EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 August 2022
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Human Medicines Division

Pharmacovigilance Risk Assessment Committee (PRAC)

Minutes of the meeting on 29 November – 02 December 2021

Chair: Sabine Straus – Vice-Chair: Martin Huber

Disclaimers

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

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

Note on access to documents

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

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1. Introduction

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

The Chair opened the meeting by welcoming all participants. Due to the current coronavirus (COVID-19 outbreak) and the associated EMA Business Continuity Plan (BCP), the meeting was held remotely.

In accordance with the Agency's policy on handling of declarations of interests of scientific Committees' members and experts, based on the declarations of interest submitted by the Committee members, alternates 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. All decisions taken at this meeting were made in the presence of a quorum of members. All decisions, recommendations and advice were agreed unanimously, unless otherwise specified.

1.2. Agenda of the meeting on 29 November – 02 December 2021

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

1.3. Minutes of the previous meeting on 25-28 October 2021

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 25-28 October 2021 were published on the EMA website on 02 August 2022.

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

2.1. Newly triggered procedures

None

2.2. Ongoing procedures

None

2.3. Procedures for finalisation

None

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

3.1. Newly triggered procedures

None

3.2. Ongoing procedures

3.2.1. Amfepramone (NAP) - EMEA/H/A-31/1501

Applicant(s): Artegodan GmbH, Temmler Pharma GmbH

PRAC Rapporteur: Anette Kirstine Stark; PRAC Co-rapporteur: Eva Jirsová

Scope: Review of the benefit-risk balance following notification by Romania 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 amfepramone-containing products reviewing the benefit-risk balance, in light of the known serious safety concerns related to the therapeutic class of anorexigens, the reported cases of cardiac-related adverse drug reactions, cases of pulmonary hypertension, and the off-label use despite the risk minimisation measures in place, and taking into account the uncertainties as to clinical relevance of this treatment. For further background, see PRAC minutes February 2021, PRAC minutes July 2021, PRAC minutes October 2021[1] and PRAC minutes November 2021[2].

Summary of recommendation(s)/conclusions

- PRAC adopted a revised timetable (EMA/PRAC/51714/2021 Rev.4) to allow for further data to be taken into consideration in the framework of the procedure.

3.3. Procedures for finalisation

None

3.4. Re-examination procedures[3]

None

3.5. Others

None

[1] Held 27-30 September 2021
[2] Held 25-28 October 2021
[3] Re-examination of PRAC recommendation under Article 32 of Directive 2001/83/EC

4. Signals assessment and prioritisation[4]

4.1. New signals detected from EU spontaneous reporting systems

See Annex 14.1.

4.2. New signals detected from other sources

See also Annex 14.2.

4.2.1. Coronavirus (COVID-19) mRNA[5] vaccine (nucleoside-modified) - SPIKEVAX (CAP)

Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Hans Christian Siersted

Scope: Signal of autoimmune hepatitis

EPITT 19750 – New signal

Lead Member State(s): DK

Background

COVID-19 nucleoside-modified messenger ribonucleic acid (mRNA) vaccine is indicated, as Spikevax, for active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 12 years of age and older.

Based on a literature and EudraVigilance review, a signal of autoimmune hepatitis (AIH) was identified by EMA, based on thirteen cases, that are supportive and well documented in the literature. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by PRAC.

Discussion

Having considered the available evidence, where AIH diagnosis was confirmed through liver biopsy with well described histology and laboratory tests, PRAC agreed that further evaluation on the signal of AIH is warranted.

Summary of recommendation(s)

- The MAH should submit to EMA, within 60 days, a detailed review of cases of AIH, including an ascertained diagnosis and causality assessment. The MAH should discuss probable mechanism(s) underlying the occurrence of vaccine associated AIH following administration of Spikevax (COVID-19 mRNA vaccine (nucleoside-modified)) and the timing of development of clinical symptoms in relationship to the proposed mechanism of action, and if possible, the type of AIH involved. The review should explore possible risk factors, considering the gender/age, medical history of autoimmunity and dose distribution of reported cases. The MAH should discuss whether any patterns or trends

[4] 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

[5] Messenger ribonucleic acid

can be identified concerning risk factors. Finally, the MAH should propose to update the product information/RMP as warranted.

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

4.2.2. Tozinameran (previously COVID-19 mRNA[6] vaccine (nucleoside modified)) - COMIRNATY (CAP)

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Signal of autoimmune hepatitis

EPITT 19749 – New signal

Lead Member State(s): NL

Background

Tozinameran is a nucleoside-modified messenger ribonucleic acid (mRNA) vaccine indicated, as Comirnaty, for the active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 12 years of age and older.

Based on a literature and EudraVigilance review, a signal of autoimmune hepatitis (AIH) was identified by EMA, based on six supportive and well documented cases. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by PRAC.

Discussion

Having considered the available evidence, where AIH diagnosis was confirmed through liver biopsy with well described histology and laboratory tests, PRAC agreed that further evaluation on the signal of AIH is warranted.

Summary of recommendation(s)

- The MAH should submit to EMA, within 60 days, a detailed review of cases of AIH, including an ascertained diagnosis and causality assessment. The MAH should discuss probable mechanism(s) underlying the occurrence of vaccine associated AIH following administration of Comirnaty (tozinameran) and the timing of development of clinical symptoms in relationship to the proposed mechanism of action, and if possible, the type of AIH involved. The review should explore possible risk factors, considering the gender/age, medical history of autoimmunity and dose distribution of reported cases. The MAH should discuss whether any patterns or trends can be identified concerning risk factors. Finally, the MAH should propose to update the product information/RMP as warranted.
- A 60 day-timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

[6] Messenger ribonucleic acid

4.3. Signals follow-up and prioritisation

4.3.1. Coronavirus (COVID-19) mRNA[7] vaccine (nucleoside-modified) - SPIKEVAX (CAP) - EMEA/H/C/005791/SDA/033.2

Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Hans Christian Siersted

Scope: Signal of myocarditis and pericarditis

EPITT 19713 – Follow-up to November 2021

Background

For background information, see PRAC minutes November 2021[8].

The MAH replied to the request for information on the signal of myocarditis and pericarditis and the responses were assessed by the Rapporteur. In addition to the available evidence from the study entitled 'SARS-CoV-2 vaccination and myocarditis in a Nordic cohort study of 23 million residents'[9], PRAC also considered further studies in and outside the EEA, including the EPI-PHARE study entitled 'Association of Covid-19 mRNA vaccines with myocarditis and pericarditis'[10] as well as an updated observed to expected (O/E) analysis based on EudraVigilance.

