUSA/00001639/202204

Applicant(s): various

PRAC Lead: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.3.13. Isotretinoin[57] (NAP) - PSUSA/00010488/202205

Applicant(s): various

PRAC Lead: Krõõt Aab

Scope: Evaluation of a PSUSA procedure

16.3.14. Itraconazole (NAP) - PSUSA/00001798/202203

Applicant(s): various

PRAC Lead: Marie Louise Schougaard Christiansen

Scope: Evaluation of a PSUSA procedure

16.3.15. Lidocaine, prilocaine[58] (NAP) - PSUSA/00001867/202203

Applicant(s): various

PRAC Lead: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

[56] Implant(s) only
[57] Oral formulation(s) only
[58] Centrally authorised product(s) excluded

16.3.16. Linezolid (NAP) - PSUSA/00001888/202204

Applicant(s): various

PRAC Lead: Anna Mareková

Scope: Evaluation of a PSUSA procedure

16.3.17. Methyl salicylate (NAP); menthol, methyl salicylate (NAP); menthol, methyl salicylate, camphor (NAP); methyl salicylate, camphor (NAP); methyl salicylate, menthol, camphor, tocopherol (NAP); methyl salicylate, camphor, menthol, turpentine (essence, oil) (NAP); methyl salicylate, menthol, camphor, hydroxyethyl salicylate (NAP); methyl salicylate, menthol, camphor, hydroxyethyl salicylate, benzyl nicotinate (NAP) - PSUSA/00010658/202204

Applicant(s): various

PRAC Lead: Inês Ribeiro-Vaz

Scope: Evaluation of a PSUSA procedure

16.3.18. Moclobemide (NAP) - PSUSA/00002079/202204

Applicant(s): various

PRAC Lead: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

16.3.19. Mometasone furoate, olopatadine (NAP) - PSUSA/00010957/202204

Applicant(s): various

PRAC Lead: Mari Thorn

Scope: Evaluation of a PSUSA procedure

16.3.20. Mupirocin (NAP) - PSUSA/00002096/202203

Applicant(s): various

PRAC Lead: Polona Golmajer

Scope: Evaluation of a PSUSA procedure

16.3.21. Nefopam (NAP) - PSUSA/00002131/202203

Applicant(s): various

PRAC Lead: Nikica Mirošević Skvrce

Scope: Evaluation of a PSUSA procedure

16.3.22. Ozenoxacin (NAP) - PSUSA/00010651/202205

Applicant(s): various

PRAC Lead: Monica Martinez Redondo

Scope: Evaluation of a PSUSA procedure

16.3.23. Sertraline (NAP) - PSUSA/00002696/202203

Applicant(s): various

PRAC Lead: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

16.3.24. Sulprostone (NAP) - PSUSA/00002828/202204

Applicant(s): various

PRAC Lead: Nathalie Gault

Scope: Evaluation of a PSUSA procedure

16.3.25. Tretinoin[59] (NAP) - PSUSA/00003015/202203

Applicant(s): various

PRAC Lead: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

16.4. Follow-up to PSUR/PSUSA procedures

16.4.1. Cabozantinib - CABOMETYX (CAP) - EMEA/H/C/004163/LEG 007

Applicant: Ipsen Pharma

PRAC Rapporteur: Menno van der Elst

Scope: Causality assessment of pneumonia cases already reported as confounded by the MAH as well as of any newly reported cases, as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00010180/202111) adopted in July 2022

16.4.2. Cabozantinib - COMETRIQ (CAP) - EMEA/H/C/002640/LEG 022

Applicant: Ipsen Pharma

PRAC Rapporteur: Menno van der Elst

Scope: Causality assessment of pneumonia cases already reported as confounded by the MAH as well as of any newly reported cases as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00010180/202111) adopted in July 2022

16.4.3. Capecitabine - XELODA (CAP) - EMEA/H/C/000316/LEG 035

Applicant: CHEPLAPHARM Arzneimittel GmbH

PRAC Rapporteur: Martin Huber

Scope: Comprehensive review concerning dihydropyrimidine dehydrogenase (DPD)

[59] Oral formulation(s) only

phenotyping as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00000531/201804) adopted in January 2019

16.4.4. Lopinavir, ritonavir - ALUVIA (Art 58[60]) - EMEA/H/W/000764/LEG 034

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Nathalie Gault

Scope: Comprehensive reviews of available evidence to fully characterize the risk of QT prolongation, as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (EMEA/H/W/*000764*/*PSUV*/*0115*) adopted in June 2022

16.4.5. Lopinavir, ritonavir - KALETRA (CAP) - EMEA/H/C/000368/LEG 124

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Nathalie Gault

Scope: Comprehensive reviews of available evidence to fully characterize the risk of QT prolongation, as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00001905/202109) adopted in June 2022

16.5. Variation procedure(s) resulting from PSUSA evaluation

16.5.1. Daratumumab - DARZALEX (CAP) - EMEA/H/C/004077/II/0063, Orphan

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Inês Ribeiro-Vaz

Scope: Update of section 4.4 of the SmPC in order to update the warnings and precautions for myocardial infarction and ocular events following PSUR single assessment (PSUSA) procedure (PSUSA/00010498/202111) concluded in June 2022, based on the cumulative review of the relevant cases retrieved from the MAH's global safety database, clinical database, epidemiological evaluation and literature review. The package leaflet is updated accordingly

16.6. Expedited summary safety reviews[61]

16.6.1. Coronavirus (COVID-19) vaccine (inactivated, adjuvanted, adsorbed) - COVID-19 VACCINE (INACTIVATED, ADJUVANTED) VALNEVA (CAP) - EMEA/H/C/006019/MEA 009.3

Applicant: Valneva Austria GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Fourth expedited summary safety report (SSR) for covid-19 vaccine (inactivated, adjuvanted) Valneva during the coronavirus disease (COVID-19) pandemic

[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).
[61] Submission of expedited summary safety reports for review in addition to the requirements for submission of PSUR(s) falling within the pandemic period and requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC

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, the 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)[62]

17.1.1. Alemtuzumab - LEMTRADA (CAP) - EMEA/H/C/PSA/S/0088.1

Applicant: Sanofi Belgium

PRAC Rapporteur: Anette Kirstine Stark

Scope: Substantial amendment to a non-interventional post-authorisation safety study to investigate the risk of mortality in multiple sclerosis patients treated with alemtuzumab (LEMTRADA) relative to comparable multiple sclerosis patients using other disease modifying therapies: a cohort study [MAH's response to PSA/S/0088]

17.1.2. Axicabtagene ciloleucel - YESCARTA (CAP) - EMEA/H/C/PSA/S/0087.1

Applicant: Kite Pharma EU B.V., ATMP[63]

PRAC Rapporteur: Anette Kirstine Stark

Scope: Substantial amendment to a protocol for a long-term, non-interventional study of recipients of Yescarta for treatment of relapsed or refractory Diffuse Large B-cell Lymphoma and Primary Mediastinal B-cell Lymphoma

17.1.3. Blinatumomab - BLINCYTO (CAP) - EMEA/H/C/PSA/S/0096

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Eva Jirsová

Scope: Substantial amendment to a protocol for an observational PASS to describe the long-term safety profile of first-relapse B-precursor acute lymphocytic leukemia (ALL) paediatric patients who have been treated with blinatumomab or chemotherapy prior to undergoing haemopoietic stem cell transplant

17.1.4. Velmanase alfa - LAMZEDE (CAP) - EMEA/H/C/PSA/S/0094

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Jan Neuhauser

Scope: Substantial amendment to a protocol for study: THE ALPHA-MANNOSIDOSIS REGISTRY: a multi-centre, multi-country, non-interventional, prospective cohort, in alpha-mannosidosis patients to evaluate the long-term effectiveness and safety profile of treatment with Lamzede under conditions of routine clinical care and to characterise the

[62] In accordance with Article 107n of Directive 2001/83/EC
[63] Advanced therapy medicinal product

entire alpha-mannosidosis population, including variability of clinical manifestation, progression and natural history

17.1.5. Lonafarnib - ZOKINVY (CAP) - EMEA/H/C/PSP/S/0102

Applicant: EigerBio Europe Limited

PRAC Rapporteur: Adam Przybylkowski

Scope: Prospective observational study to evaluate the long-term safety and effectiveness of lonafarnib treatment among patients with Hutchinson-Gilford Progeria Syndrome (HGPS) or a processing deficient progeroid laminopathy (PDPL) in real-world clinical care settings

17.1.6. Rurioctocog alfa pegol - ADYNOVI (CAP) - EMEA/H/C/PSA/S/0095

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Substantial amendment to a protocol for study: evaluation of long-term safety of ADYNOVI/ADYNOVATE (Antihaemophilic Factor [Recombinant] PEGylated, rurioctocog alfa pegol) in adults and adolescents ⩾12 years of age with haemophilia A

17.2. Protocols of PASS non-imposed in the marketing authorisation(s)[64]

17.2.1. Anifrolumab - SAPHNELO (CAP) - EMEA/H/C/004975/MEA 002

Applicant: AstraZeneca AB

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Protocol for study D3461R00046: a non-interventional cohort study and meta-analysis on the risk of malignancy in systemic lupus erythematosus patients receiving anifrolumab

17.2.2. Avacopan - TAVNEOS (CAP) - EMEA/H/C/005523/MEA 002.1

Applicant: Vifor Fresenius Medical Care Renal Pharma France

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: MAH's response to MEA 002 [protocol and feasibility report for study CS-AVA-2022-0016 (listed as category 3 study in the RMP): avacopan real world evidence in anti-neutrophil cytoplasmic autoantibody (ANCA) associated vasculitis - characterisation of the safety concerns of avacopan (i.e. liver injury, serious infections, malignancies and cardiovascular events) beyond the known safety profile based on clinical trial data limited to 52 weeks of exposure] as per request for supplementary information (RSI) adopted in July 2022

17.2.3. Ciltacabtagene autoleucel - CARVYKTI (CAP) - EMEA/H/C/005095/MEA 007

Applicant: Janssen-Cilag International NV, ATMP[65]

[64] In accordance with Article 107m of Directive 2001/83/EC, supervised by PRAC in accordance with Article 61a (6) of Regulation (EC) No 726/2004

PRAC Rapporteur: Jo Robays

Scope: Protocol for study PCSONCA0014: a survey to evaluate the effectiveness of the ciltacabtagene autoleucel HCP Educational Program and the Product Handling Training

17.2.4. Coronavirus (COVID-19) vaccine (inactivated, adjuvanted, adsorbed) - COVID-19 VACCINE (INACTIVATED, ADJUVANTED) VALNEVA (CAP) - EMEA/H/C/006019/MEA 001