Discussion

Having considered the available evidence from large observational studies in and outside the EU, the data provided by the MAH together with the Rapporteur's assessment, PRAC agreed that there is sufficient evidence to further strengthened the wording of the product information for Spikevax (COVID-19 mRNA vaccine (nucleoside-modified)) with regard to myocarditis and pericarditis.

Summary of recommendation(s)

- The MAH for Spikevax (COVID-19 mRNA vaccine (nucleoside-modified)) should submit to EMA, within 5 days, a variation to amend[11] the product information to refine the existing warning on myocarditis and pericarditis and amend the frequency of these undesirable effects from 'not known' to 'very rare' with a description of myocarditis.

For the full PRAC recommendation, see EMA/PRAC/683817/2021 published on 06 January 2022 on the EMA website.

4.3.2. Olmesartan (NAP); olmesartan, amlodipine (NAP); olmesartan, hydrochlorothiazide (NAP); olmesartan medoxomil, amlodipine besilate, hydrochlorothiazide (NAP)

Applicant(s): various

PRAC Rapporteur: Martin Huber

Scope: Signal of autoimmune hepatitis

[7] Messenger ribonucleic acid
[8] Held 25-28 October 2021
[9] Karlstad, Øystein, et al. SARS-CoV-2 vaccination and myocarditis in a Nordic cohort study of 23 million residents
[10] Le Vu et al. Association between COVID-19 messenger RNA vaccines and the occurrence of myocarditis and pericarditis in people aged 12 to 50 in France - Study based on data from the National Health Data System (SNDS)
[11] Update of sections 4.4 and 4.8 of the SmPC. The package leaflet is to be updated accordingly

EPITT 19258 – Follow-up to November 2021

Background

For background information, see PRAC minutes November 2021[12].

The MAHs for olmesartan-, olmesartan/amlodipine-, olmesartan/hydrochlorothiazide-and olmesartan/amlodipine/hydrochlorothiazide-containing products were requested to comment on a proposed wording to update the product information with autoimmune hepatitis (AIH) in the context of the signal on AIH further information was assessed by the Rapporteur.

Discussion

Taking into consideration the available evidence from the published literature and EudraVigilance, PRAC concluded that a causal association between AIH and patients treated with olmesartan-containing products is a reasonable possibility.

Summary of recommendation(s)

- The MAHs for olmesartan-, olmesartan/amlodipine-, olmesartan/hydrochlorothiazide-and olmesartan/amlodipine/hydrochlorothiazide-containing products should submit to the relevant National Competent Authorities (NCAs) of the EU Member States, within 60 days, a variation to amend[13] the product information with AIH with a frequency 'not known'.

For the full PRAC recommendation, see EMA/PRAC/683817/2021 published on 06 January 2022 on the EMA website.

4.3.3. Tozinameran (previously COVID-19 mRNA[14] vaccine (nucleoside modified)) - COMIRNATY (CAP) - EMEA/H/C/005735/SDA/032.2

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Signal of myocarditis and pericarditis

EPITT 19712 – Follow-up to November 2021

Background

For background information, see PRAC minutes November 2021[15].

The MAH replied to the request for information on the signal of myocarditis and pericarditis and the responses were assessed by the Rapporteur. In addition to the available evidence from the study entitled 'SARS-CoV-2 vaccination and myocarditis in a Nordic cohort study of 23 million residents'[16], PRAC also considered further studies in and outside the EEA, including the EPI-PHARE study entitled 'Association of Covid-19 mRNA vaccines with myocarditis and pericarditis'[17] as well as an updated observed to expected (O/E) analysis based on EudraVigilance.

[12] Held 25-28 October 2021
[13] Update of SmPC sections 4.6. The package leaflet is to be updated accordingly
[14] Messenger ribonucleic acid
[15] Held 25-28 October 2021
[16] Karlstad, Øystein, et al . SARS-CoV-2 vaccination and myocarditis in a Nordic cohort study of 23 million residents
[17] Le Vu et al. Association between COVID-19 messenger RNA vaccines and the occurrence of myocarditis and pericarditis in people aged 12 to 50 in France - Study based on data from the National Health Data System (SNDS)

Discussion

Having considered the available evidence from large observational studies in and outside the EU, the data provided by the MAH together with the Rapporteur's assessment, PRAC agreed that there is sufficient evidence to further strengthened the wording of the product information for Comirnaty (tozinameran) with regard to myocarditis and pericarditis.

Summary of recommendation(s)

- The MAH for Comirnaty (tozinameran) should submit to EMA, within 5 days, a variation to amend[18] the product information to refine the existing warning on myocarditis and pericarditis and amend the frequency of these undesirable effects from 'not known' to 'very rare' with a description of myocarditis.

For the full PRAC recommendation, see EMA/PRAC/683817/2021 published on 06 January 2022 on the EMA website.

4.4. Variation procedure(s) resulting from signal evaluation

4.4.1. Coronavirus (COVID-19) mRNA[19] vaccine (nucleoside-modified) - SPIKEVAX (CAP) - EMEA/H/C/005791/II/0028

Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Hans Christian Siersted

Scope: Submission of an updated RMP (version 2.1) to include myocarditis and pericarditis in the list of safety concerns as an important identified risk, as requested in the outcome of the signal procedure on myocarditis and pericarditis (EPITT 19713) adopted in July 2021 (SDA 033)

Background

COVID-19 nucleoside-modified messenger ribonucleic acid (mRNA) vaccine is indicated, as Spikevax, for active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 12 years of age and older.

Following the evaluation of a signal procedure concluded in July 2021 on myocarditis and pericarditis (EPITT 19713), the MAH for Spikevax (COVID-19 mRNA vaccine (nucleoside-modified)) submitted to EMA a variation to update the RMP to include myocarditis and pericarditis in the list of safety concerns. In addition, the MAH proposed the inclusion of an observational cohort study in the pharmacovigilance plan to further characterise long-term consequences of myocarditis and pericarditis following vaccination with Spikevax (COVID-19 mRNA vaccine (nucleoside-modified)). For background information, see PRAC minutes July 2021, PRAC minutes September 2021[20] and PRAC minutes November 2021[21]. PRAC is responsible for adopting an outcome based on the assessment report from the PRAC Rapporteur, to be further considered at the level of CHMP, responsible for adopting an opinion on this variation.