Applicant: Valneva Austria GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Protocol for pregnancy exposure registry (C-VIPER): a study to estimate the risk of the most common obstetric outcomes, i.e. pregnancy losses, placentation disorders, gestational diabetes, premature delivery, and COVID-19, neonatal outcomes, i.e. congenital anomalies, low birth weight for gestational age, neonatal intensive care unit admission, and COVID-19, among pregnant women exposed to COVID-19 vaccine (inactivated, adjuvanted) Valneva from 30 days prior to the first day of the last menstrual period (LMP) to end of pregnancy and their offspring relative to a matched unexposed reference group

17.2.5. Coronavirus (COVID-19) vaccine (inactivated, adjuvanted, adsorbed) - COVID-19 VACCINE (INACTIVATED, ADJUVANTED) VALNEVA (CAP) - EMEA/H/C/006019/MEA 002

Applicant: Valneva Austria GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Protocol for a post-authorisation safety study to estimate the incidence of adverse events of special interest (AESIs), including the potential risk of vaccine associated enhanced disease (VAED) and vaccine associated respiratory disease (VAERD), that are medically attended following the administration of COVID-19 Vaccine (inactivated, adjuvanted) Valneva in the real-world immunisation setting

17.2.6. Elasomeran - SPIKEVAX (CAP) - EMEA/H/C/005791/MEA 065.1

Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: MAH's response to MEA 065 [submission of a revised protocol for study mRNA-1273-P910: clinical course, outcomes and risk factors of myocarditis following administration of mRNA-1273 alongside with the first interim report of the study] as per request for supplementary information (RSI) adopted in July 2022

17.2.7. Eptinezumab - VYEPTI (CAP) - EMEA/H/C/005287/MEA 004.1

Applicant: H. Lundbeck A/S

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: MAH's response to MEA 004 [protocol for study 19756N: a long-term cardiovascular safety and real-world use of eptinezumab - an observational, historical cohort study of

[65] Advanced therapy medicinal product

patients initiating eptinezumab in routine clinical practice] as per request for supplementary information (RSI) adopted in June 2022

17.2.8. Fremanezumab - AJOVY (CAP) - EMEA/H/C/004833/MEA 005.4

Applicant: TEVA GmbH

PRAC Rapporteur: Kirsti Villikka

Scope: Submission of a protocol for study TV48125-MH-40217: a long-term observational, retrospective cohort study to evaluate the safety, including cardiovascular safety, of fremanezumab in patients with migraine in routine clinical practice in the United States and Europe (non-interventional phase IV study)

17.2.9. Lusutrombopag - MULPLEO (CAP) - EMEA/H/C/004720/MEA 002.3

Applicant: Shionogi B.V.

PRAC Rapporteur: Mari Thorn

Scope: Substantial amendment to an agreed protocol for study VV-REG-090246 hepatic safety of lusutrombopag Shionogi in patients with Child Pugh Class C liver disease

17.2.10. Naltrexone hydrochloride, bupropion hydrochloride - MYSIMBA (CAP) - EMEA/H/C/003687/MEA 003.14

Applicant: Orexigen Therapeutics Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: MAH's response to MEA 003.12 [protocol for study NB-451: an observational retrospective drug utilisation study (DUS) of Mysimba (naltrexone hydrochloride/bupropion hydrochloride) in Europe and the United States to describe the demographic and baseline characteristics of users of Mysimba (naltrexone hydrochloride/bupropion hydrochloride), evaluate patterns of Mysimba (naltrexone hydrochloride/bupropion hydrochloride) initiation and use] as per request for supplementary information (RSI) adopted in July 2022

17.2.11. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/MEA 014.6

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Amendment to a previously agreed protocol for study A3921321 (listed as category 3 study in the RMP): a Post-Authorisation Safety Study (PASS) of the Utilisation and Prescribing Patterns of Xeljanz (tofacitinib) in two European Countries Using Administrative Claims Databases and National Registries for assessment

17.2.12. Tozinameran - COMIRNATY (CAP) - EMEA/H/C/005735/MEA 009

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Amendment to a previously agreed protocol for study C4591011: active safety

surveillance of the Pfizer-BioNTech COVID-19 Vaccine in the United States (US) Department of Defense (DoD) Population following emergency use authorisation to assess whether individuals in the US DoD Military Health System (MHS) experience increased risk of safety events of interest, including myocarditis and pericarditis

17.2.13. Upadacitinib - RINVOQ (CAP) - EMEA/H/C/004760/MEA 013.2

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: MAH's response to MEA 013.1 [revised protocol for study P20-390: a cohort study of long-term safety of upadacitinib in the treatment of atopic dermatitis in Denmark and Sweden] as per request for supplementary information (RSI) adopted in July 2022

17.2.14. Vosoritide - VOXZOGO (CAP) - EMEA/H/C/005475/MEA 005.2

Applicant: BioMarin International Limited

PRAC Rapporteur: Zane Neikena

Scope: Substantial amendment to a previously agreed protocol for study BMN111-603: a multicentre, non-interventional study to evaluate long-term safety in patients with achondroplasia treated with Voxzogo (vosoritide)