Summary of outcome(s)

[18] Update of sections 4.4 and 4.8 of the SmPC. The package leaflet is to be updated accordingly
[19] Messenger ribonucleic acid
[20] Held 30 August-02 September 2021
[21] Held 25-28 October 2021

- Based on the available data and the Rapporteur's assessment, PRAC considered that the MAH should provide further clarifications and responses before the procedure can be concluded.
- The MAH should further clarify in the study protocol whether both myocarditis and pericarditis will be evaluated in the study. In addition, the MAH should clarify details relating to long-term clinical outcomes including long-term sequelae, and whether all age group-populations are covered by the study. Finally, the MAH should clarify the study length in view of the need to further characterise myocarditis and pericarditis following vaccination with the vaccine.

4.4.2. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/II/0044

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Update of sections 4.4, 4.8 and 5.1 to add warnings and safety data on serious infections, viral reactivation, non-melanoma skin cancer and fractures. This is based on the final results from study A3921133 (listed as a category 3 study in the RMP): a PASS conducted to evaluate the safety of tofacitinib 5 mg and 10 mg compared to tumour necrosis factor inhibitor (TNFi) in adult subjects aged ≥50 years with moderately or severely active rheumatoid arthritis (RA) and with at least 1 additional cardiovascular (CV) risk factor, as requested in the outcome of the signal procedure (EPITT 19382) adopted in June 2021 (SDA 016). The package leaflet is updated accordingly. The RMP (version 21.1) is also updated in accordance. In addition, the MAH took the opportunity to update the outer carton (section 4 for oral solution) to include a total volume of 240 mL as requested in the conclusions of procedure X/0024/G adopted in June 2021.

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 a signal procedure concluded in June 2021 on major adverse cardiovascular events (MACE) and malignancies excluding non-melanoma skin cancer (NMSC) based on data from study A3921133[22] (EPITT 19382), the MAH for Xeljanz (tofacitinib) submitted to EMA a variation including updated study analyses to further amend the product information. For background information, see PRAC minutes June 2021. PRAC is responsible for adopting an outcome based on the assessment report from the PRAC Rapporteur, to be further considered at the level of CHMP, responsible for adopting an opinion on this variation.

Summary of outcome(s)

- Based on the available data and the Rapporteur's assessment, PRAC considered that the MAH should provide further clarifications and responses before the procedure can be concluded.
- The MAH should provide an update to the product information to refine the rheumatoid arthritis therapeutic indication based on the study results, and propose a similar wording

[22] A phase 3b/4 randomised safety endpoint study of 2 doses of tofacitinib in comparison to a tumour necrosis fibrosis (TNF) inhibitor in subjects with rheumatoid arthritis (ORAL surveillance study)

in the other authorised indications, namely psoriatic arthritis (PsA), ulcerative colitis (UC), juvenile idiopathic arthritis (JIA) and juvenile PsA and ankylosing spondylitis (AS). The MAH should include an in-depth discussion on the possible extrapolation of safety data from study A3921133 to the other target populations, data on relative efficacy of tofacitinib versus tumour necrosis factor inhibitor (TNFi), relative benefits and risks of tofacitinib versus TNFi, the place in therapy of tofacitinib in the treatment armamentarium for each indication. The MAH should also discuss whether there is/are specific population(s) for each indication for whom it would not be appropriate to initiate TNFi therapy but who would still benefit to receive tofacitinib. In addition, the MAH should further amend the proposed warning on fractures and update the existing warnings on malignancies and NMSC. Moreover, the RMP should be updated accordingly. Finally, the MAH should submit a proposal for a direct healthcare professional communication (DHPC) to inform healthcare professional (HCP) on the overall safety profile of tofacitinib compared to TNFi and the updated indications.

5. Risk management plans (RMPs)

5.1. Medicines in the pre-authorisation phase

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

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

See also Annex I 15.1.

5.1.1. Coronavirus (COVID-19) vaccine (recombinant, adjuvanted) (NVX-CoV2373) - EMEA/H/C/005808

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

5.1.2. Daridorexant - EMEA/H/C/005634

Scope: Treatment of insomnia

5.1.3. Difelikefalin - EMEA/H/C/005612

Scope: Treatment of pruritus

5.1.4. Gefapixant - EMEA/H/C/005476

Scope: Treatment of refractory or unexplained chronic cough

5.1.5. Gefapixant - EMEA/H/C/005884

Scope: Treatment of refractory or unexplained chronic cough

5.1.6. Molnupiravir – EMEA/H/C/005789

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

5.1.7. Relugolix - EMEA/H/C/005353

Scope: Treatment of adult patients with advanced prostate cancer

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

5.2.1. Coronavirus (COVID-19) vaccine (Ad26.COV2-S, recombinant) - COVID-19 VACCINE JANSSEN (CAP)- EMEA/H/C/005737/II/0018

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of an updated RMP (version 2.2) in order to include thrombocytopenia as an important potential risk as per the outcome of the signal procedure on embolic and thrombotic events (SDA/018.1 - EPITT 19689) in May 2021 and the outcome of variation II/0006/G dated July 2021, to propose studies aimed at further characterisation of thrombosis with thrombocytopenia syndrome (TTS) and thrombocytopenia, following the outcome of the signal procedure on embolic and thrombotic events (SDA/018.1 - EPITT 19689) in May 2021, to include Guillain-Barré syndrome as an important identified risk as per the outcome of variation II/0012 dated July 2021. In addition, the MAH took the opportunity to update the RMP to include the submission milestone dates for study VAC31518COV4001: a post-authorisation, observational study to assess the safety of Ad26.COV2.S (COVID-19 Vaccine Janssen) using health insurance claims and/or electronic health record (EHR) database(s) in the United States of America, and study VAC31518COV4002: a post-authorisation, observational study to assess the effectiveness of Ad26.COV2.S (COVID-19 Vaccine Janssen) using health insurance claims and/or electronic health record (EHR) database(s) in the United States of America.

Background

COVID-19 vaccine (Ad26.COV2-S [recombinant]) is a monovalent vaccine composed of a recombinant, replication-incompetent human adenovirus type 26 vector that encodes a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) full-length spike (S) glycoprotein indicated as COVID-19 vaccine Janssen, a centrally authorised vaccine, for active immunisation and prevention of COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older.