17.3. Results of PASS imposed in the marketing authorisation(s)[66]

None

17.4. Results of PASS non-imposed in the marketing authorisation(s)[67]

17.4.1. Alglucosidase alfa - MYOZYME (CAP) - EMEA/H/C/000636/II/0092

Applicant: Genzyme Europe BV

PRAC Rapporteur: Nathalie Gault

Scope: Update of sections 4.6 and 5.3 of the SmPC in order to update information on pregnancy, lactation and fertility following the request by PRAC in the AR for MEA/024.17 and MEA/025.17 and in the PSUR single assessment (PSUSA) procedure (PSUSA/00000086/202109) concluded in June 2022. The package leaflet is updated accordingly. In addition, the MAH took the opportunity to introduce minor editorial changes to the product information

17.4.2. Delamanid - DELTYBA (CAP) - EMEA/H/C/002552/II/0061, Orphan

Applicant: Otsuka Novel Products GmbH

PRAC Rapporteur: Jo Robays

Scope: Update of sections 4.2 and 4.4 of the SmPC in order to update treatment duration based on final results from EU PASS (protocol no. 242-12-402), listed as a category 3 study

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

in the RMP. This is a "A Multicentre, EU-wide, Non-Interventional Post-Authorisation Study to Assess the Safety and Usage of Delamanid in Routine Medical Practice in Multidrug-Resistant Tuberculosis (MDR-TB) Patients". This treatment registry was for monitoring and documenting Deltyba use in routine medical practice and aimed to assess compliance with the recommendations in the authorised product information when prescribed as part of an appropriate combination regimen (ACR) for the treatment of MDR-TB. The package leaflet is updated accordingly. The RMP version 4.2 has also been submitted. In addition, the MAH took the opportunity to update Annex II section D of the SmPC

17.4.3. Idelalisib - ZYDELIG (CAP) - EMEA/H/C/003843/II/0056

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Martin Huber

Scope: Submission of the final report from study GS-EU-313-4172 listed as a category 3 study in the RMP. This is a non-interventional study to assess the safety profile of idelalisib in patients with refractory follicular lymphoma (FL) with primary objective to assess the overall safety profile of idelalisib monotherapy in patients with refractory FL

17.4.4. Liraglutide - SAXENDA (CAP) - EMEA/H/C/003780/II/0034

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Menno van der Elst

Scope: Submission of the final report from study NN8022-4246 listed as a category 3 study in the RMP. This is an in-market utilisation non-interventional PASS of liraglutide used for weight management in the UK using the clinical practice research datalink (CPRD) Primary Care Database. The RMP version 33.0 has also been submitted

17.4.5. Pegfilgrastim - NEULASTA (CAP) - EMEA/H/C/000420/II/0121

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Submission of the final report from PASS study 20170701 listed as a category 3 study in the RMP. This is a cross-sectional survey study to Assess the Effectiveness of the Neulasta Patient Alert Card and to Measure Medication Errors Related to the Use of the Neulasta On-Body Injector. The RMP version 9.0 has also been submitted

17.4.6. Talimogene laherparepvec - IMLYGIC (CAP) - EMEA/H/C/002771/II/0056

Applicant: Amgen Europe B.V., ATMP[68]

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Submission of the final report from study 20120139 listed as a category 3 study in the RMP in order to fulfil MEA/004. This is a multicentre, observational registry study to evaluate the survival and long-term safety of subjects who previously received talimogene laherparepvec in Amgen or BioVEX sponsored clinical trials

[68] Advanced therapy medicinal product

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

17.5.1. Adalimumab - IMRALDI (CAP) - EMEA/H/C/004279/MEA 003.1

Applicant: Samsung Bioepis NL B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Second interim report of the safety surveillance programme using the Register for Antirheumatic Therapies in Sweden (ARTIS): a national prospective, observational, uncontrolled cohort study to evaluate the risk of selected adverse events in rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA) and other rheumatic disease patients treated with adalimumab

17.5.2. Adalimumab - IMRALDI (CAP) - EMEA/H/C/004279/MEA 004.1

Applicant: Samsung Bioepis NL B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Second interim report of the safety surveillance programme using the Spanish Registry for Adverse Events for Biological Therapy in Rheumatic Diseases (BIOBASASER)

17.5.3. Elasomeran - SPIKEVAX (CAP) - EMEA/H/C/005791/MEA 003.8

Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: MAH's response to MEA 003.6 [Fifth interim report for a study (listed as a category 3 study in the RMP): a post authorisation safety of Spikevax (elasomeran) in the US - an enhanced pharmacovigilance study to provide additional evaluation of adverse events of special interest (AESI) and emerging validated safety signals [P903] as per request for supplementary information (RSI) adopted in July 2022

17.5.4. Human papillomavirus vaccine [types 16, 18] (recombinant, adjuvanted, adsorbed) - CERVARIX (CAP) - EMEA/H/C/000721/II/0117

Applicant: GlaxoSmithkline Biologicals SA

PRAC Rapporteur: Jean-Michel Dogné

Scope: Submission of the interim report from study EPI-HPV-099 (217743). This is an observational, retrospective database post-authorisation safety study (PASS) assessing trends and changes over time in incidence of anal cancer and feasibility for a case-control study in European countries that introduced Cervarix in their National Immunisation Programme. The study was set up to address the missing information on the impact and effectiveness of Cervarix against anal lesions and cancer in the Cervarix RMP. The RMP version 26 has also been submitted

17.5.5. Nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/MEA 008.10

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Sixth annual interim report for study CA209234 (listed as a category 3 study in the RMP): a PASS exploring the pattern of use, safety, and effectiveness of nivolumab in routine oncology practice [final clinical study report (CSR) expected in December 2024]