PRAC is evaluating a type II variation procedure for COVID-19 vaccine Janssen, a centrally authorised vaccine containing COVID-19 vaccine (Ad26.COV2-S [recombinant]), to update the RMP to reflect thrombocytopenia and Guillain-Barré syndrome as well as to update some study milestones. For further background, see PRAC minutes May 2021, PRAC minutes July 2021 and PRAC minutes October 2021[23]. PRAC is responsible for adopting an outcome based on the assessment report from the PRAC Rapporteur, to be further considered at the level of CHMP, responsible for adopting an opinion on this variation.

Summary of advice

[23] Held 27-30 September 2021

- The RMP version 2.5 for COVID-19 vaccine Janssen (COVID-19 vaccine (Ad26.COV2-S [recombinant])) in the context of the variation procedure under evaluation by PRAC is acceptable.
- PRAC agreed with the inclusion of 'thrombocytopenia (including immune thrombocytopenia)' and 'Guillain-Barré syndrome (GBS)' as important identified risks. PRAC also agreed with the proposed studies to further characterise the safety concerns of 'thrombosis with thrombocytopenia syndrome (TTS)' and 'thrombocytopenia (including immune thrombocytopenia)'.

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

See also Annex 15.3.

5.3.1. Autologous peripheral blood T cells CD[24]4 and CD8 selected and CD3 and CD28 activated transduced with retroviral vector expressing anti-CD19 CD28/CD3-zeta chimeric antigen receptor and cultured - TECARTUS (CAP) - EMEA/H/C/005102/WS2206/0015; axicabtagene ciloleucel - YESCARTA (CAP) - EMEA/H/C/004480/WS2206/0045

Applicant: Kite Pharma EU B.V., ATMP[25]

PRAC Rapporteur: Menno van der Elst

Scope: Update of sections 4.2 and 4.4 of the SmPC and Annex II-D on 'Conditions or restrictions with regard to the safe and effective use of the medicinal product' in order to add statements for the use of Tecartus (autologous peripheral blood T cells CD4 and CD8 selected and CD3 and CD28 activated transduced with retroviral vector expressing anti-CD19 CD28/CD3-zeta chimeric antigen receptor and cultured) and Yescarta (axicabtagene ciloleucel) exceptionally during shortage of tocilizumab following the 'CAT recommendation for the use of chimeric antigen receptor (CAR)-T cell-based therapies in EU during shortages of tocilizumab'. The RMPs for both products are updated accordingly (version 1.2 for Tecartus and version 5.2 for Yescarta).

Background

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

CHMP is evaluating a work-sharing variation for Tecartus and Yescarta, centrally authorised products containing 'autologous peripheral blood T cells CD4 and CD8 selected and CD3 and CD28 activated transduced with retroviral vector expressing anti-CD19 CD28/CD3-zeta chimeric antigen receptor and cultured' and 'axicabtagene ciloleucel' respectively, to update the product information of the medicinal products with statements for their exceptional use during shortage of tocilizumab following the 'CAT recommendation for the use of chimeric antigen receptor (CAR)-T cell-based therapies in EU during shortages of tocilizumab'. For further background, see PRAC minutes November 2021[26]. PRAC is responsible for providing advice to CHMP on the necessary updates to the RMP to support this procedure.

[24] Cluster of differentiation
[25] Advanced therapy medicinal product
[26] Held 25-28 October 2021

Summary of advice

- The RMPs for Tecartus (autologous peripheral blood T cells CD4 and CD8 selected and CD3 and CD28 activated transduced with retroviral vector expressing anti-CD19 CD28/CD3-zeta chimeric antigen receptor and cultured) and Yescarta (axicabtagene ciloleucel) in the context of the variation procedure under evaluation by CHMP could be considered acceptable provided that an update to RMPs version 1.2 and version 5.2 respectively are submitted.
- The MAH should further update the educational materials with regard to the use of tocilizumab and the access to suitable alternative measures in case of a tocilizumab shortage.

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. Apixaban - ELIQUIS (CAP) - PSUSA/00000226/202105

Applicants: Bristol-Myers Squibb / Pfizer EEIG

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 Eliquis, a centrally authorised medicine containing apixaban 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 Eliquis (apixaban) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include cutaneous vasculitis as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[27].
- In the next PSUR, the MAH should provide detailed reviews of cases of headache/(aggravated) migraine and of cases of severe uterine bleeding requiring intervention. The MAH should include a proposal to update the product information as warranted. The MAH should also provide an update of the implementation of websites

[27] 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.

providing a digital platform in addition to the paper based additional risk minimisation material.

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. Atezolizumab - TECENTRIQ (CAP) - PSUSA/00010644/202105

Applicant: Roche Registration GmbH

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

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, the 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 include a recommendation to permanently discontinue atezolizumab for ≥ grade 2 myocarditis and, given the potential for life-threatening or fatal evolution of myocarditis, to reinforce the need to suspend treatment with atezolizumab and initiate treatment with systemic corticosteroids as soon as myocarditis is suspected. In addition, the product information should be updated to include a recommendation that patients with possible myositis should be monitored for signs of myocarditis. Finally, the package leaflet should be updated to include specific signs of diabetic ketoacidosis. Therefore, the current terms of the marketing authorisation(s) should be varied[28].
- In the next PSUR, the MAH should include detailed reviews of cases of sclerosing cholangitis and of cases of gastrointestinal perforation. In addition, the MAH should include a literature review on immune checkpoint inhibitor (ICI)-associated tumour lysis syndrome (TLS) together with a discussion on the possible relationship between atezolizumab and TLS. The MAH 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.

[28] Update of SmPC sections 4.2 and 4.4. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion.

6.1.3. Cefiderocol - FETCROJA (CAP) - PSUSA/00010849/202105

Applicant: Shionogi B.V.

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

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

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Fetcroja, a centrally authorised medicine containing cefiderocol 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 Fetcroja (cefiderocol) 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, a detailed review of heteroresistance against cefiderocol based on the publications by *Choby et al*[29,30]. The MAH should discuss risk minimisation measures against treatment failure as well as ways to ensure that cefiderocol is only used in patients with severe infections caused by appropriate susceptible bacteria. The MAH should also 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.

6.1.4. Delamanid - DELTYBA (CAP) - PSUSA/00010213/202104

Applicant: Otsuka Novel Products GmbH

PRAC Rapporteur: Laurence de Fays

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

[29] Choby JE, et al. Widespread cefiderocol heteroresistance in carbapenem-resistant gram-negative pathogens. Lancet Infect Dis. 2021 May; 21(5): 597–598. doi:10.1016/S1473-3099(21)00194-8
[30] Choby JE, et al. Does cefiderocol heteroresistance explain the discrepancy between the APEKS-NP and CREDIBLE-CR clinical trial results? https://doi.org/10.1016/S2666-5247(21)00271-8

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Deltyba (delamanid) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include hallucination as an undesirable effect with a frequency 'common' and to specify that cases of hallucination have been reported predominantly in the paediatric population in post-marketing settings. In addition, information on in-vitro studies and cross-resistance with pretomanid should be added in the pharmacodynamic property section in light of the shared activation pathway for pretomanid and delamanid. Therefore, the current terms of the marketing authorisation(s) should be varied[31].

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. Dolutegravir, rilpivirine - JULUCA (CAP) - PSUSA/00010689/202105

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Nathalie Gault

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 Juluca, a centrally authorised medicine containing dolutegravir/rilpivirine 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 Juluca (dolutegravir/rilpivirine) 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, a variation to add panic attack to the product information as an undesirable effect with a frequency 'uncommon'.
- In the next PSUR, the MAH should provide a review of cased with a fatal outcome. In addition, the MAH should further review any case reporting drug reaction with eosinophilia and systemic symptoms (DRESS).

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

[31] Update of SmPC sections 4.8 and 5.1. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion.

6.1.6. Durvalumab - IMFINZI (CAP) - PSUSA/00010723/202104

Applicant: AstraZeneca AB

PRAC Rapporteur: David Olsen

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 Imfinzi, a centrally authorised medicine containing durvalumab 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 Imfinzi (durvalumab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add pancreatitis as a warning and as an undesirable effect with a frequency 'uncommon'. Therefore, the current terms of the marketing authorisation(s) should be varied[32].
- In the next PSUR, the MAH should include a detailed review of cases of psoriasis 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. Empagliflozin - JARDIANCE (CAP); empagliflozin, metformin - SYNJARDY (CAP) – PSUSA/00010388/202104

Applicant(s): Boehringer Ingelheim International GmbH

PRAC Rapporteur: Eva Segovia

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(s), PRAC reviewed the benefit-risk balance of Jardiance and Synjardy, centrally authorised medicines containing empagliflozin and empagliflozin/metformin respectively and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

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

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Jardiance (empagliflozin) and Synjardy (empagliflozin/metformin) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add tubulointerstitial nephritis as an undesirable effect with a frequency 'very rare' and to reflect the drug-drug interaction between empagliflozin and lithium in order to ensure that serum concentration of lithium is monitored more frequently after empagliflozin initiation and dose changes. Therefore, the current terms of the marketing authorisation(s) should be varied[33].

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

PRAC considered that the risk of tubulointerstitial nephritis and the drug-drug interaction between empagliflozin and lithium are also relevant to empagliflozin/linagliptin fixed dose combination, and relevant variation(s) should be submitted to EMA accordingly.

In addition, cases of tubulointerstitial nephritis have been also reported with other sodium-glucose co-transporter 2 (SGLT2) inhibitors and the drug-drug interaction with lithium and empagliflozin cannot be excluded for other SGLT2 inhibitors in light of the plausible mechanism. Therefore, PRAC considered that a class effect cannot not be excluded and both risks should be evaluated for all other authorised SGLT2 inhibitors as part of their respective upcoming PSUR and PSUR single assessment (PSUSA).

Finally, PRAC considered that the drug-drug interaction with lithium is also relevant for lithium-containing product(s) (excluding diagnostic indication(s)) in order to inform that co-administration of empagliflozin with lithium may lead to decreased lithium concentrations which may lead to a reduction in effectiveness of lithium. Further consideration is to be given at CMDh.

6.1.8. Eslicarbazepine acetate - ZEBINIX (CAP) - PSUSA/00001267/202104

Applicant: Bial - Portela & Cª, S.A.

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

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

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

Summary of recommendation(s) and conclusions

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

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Zebinix (eslicarbazepine acetate) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add syndrome of inappropriate antidiuretic hormone secretion (SIADH)-like syndrome as an undesirable effect with a frequency 'not known' and to replace 'transaminases increased' by the broader term 'hepatic enzymes increased' as an undesirable effect with an unchanged frequency. In addition, warnings and recommendations on use during pregnancy and in women of childbearing potential should be added to the product information. Therefore, the current terms of the marketing authorisation(s) should be varied[34].
- In the next PSUR, the MAH should include in the PSUR summary of safety concerns 'suicidal ideation and behaviour' as an important risk and 'use during pregnancy' 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.

6.1.9. Fexinidazole - FEXINIDAZOLE WINTHROP (Art 58[35]) - EMEA/H/W/002320/PSUV/0008

Applicant: sanofi-aventis groupe

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUR procedure

Background

For background information on substance(s) and indication(s) of centrally authorised product(s) identified as 'Art 58', 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 Fexinidazole Winthrop, a medicine for use outside the European Union containing fexinidazole acetate and issued a recommendation on its scientific opinion.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Fexinidazole Winthrop (fexinidazole) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include information on suicidal ideation in the existing warning on neuropsychiatric adverse reactions and as an undesirable effect with a frequency 'uncommon'. Therefore, the current terms of the marketing authorisation(s) should be varied[36].

The frequency of submission of the subsequent PSURs should be changed from 6-monthly to three-yearly. Annex II should be updated accordingly.

[34] Update of SmPC sections 4.6 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion.
[35] 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).
[36] Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion.

6.1.10. Laronidase - ALDURAZYME (CAP) - PSUSA/00001830/202104

Applicant: Genzyme Europe BV

PRAC Rapporteur: Nathalie Gault

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 Aldurazyme, a centrally authorised medicine containing laronidase 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 Aldurazyme (laronidase) 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 120 days, a cumulative review of hypersensitivity reactions including anaphylaxis to laronidase together with time-to-event data, a safety review on immunogenicity and a cumulative review of infusion-site reactions. In addition, the MAH should submit a cumulative review of cases of overdose and cases suggestive of overdose, associated risks and their management as well as a cumulative review of cases reporting laronidase use by intrathecal route and associated risks. For each review, the MAH 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.

6.1.11. Meningococcal group a, c, w135, y conjugate vaccine[37] - MENQUADFI (CAP); NIMENRIX (CAP) - PSUSA/00010044/202104

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

PRAC Rapporteur: David Olsen

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(s), PRAC reviewed the benefit-risk balance of MenQuadfi and Nimenrix, centrally authorised meningococcal group a, c, w135, y conjugate vaccines and issued a recommendation on their marketing authorisations.