17.5.6. Romosozumab - EVENITY (CAP) - EMEA/H/C/004465/MEA 001.5

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Tiphaine Vaillant

Scope: Fourth interim report for study OP0005: a European non-interventional PASS to study the adherence to the risk minimisation measures (RMMs) in the product information by estimating the compliance with contraindications and target indication(s) amongst incident romosozumab users, and analysing the utilisation pattern using the EU-adverse drug reactions (EU-ADR) Alliance

17.5.7. Romosozumab - EVENITY (CAP) - EMEA/H/C/004465/MEA 002.5

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Tiphaine Vaillant

Scope: Fourth interim report for study OP0004: a European non-interventional PASS to evaluate potential differences in terms of serious cardiovascular adverse events between romosozumab and currently available therapies used in comparable patients in real-world conditions using the EU-adverse drug reactions (EU-ADR) Alliance

17.5.8. Romosozumab - EVENITY (CAP) - EMEA/H/C/004465/MEA 003.3

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Tiphaine Vaillant

Scope: Second interim report for study OP0006: a European non-interventional PASS to evaluate potential differences in terms of serious infection between romosozumab and currently available therapies used in comparable patients in real-world conditions using the EU-adverse drug reactions (EU-ADR) Alliance [final study results expected in December 2024]

17.5.9. Siponimod - MAYZENT (CAP) - EMEA/H/C/004712/MEA 003.1

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Maria del Pilar Rayon

Scope: First annual interim report for study CBAF312A2403: a post-authorisation safety study for assessment of pregnancy outcomes in patients treated with Mayzent (siponimod): an OTIS observational pregnancy surveillance study

17.5.10. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/MEA 013.5

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: First interim report for study A3921344 (listed as category 3 study in the RMP): an active surveillance, post-authorisation study to characterise the safety of tofacitinib in patients with moderately to severely active ulcerative colitis in the real-world setting using data from the Swedish Quality Register for Inflammatory Bowel Disease

17.5.11. Tozinameran - COMIRNATY (CAP) - EMEA/H/C/005735/MEA 011.6

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Interim report for study C4591010: a post-approval active surveillance safety study to monitor real-world safety of Comirnaty (tozinameran) vaccine in the EU

17.5.12. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/MEA 044.15

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: MAH's response to MEA 044.14 [Fourth interval safety registry for study CNTO1275PSO4056: an observational PASS of ustekinumab in the treatment of paediatric patients aged 12 years and older with moderate to severe plaque psoriasis (adolescent registry)] as per request for supplementary information (RSI) adopted in July 2022

17.6. Others

17.6.1. Alemtuzumab - LEMTRADA (CAP) - EMEA/H/C/003718/ANX 010.5

Applicant: Sanofi Belgium

PRAC Rapporteur: Anette Kirstine Stark

Scope: Feasibility report for a non-interventional PASS to investigate the risk in mortality of multiple sclerosis (MS) patients treated with alemtuzumab relative to comparable other MS patients using other DMTs (disease modifying therapies)

17.6.2. Darolutamide - NUBEQA (CAP) - EMEA/H/C/004790/REC 004.1

Applicant: Bayer AG

PRAC Rapporteur: Jan Neuhauser

Scope: MAH's response to REC 004 [submission of an addendum to the final clinical report for study (17712): efficacy and safety study of darolutamide (ODM-201) in men with high-risk non-metastatic castration-resistant prostate cancer (ARAMIS)] as per request for supplementary information (RSI) adopted in July 2022

17.6.3. Natalizumab - TYSABRI (CAP) - EMEA/H/C/000603/MEA 071.2

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: MAH's response to MEA 071.1 [feasibility assessment report for study OXON 214-04 (listed as a category 3 study in the RMP): an observational study utilising data from EU national multiple sclerosis (MS) registries to estimate the incidence of anti-natalizumab antibody among patients who receive subcutaneous administration (SC) of natalizumab for treatment of relapsing remitting MS in order to investigate immunogenic potential of SC administration (PASS 101MS412) (from X/0116)] as per the request for supplementary information (RSI) adopted in June 2022

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. Asfotase alfa - STRENSIQ (CAP) - EMEA/H/C/003794/S/0059 (without RMP)

Applicant: Alexion Europe SAS

PRAC Rapporteur: Rhea Fitzgerald

Scope: Annual reassessment of the marketing authorisation

18.1.2. Cerliponase alfa - BRINEURA (CAP) - EMEA/H/C/004065/S/0038 (without RMP)

Applicant: BioMarin International Limited

PRAC Rapporteur: Mari Thorn

Scope: Annual reassessment of the marketing authorisation

18.1.3. Lomitapide - LOJUXTA (CAP) - EMEA/H/C/002578/S/0052 (without RMP)

Applicant: Amryt Pharmaceuticals DAC

PRAC Rapporteur: Menno van der Elst

Scope: Annual reassessment of the marketing authorisation

18.1.4. Mecasermin - INCRELEX (CAP) - EMEA/H/C/000704/S/0078 (without RMP)

Applicant: Ipsen Pharma

PRAC Rapporteur: Kirsti Villikka

Scope: Annual reassessment of the marketing authorisation

18.1.5. Odevixibat - BYLVAY (CAP) - EMEA/H/C/004691/S/0008 (without RMP)

Applicant: Albireo

PRAC Rapporteur: Adam Przybylkowski

Scope: Annual reassessment of the marketing authorisation

18.2. Conditional renewals of the marketing authorisation

18.2.1. Coronavirus (COVID-19) vaccine (Ad26.COV2-S, recombinant) - JCOVDEN (CAP) - EMEA/H/C/005737/R/0063 (without RMP)

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Conditional renewal of the marketing authorisation

18.2.2. Delamanid - DELTYBA (CAP) - EMEA/H/C/002552/R/0062 (without RMP)

Applicant: Otsuka Novel Products GmbH

PRAC Rapporteur: Jo Robays

Scope: Conditional renewal of the marketing authorisation

18.2.3. Dostarlimab - JEMPERLI (CAP) - EMEA/H/C/005204/R/0017 (without RMP)

Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Inês Ribeiro-Vaz

Scope: Conditional renewal of the marketing authorisation

18.2.4. Parathyroid hormone - NATPAR (CAP) - EMEA/H/C/003861/R/0046 (without RMP)

Applicant: Takeda Pharmaceuticals International AG

PRAC Rapporteur: Rhea Fitzgerald

Scope: Conditional renewal of the marketing authorisation

18.2.5. Pemigatinib - PEMAZYRE (CAP) - EMEA/H/C/005266/R/0007 (without RMP)

Applicant: Incyte Biosciences Distribution B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Conditional renewal of the marketing authorisation

18.3. Renewals of the marketing authorisation

18.3.1. Adalimumab - HEFIYA (CAP) - EMEA/H/C/004865/R/0038 (without RMP)

Applicant: Sandoz GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: 5-year renewal of the marketing authorisation

18.3.2. Adalimumab - HYRIMOZ (CAP) - EMEA/H/C/004320/R/0037 (without RMP)

Applicant: Sandoz GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: 5-year renewal of the marketing authorisation

18.3.3. Carmustine - CARMUSTINE OBVIUS (CAP) - EMEA/H/C/004326/R/0009 (with RMP)

Applicant: Obvius Investment B.V

PRAC Rapporteur: Jan Neuhauser

Scope: 5-year renewal of the marketing authorisation

18.3.4. Erenumab - AIMOVIG (CAP) - EMEA/H/C/004447/R/0024 (with RMP)

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Kirsti Villikka

Scope: 5-year renewal of the marketing authorisation

18.3.5. Insulin glargine - SEMGLEE (CAP) - EMEA/H/C/004280/R/0040 (without RMP)

Applicant: Viatris Limited

PRAC Rapporteur: Menno van der Elst

Scope: 5-year renewal of the marketing authorisation

18.3.6. Pemetrexed - PEMETREXED KRKA (CAP) - EMEA/H/C/003958/R/0009 (with RMP)

Applicant: KRKA, d.d., Novo mesto

PRAC Rapporteur: Tiphaine Vaillant

Scope: 5-year renewal of the marketing authorisation

18.3.7. Sodium zirconium cyclosilicate - LOKELMA (CAP) - EMEA/H/C/004029/R/0027 (without RMP)

Applicant: AstraZeneca AB

PRAC Rapporteur: Kirsti Villikka

Scope: 5-year renewal of the marketing authorisation

18.3.8. Trastuzumab - KANJINTI (CAP) - EMEA/H/C/004361/R/0022 (without RMP)

Applicant: Amgen Europe B.V., BREDA

PRAC Rapporteur: Brigitte Keller-Stanislawski

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 28 November - 01 December 2022 meeting.

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Sabine Straus	Chair	The Netherlands	No interests declared	
Jan Neuhauser	Member	Austria	No interests declared	
Sonja Hrabcik	Alternate	Austria	No interests declared	
Jean-Michel Dogné	Member	Belgium	No interests declared	
Jo Robays	Alternate	Belgium	No interests declared	
Maria Popova-Kiradjieva	Member	Bulgaria	No interests declared	
Nikica Mirošević Skvrce	Member	Croatia	No interests declared	
Željana Margan Koletić	Alternate	Croatia	No interests declared	
Panagiotis Psaras	Alternate	Cyprus	No interests declared	
Eva Jirsová	Member	Czechia	No interests declared	
Jana Lukacisinova	Alternate	Czechia	No interests declared	
Anette Stark	Member	Denmark	No interests declared	
Marie Louise Schougaard Christiansen	Alternate	Denmark	No interests declared	
Kroot Aab	Alternate	Estonia	No interests declared	
Kirsti Villikka	Member	Finland	No interests declared	
Kimmo Jaakkola	Alternate	Finland	No interests declared	
Tiphaine Vaillant	Member	France	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Nathalie Gault	Alternate	France	No interests declared	
Martin Huber	Member (Vice-Chair)	Germany	No interests declared	
Brigitte Keller-Stanislawski	Alternate	Germany	No interests declared	
Sophia Trantza	Member	Greece	No interests declared	
Georgia Gkegka	Alternate	Greece	No interests declared	
Julia Pallos	Member	Hungary	No participation in final deliberations and voting on:	7.1.1. Lisocabtagene maraleucel - BREYANZI (CAP) - EMEA/H/C/PSP/S/0098.1 15.3.17. Ipilimumab - YERVOY (CAP) - EMEA/H/C/002213/II/0100 15.3.19. Nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/II/0125/G 16.1.4. Azacitidine - ONUREG (CAP) - PSUSA/00010935/202205 16.1.16. Entecavir - BARACLUDE (CAP) - PSUSA/00001224/202203 16.1.33. Ozanimod - ZEPOSIA (CAP) - PSUSA/00010852/202205 16.2.2. Efavirenz –