[37] Conjugated to tetanus toxoid carrier protein

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of MenQuadfi and Nimenrix (meningococcal group a, c, w135, y conjugate vaccines) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) for MenQuadfi (meningococcal group a, c, w135, y conjugate vaccine) should be maintained.
- The product information for Nimenrix (meningococcal group a, c, w135, y conjugate vaccine) should be updated to add urticaria and febrile convulsions as undesirable effects with a frequency 'uncommon' and 'rare' respectively. Therefore, the current terms of the marketing authorisation(s) should be varied[38].
- In the next PSUR, the MAH of Nimenrix (meningococcal group a, c, w135, y conjugate vaccine) should provide a detailed review of cases of haemolytic anaemia 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.

6.1.12. Selpercatinib - RETSEVMO (CAP) - PSUSA/00010917/202105

Applicant: Eli Lilly Nederland 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 Retsevmo, a centrally authorised medicine containing selpercatinib 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 Retsevmo (selpercatinib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add a warning in relation to the risk factors for tumour lysis syndrome (TLS) and how to deal with TLS. Therefore, the current terms of the marketing authorisation(s) should be varied[39].
- In the next PSUR, the MAH should include growth plate abnormalities in paediatrics and TLS as important potential risks in the PSUR summary of safety concerns.

[38] 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.
[39] 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.

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.

6.2.1. Mycophenolate mofetil - CELLCEPT (CAP); MYCLAUSEN (CAP); MYCOPHENOLATE MOFETIL TEVA (CAP); MYFENAX (CAP); NAP - mycophenolic acid (NAP) - PSUSA/00010550/202105

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

PRAC Rapporteur: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

Background

Mycophenolate mofetil is a prodrug of mycophenolic acid, a cytostatic and immunosuppressive agent acting as a potent inhibitor of *de novo* synthesis of purines essential for T- and B-cell proliferation. Mycophenolate mofetil or mycophenolic acid in combination with corticosteroids and either ciclosporin A or tacrolimus is indicated for the prophylaxis of acute organ rejection and for the treatment of first or refractory organ rejection in patients receiving allogeneic renal transplant, for the prophylaxis of acute organ rejection in patients receiving allogeneic cardiac transplants as well as for the prophylaxis of acute organ rejection in patients receiving allogeneic hepatic transplants.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of mycophenolate mofetil- and mycophenolic acid-containing products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the existing warning on infections regarding the need to consider appropriate clinical action in case of increased severity of COVID-19. Therefore, the current terms of the marketing authorisations should be varied[40].
- In the next PSUR, MAH(s) should ensure that their PSUR summary of safety concerns includes 'adverse pregnancy outcome' as an important identified risk. In addition, any new information concerning COVID-19 infections should be evaluated as part of the

[40] Update of SmPC section 4.4. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion.

important identified risk of 'bone marrow depression resulting in cytopenia and associated infections or haemorrhages'.

The frequency of PSUR submission should be revised from yearly to two-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. Tacrolimus[41] - ADVAGRAF (CAP); ENVARSUS (CAP); MODIGRAF (CAP); NAP - PSUSA/00002839/202103

Applicants: Astellas Pharma Europe B.V. (Advagraf, Modigraf), Chiesi Farmaceutici S.p.A. (Envarsus), various

PRAC Rapporteur: Ronan Grimes

Scope: Evaluation of a PSUSA procedure

Background

Tacrolimus is a calcineurin inhibitor indicated for the prophylaxis and for the treatment of allograft rejection in solid organ transplant as well as for the prophylaxis and for the treatment of graft rejection and graft-versus-host disease (GVHD) in bone marrow allograft recipients. It is also indicated for the treatment of myasthenia gravis, rheumatoid arthritis which is not adequately responsive to conventional therapies, lupus nephritis, refractory (corticosteroid-resistant or -dependent) active ulcerative colitis (limited to moderate to severe cases) and for the treatment of interstitial pneumonia associated with polymyositis/dermatomyositis.

Based on the assessment of the PSURs, PRAC reviewed the benefit-risk balance of Advagraf, Envarsus and Modigraf, centrally authorised medicines containing tacrolimus, and nationally authorised medicines containing tacrolimus for systemic use 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 tacrolimus-containing product(s) for systemic use in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add cytomegalovirus infection (CMV) to the existing warning and undesirable effect on infections including opportunistic infections. Progressive multifocal leukoencephalopathy (PML) is also added to the package leaflet to inform patients on signs and symptoms of PML. In addition, flucloxacillin should be added to the existing warning on metabolic interactions as a weak CYP3A4[42] inducer. Trimethoprim and sulfamethoxazole/trimethoprim should be also added to the existing warning on metabolic interactions as trimethoprim is known to act as a potassium-sparing diuretic like amiloride. Moreover, the product information should be amended to add a new warning on nephrotoxicity for Envarsus and nationally approved products containing tacrolimus, and to update the existing warning of Advagraf/Modigraf on nephrotoxicity to add the risk progression to chronic renal

[41] Systemic formulation(s) only
[42] Cytochrome P450 3A4

impairment. Therefore, the current terms of the marketing authorisations should be varied[43].

- In the next PSUR, the MAHs should provide a discussion on antimicrobial prophylaxis for CMV and propose to update the product information as warranted. The MAHs should also provide cumulative reviews of cases of pneumocystic jirovecci pneumonia, focal segmental glomerulosclerosis and of Kaposi's sarcoma and propose to update the product information as warranted. In addition, the MAHs should provide a detailed review on the impact of P-glycoprotein (P-gp) inhibition on tacrolimus blood levels and propose to update the product information as warranted. Finally, the MAHs should discuss the need to update the product information to add hepatic cirrhosis and/or fibrosis, as well as diabetic ketoacidosis.

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.

6.2.3. Ulipristal acetate[44] - ELLAONE (CAP); NAP - PSUSA/00003074/202105

Applicants: Laboratoire HRA Pharma (ellaOne), various

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

Background

Ulipristal acetate is a selective progesterone receptor modulator indicated for emergency contraception within 120 hours (five days) of unprotected sexual intercourse or contraceptive failure.

Based on the assessment of the PSURs, PRAC reviewed the benefit-risk balance of EllaOne, a centrally authorised medicine containing ulipristal acetate, and nationally authorised medicine(s) containing ulipristal acetate[45] 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 ulipristal acetate[46]-containing products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to extend the existing undesirable effect on urticaria with a frequency 'rare' to hypersensitivity reactions including also rash and angioedema. Therefore, the current terms of the marketing authorisations should be varied[47].