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				STOCRIN (CAP); SUSTIVA (CAP); NAP – PSUSA/00001200/202204 17.5.5. Nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/MEA 008.10
Guðrún Stefánsdóttir	Member	Iceland	No participation in final deliberations and voting on:	5.1.1. Eculizumab - BKEMV (CAP MAA) - EMEA/H/C/005652 14.1.1. Evolocumab – REPATHA (CAP) 15.3.15. Evolocumab - REPATHA (CAP) - EMEA/H/C/003766/II/0061 17.1.3. Blinatumomab - BLINCYTO (CAP) - EMEA/H/C/PSA/S/0096 17.4.4. Pegfilgrastim - NEULASTA (CAP) - EMEA/H/C/000420/II/0121 17.4.5. Talimogene laherparepvec – IMLYGIC (CAP) – EMEA/H/C/002771/II/0056 18.3.8. Trastuzumab - KANJINTI (CAP) -

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				EMEA/H/C/004361/R/0022 (without RMP)
Gudrun Thengilsdottir	Alternate	Iceland	No restrictions applicable to this meeting	
Rhea Fitzgerald	Member	Ireland	No interests declared	
Ronan Grimes	Alternate	Ireland	No interests declared	
Amelia Cupelli	Member	Italy	No interests declared	
Valentina Di Giovanni	Alternate	Italy	No interests declared	
Zane Neikena	Member	Latvia	No interests declared	
Rugile Pilviniene	Member	Lithuania	No interests declared	
Lina Seibokiene	Alternate	Lithuania	No restrictions applicable to this meeting	
Anne-Cécile Vuillemin	Alternate	Luxembourg	No interests declared	
John Joseph Borg	Member	Malta	No interests declared	
Menno van der Elst	Member	Netherlands	No interests declared	
Liana Gross-Martirosyan	Alternate	Netherlands	No interests declared	
David Olsen	Member	Norway	No participation in final deliberations and voting on:	5.3.2. Riociguat - ADEMPAS (CAP) - EMEA/H/C/002737/II/0037 6.3.4. Ethinylestradiol, levonorgestrel (NAP) - PSUSA/00001309/202204 6.3.10. Omeprazole (NAP) -

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				PSUSA/00002215/202204 15.3.9. Darolutamide - NUBEQA (CAP) - EMEA/H/C/004790/II/0009 15.3.10. Darolutamide - NUBEQA (CAP) - EMEA/H/C/004790/II/0012 16.2.3. Hydrochlorothiazide, telmisartan - KINZALKOMB (CAP); MICARDISPLUS (CAP); PRITORPLUS (CAP); telmisartan - KINZALMONO (CAP); MICARDIS (CAP); PRITOR (CAP); NAP - PSUSA/00002882/202203 16.3.24. Sulprostone (NAP) - PSUSA/00002828/202204 17.6.2. Darolutamide - NUBEQA (CAP) - EMEA/H/C/004790/REC 004.1
Karen Pernille Harg	Alternate	Norway	No interests declared	
Adam Przybylkowski	Member	Poland	No interests declared	
Ana Diniz Martins	Member	Portugal	No interests declared	
Inês Ribeiro-Vaz	Alternate	Portugal	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Roxana Dondera	Member	Romania	No interests declared	
Alexandra - Maria Spurni	Alternate	Romania	No interests declared	
Anna Mareková	Member	Slovakia	No interests declared	
Lucia Kuráková	Alternate	Slovakia	No interests declared	
Milena Radoha-Bergoc	Alternate	Slovenia	No participation in final deliberations and voting on:	16.2.4. Olanzapine - ZALASTA (CAP); ZYPADHERA (CAP); ZYPREXA (CAP); ZYPREXA VELOTAB (CAP); NAP - PSUSA/00010540/202203 16.3.2. Amlodipine, candesartan (NAP) - PSUSA/00010191/202204 16.3.3. Amlodipine, olmesartan (NAP) - PSUSA/00002208/202204 16.3.16. Linezolid (NAP) - PSUSA/00001888/202204 18.3.6. Pemetrexed - PEMETREXED KRKA (CAP) - EMEA/H/C/003958/R/0009 (with RMP)
Maria del Pilar Rayon	Member	Spain	No interests declared	
Monica Martinez Redondo	Alternate	Spain	No participation in discussion,	5.3.1. Emicizumab - HEMLIBRA (CAP) -

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			final deliberations and voting on:	EMEA/H/C/004406/II/0027 6.1.1. Atezolizumab - TECENTRIQ (CAP) - PSUSA/00010644/202205 6.1.6. Tocilizumab - ROACTEMRA (CAP) - PSUSA/00002980/20220 15.3.20. Ocrelizumab - OCREVUS (CAP) - EMEA/H/C/004043/II/0034/G 15.3.32. Tocilizumab - ROACTEMRA (CAP) - EMEA/H/C/000955/II/0114 16.3.13. Isotretinoin (NAP) - PSUSA/00010488/202205 17.6.3. Natalizumab - TYSABRI (CAP) - EMEA/H/C/000603/MEA 071.2
Ulla Wändel Liminga	Member	Sweden	No interests declared	
Mari Thorn	Alternate	Sweden	No restrictions applicable to this meeting	
Annalisa Capuano	Member	Independent scientific expert	No interests declared	
Milou Daniel Drici	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
Maria Teresa Herdeiro	Member	Independent scientific expert	No interests declared	
Patricia McGettigan	Member	Independent scientific expert	No interests declared	
Hedvig Nordeng	Member	Independent scientific expert	No interests declared	
Roberto Frontini	Member	Healthcare Professionals' Representative	No restrictions applicable to this meeting	
Salvatore Messana	Alternate	Healthcare Professionals' Representative	No interests declared	
Marko Korenjak	Alternate	Patients' Organisation Representative	No participation in discussion, final deliberations and voting on:	6.3.11. Triptorelin (NAP) - PSUSA/00003048/202203 16.4.1. Cabozantinib - CABOMETYX (CAP) - EMEA/H/C/004163/LEG 007 16.4.2. Cabozantinib - COMETRIQ (CAP) - EMEA/H/C/002640/LEG 022 18.1.4. Mecasermin - INCRELEX (CAP) - EMEA/H/C/000704/S/0078 (without RMP)
Françoise Wuillaume	Expert	Belgium	No interests declared	
Evelien De Clercq	Expert	Belgium	No interests declared	
Flora Musuamba Tshinanu	Expert	Belgium	No restrictions applicable to this meeting	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Petar Mas	Expert	Croatia	No interests declared	
Barbara Kovacic	Expert	Croatia	No interests declared	
Ana Jeroncic	Expert	Croatia	No interests declared	
Caroline Marie Voss	Expert	Denmark	No interests declared	
Marian Hjortlund Allon	Expert	Denmark	No interests declared	
Annette Cleveland Nielsen	Expert	Denmark	No restrictions applicable to this meeting	
Hanna Belcik Christensen	Expert	Denmark	No restrictions applicable to this meeting	
Helle Gerda Olsen	Expert	Denmark	No interests declared	
Alexander Braathen	Expert	Denmark	No interests declared	
Aynur Sert	Expert	Denmark	No interests declared	
Ane Blicher Schelde	Expert	Denmark	No restrictions applicable to this meeting	
Katrine Jønsson	Expert	Denmark	No interests declared	
Marianne Hald Clemmensen	Expert	Denmark	No restrictions applicable to this meeting	
Moritz Sander	Expert	Denmark	No interests declared	
Vincent Gazin	Expert	France	No interests declared	
Marie-Caroline Pesquidous	Expert	France	No restrictions applicable to this meeting	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Sarah Bendahou	Expert	France	No interests declared	
Cecile Taddei	Expert	France	No interests declared	
Thomas Berbain	Expert	France	No interests declared	
Camille de Kervasdoue	Expert	France	No interests declared	
Martine Reidiboym	Expert	France	No interests declared	
Benjamin Burrus	Expert	France	No interests declared	
Stephanie Hueber	Expert	France	No interests declared	
Dennis Lex	Expert	Germany	No interests declared	
Gabriele Maurer	Expert	Germany	No restrictions applicable to this meeting	
Anne Kleinau	Expert	Germany	No interests declared	
Kerstin Löschcke	Expert	Germany	No interests declared	
Karin Seifert	Expert	Germany	No interests declared	
Eamon O Murchu	Expert	Ireland	No interests declared	
Paul ten Berg	Expert	Netherlands	No interests declared	
Anita Volkers	Expert	Netherlands	No interests declared	
Anja van Haren	Expert	Netherlands	No interests declared	
Carla Torre	Expert	Portugal	No interests declared	
Marcia Sofia Sanches de Castro Lopes Silva	Expert	Portugal	No interests declared	
Karin Nylén	Expert	Sweden	No interests declared	
Charlotte Backman	Expert	Sweden	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Consuelo Mejías	Expert	Spain	No interests declared	
María Martínez Gonzalez	Expert	Spain	No interests declared	
Natividad Galiana	Expert	Spain	No restrictions applicable to this meeting	
Luz Medrano	Expert	Spain	No interests declared	
A representative from the European Commission attended the meeting.				
Meeting run with support from relevant EMA staff.				

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

20. Annex III - List of acronyms and abbreviations

For a list of acronyms and abbreviations used in the PRAC minutes, see:
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:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000150.jsp&mid=WC0b01ac05800240d0

Signals assessment and prioritisation

(Item 4 of the PRAC minutes)

A safety signal is information on a new or incompletely documented adverse event that is potentially caused by a medicine and that warrants further investigation. Signals are generated from several sources such as spontaneous reports, clinical studies and the scientific literature. The evaluation of safety signals is a routine part of pharmacovigilance and is essential to ensuring that regulatory authorities have a comprehensive knowledge of a medicine's benefits and risks.
The presence of a safety signal does not mean that a medicine has caused the reported adverse event.

The adverse event could be a symptom of another illness or caused by another medicine taken by the patient. The evaluation of safety signals is required to establish whether or not there is a causal relationship between the medicine and the reported adverse event.
The evaluation of safety signals may not necessarily conclude that the medicine caused the adverse event in question. In cases where a causal relationship is confirmed or considered likely, regulatory action may be necessary and this usually takes the form of an update of the summary of product characteristics and the package leaflet.

Risk Management Plans (RMPs)

(Item 5 of the PRAC minutes)

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

Assessment of Periodic Safety Update Reports (PSURs)

(Item 6 of the PRAC minutes)

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

Post-authorisation Safety Studies (PASS)

(Item 7 of the PRAC minutes)

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

Product related pharmacovigilance inspections

(Item 9 of the PRAC minutes)

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

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