[43] Update of SmPC sections 4.4, 4.5 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion.
[44] Indicated for female emergency contraception only
[45] Indicated for female emergency contraception only
[46] Indicated for female emergency contraception only
[47] 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.

- In the next PSUR, the MAHs should present a detailed review of ectopic pregnancy, including a discussion on possible other causes 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.

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

See also Annex 16.3.

6.3.1. Chloroquine (NAP) - PSUSA/00000685/202104

Applicant(s): various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

Background

Chloroquine is a 4-aminoquinoline derivative indicated for the prophylaxis and treatment of malaria. It is also indicated for the treatment of rheumatoid arthritis, lupus erythematosus, light sensitive eruptions and extra intestinal amoebiasis.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing chloroquine 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 chloroquine-containing product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add the interaction with macrolides including azithromycin due to the increased risk of ventricular arrhythmia. Therefore, the current terms of the marketing authorisation(s) should be varied[48].

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.

PRAC considered that the increased risk for ventricular arrythmia following an interaction with macrolides including azithromycin is also relevant for medicinal product(s) containing chloroquine-fixed dose combination(s). Further consideration is to be given at CMDh.

6.3.2. Chlorprothixene (NAP) - PSUSA/00000717/202103

Applicant(s): various

PRAC Lead: Zane Neikena

[48] Update of SmPC section 4.5. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position.

Scope: Evaluation of a PSUSA procedure

Background

Chlorprothixene is a sedative neuroleptic indicated for the treatment of schizophrenia and other psychoses with psychomotor unrest, agitation and anxiety, for the treatment of withdrawal treatment of alcoholics and drug addicts, for the treatment of depressive syndromes, neuroses, psychosomatic disorders associated with anxiety, tension, restlessness, insomnia and sleep disturbances. It is also indicated for the treatment of epilepsy and oligophrenia associated with mental disorders such as erethism, agitation, lability of mood and behaviour disturbances, for the treatment of chronic pain as well as for the geriatric treatment of hyperactivity, excitement, irritability, confusion, anxiety, behaviour and sleep disturbances. Finally, it is indicated to modulate psychomotor restlessness and states of agitation in the context of acute psychotic syndromes, and for the treatment of maniform syndromes.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing chlorprothixene 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 chlorprothixene-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, MAH Neuraxpharm should include in the PSUR list of safety concerns, the risks with potential life-threatening outcome as QTc prolongation, Torsade de Pointes and neuroleptic malignant syndrome as important risks. Increased mortality in elderly people with dementia, priapism as a class effect of antipsychotic drugs as important risks and use in pregnant women as missing information should be removed. In addition, off label use in paediatric population should be removed as an important identified risk. MAH Lundbeck should remove from the PSUR list of safety concerns suicide and self-injury as an important potential risk and off label use in paediatric population 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.

6.3.3. Fentanyl[49] [50] (NAP) - PSUSA/00001370/202104

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

[49] Transdermal patches and solution for injection only
[50] Nationally authorised product(s) only

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) containing fentanyl[51] [52] and issued a recommendation on their marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of fentanyl[53] [54]-containing product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information of fentanyl solution for injection should be updated to strengthen the existing warning on opioid use disorder (OUD) (abuse and dependence). In addition, fentanyl solution for injection and transdermal patch-product information should be updated to add the additive effects of gabapentinoids (gabapentin and pregabalin) to fentanyl on central nervous system (CNS) depression. Finally, the package leaflet of fentanyl transdermal patches should be updated to reflect additional information on the lack of efficacy if the patch falls off. Therefore, the current terms of the marketing authorisation(s) should be varied[55].
- In the next PSUR, the MAH(s) for transdermal patches should provide detailed follow-up reviews of cases of 'drug abuse, dependence and withdrawal' and of cases of (accidental) overdose in the EU. This should include (shifts in) trends and their significance on the safety profile of fentanyl transdermal patches together with the need for further action as warranted. The MAH(s) should also propose routine risk minimisation measures (RMM) to prevent dependence/addiction, including a proposal for an outer packaging warning. The MAH(s) should propose to update the package leaflet as warranted to improve patient understanding and identification of symptoms of dependence/opioid use disorder based on user testing studies and/or consultation of patient representatives to generate data and findings. In addition, the MAH(s) should discuss the need for a warning on the outer packaging relating to accidental exposure that may cause harm and be fatal and propose to update the outer and immediate packaging accordingly. In addition, the MAH(s) should include a detailed review on any new relevant cases regarding patch adhesion-related issues with a discussion on ways to improve patches adhesion and a proposal to update the product information as warranted. Moreover, the MAH(s) should closely monitor the risks of hypoglycaemia and hypoadrenalism. Finally, the MAH(s) should remove the important identified risk of serotonin syndrome from the list of PSUR safety concerns.
- In the next PSUR, the MAH Janssen should include a proposal to update the product information to improve patient understanding and identification of symptoms of dependence/OUD, as well as to instruct patients what to do when experiencing such

[51] Transdermal patches and solution for injection only
[52] Nationally authorised product(s) only
[53] Transdermal patches and solution for injection only
[54] Nationally authorised product(s) only
[55] Update of SmPC sections 4.4 and 4.5. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position.

symptoms. The MAH Janssen should also discuss recommendations for frequent contact between physician and patient, establishment of a treatment plan, reference to pain management guideline(s), and stopping agreements between physician and patient. A proposal to update the product information should be made accordingly. The MAH Janssen should remove the important potential risk of potential product quality issues from the list of PSUR safety concerns. The MAHs Sandoz, Hexal, Lek Pharmaceuticals and 1a Pharma should provide a review focussing on whether there is a higher reporting rate of EU cases of abuse, misuse, dependence and overdose with transdermal patches containing a higher amount of fentanyl than the originator-medicinal product with transdermal patches containing the same amount of fentanyl as the originator-medicinal product. Finally, the MAH Piramal should remove cardiovascular depression, muscle rigidity, and use in patient with renal impairment from the list of PSUR safety concerns.

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.

PRAC considered that the increased risk of respiratory depression due to concomitant use of gabapentinoids with fentanyl (transdermal patches and fentanyl solution) for injection is also relevant for medicinal product(s) containing fentanyl for transmucosal route of administration. Further consideration is to be given at CHMP/CMDh.

6.3.4. Hydroxychloroquine (NAP) - PSUSA/00001693/202104

Applicant(s): various

PRAC Lead: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

Background

Hydroxychloroquine is an aminoquinoline indicated for the treatment of lupus erythematosus, systemic lupus erythematosus (SLE), cutaneous lupus erythematosus (CLE), discoid lupus erythematosus (DLE) and lupus erythematosus disseminated. It is also indicated for the treatment of rheumatoid arthritis (RA), juvenile chronic polyarthritis, systemic juvenile chronic arthritis and juvenile arthritis. In addition, it is indicated for the suppressive treatment and treatment of acute attacks of malaria due to *Plasmodium vivax, Plasmodium malariae, Plasmodium ovale* and susceptible strains of *Plasmodium falciparum.* Finally, it is indicated for the treatment of polymorphic light eruption (PLE), scleroderma and photosensitive dermatitis.

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

- Nevertheless, the product information should be updated to add Sweet's syndrome as an undesirable effect with a frequency 'not known' and to add a warning on severe cutaneous adverse reactions (SCARs).

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

PRAC considered that the risk of hepatotoxicity and congenital malformations needs to be further assessed. Further consideration is to be given at CMDh.

PRAC also considered that the risk for QT-prolongation and subsequent risk of ventricular arrhythmia related to concomitant use of hydroxychloroquine and azithromycin is also relevant for medicinal product(s) containing azithromycin. Further consideration is to be given at CMDh.

6.3.5. Hydrochlorothiazide, quinapril (NAP) - PSUSA/00002592/202104

Applicant(s): various

PRAC Lead: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

Background

Quinapril is an angiotensin-converting enzyme (ACE) inhibitor and hydrochlorothiazide a diuretic. In combination, hydrochlorothiazide/quinapril is indicated for the treatment of hypertension in patients for whom combination therapy with quinapril and a diuretic is appropriate.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing hydrochlorothiazide/quinapril 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 hydrochlorothiazide/quinapril-containing product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include hyponatremia and syndrome of inappropriate antidiuretic hormone secretion (SIADH) as a warning. Hyponatremia and SIADH should be also added as undesirable effects with a frequency 'common' and 'not known' respectively. Therefore, the current terms of the marketing authorisation(s) should be varied[56].
- In the next PSUR, the MAH should closely monitor the increased risk of acute kidney injury in combination with ciprofloxacin and the risk of lung cancer.

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

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. Isotretinoin[57] (NAP) - PSUSA/00010488/202105

Applicant(s): various

PRAC Lead: Krõõt Aab

Scope: Evaluation of a PSUSA procedure

Background

Isotretinoin is a stereoisomer of all-trans retinoic acid (tretinoin) indicated as oral formulation(s) for the treatment of severe forms of acne, i.e. nodular or conglobate acne, or acne at risk of permanent scarring. It is also indicated for the treatment of acne which has failed to respond to standard therapies with systemic antibiotics and topical therapy.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing isotretinoin oral formulation(s) 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 isotretinoin-containing product(s) as oral formulation(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include sacroiliitis as a warning and as an undesirable effect with a frequency 'not known'. In addition, the existing warning on dry eyes should be refined to reflect that cases of dry eyes not resolving after discontinuation of therapy with isotretinoin, have been reported. Moreover, urethritis should be added to the product information as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[58].
- In the next PSUR, the MAH(s) should provide cumulative reviews of cases of insomnia/sleep disorders, oligomenorrhoea/amenorrhoea/polycystic ovarian syndrome/menstruation irregular, blepharospasm, low density lipoprotein increase, uveal melanoma, homocysteine increase and folic acid decrease. In addition, the MAH(s) should provide a detailed analysis of cases of hepatic fibrosis with a proposal to update the product information as warranted. Moreover, the MAH(s) should add fulminant hepatitis as an adverse event of special interest with a proposal to update the product information as warranted. Finally, MAH Pierre Fabre should include a review of cases of neurodevelopmental disorders in absence of central nervous system (CNS) malformation.

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

[57] Oral formulation(s) only
[58] 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.

6.3.7. Latanoprost[59] (NAP) - PSUSA/00001832/202104

Applicant(s): various

PRAC Lead: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

Background

Latanoprost is a prostaglandin F2α analogue indicated for the reduction of elevated intraocular pressure (IOP) in patients with open angle glaucoma and ocular hypertension.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing latanoprost[60] 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 latanoprost[61]-containing product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include nausea and vomiting as undesirable effects with a frequency 'uncommon'. Therefore, the current terms of the marketing authorisation(s) should be varied[62].

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.

PRAC considered that nausea and vomiting added as undesirable effects is also relevant for medicinal product(s) containing latanoprost alone with (a) paediatric indication(s) and also in fixed-dose combination(s). Further consideration is to be given at CMDh.

6.3.8. N(2)-L-alanyl-L-glutamine (NAP) - PSUSA/00003158/202103

Applicant(s): various

PRAC Lead: Alexandra Maria Spurni

Scope: Evaluation of a PSUSA procedure

Background

N(2)-L-alanyl-L-glutamine contains amino acids and is indicated as part of a clinical nutrition regimen in patients in hypercatabolic and/or hypermetabolic states.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing N(2)-L-alanyl-L-glutamine and issued a recommendation on their marketing authorisation(s).

Summary of recommendation(s) and conclusions

[59] Except medicinal product(s) with paediatric indication(s)
[60] Except medicinal product(s) with paediatric indication(s)
[61] Except medicinal product(s) with paediatric indication(s)
[62] 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

- Based on the review of the data on safety and efficacy, the benefit-risk balance of N(2)-L-alanyl-L-glutamine-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 MAH should provide a cumulative review of cases of gastrointestinal disorders 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.

PRAC considered that the MAH(s) for N (2)-L-alanyl-L-glutamine-containing product(s) should further evaluate in depth any new evidence for N (2)-L-alanyl-L-glutamine that is available in published literature and updated guidelines together with an evaluation of all new available data for use of N (2)-L-alanyl-L-glutamine from case report and clinical studies. In addition, the MAH should include a proposal to update the product information and further other risk minimisation measure(s) as warranted. Further consideration is to be given at CMDh.

6.3.9. Nadroparin (NAP) - PSUSA/00002104/202103

Applicant(s): various

PRAC Lead: Eva Segovia

Scope: Evaluation of a PSUSA procedure

Background

Nadroparin is a low molecular weight heparin (LMWH) indicated for the prophylaxis and treatment of thromboembolic disorders, for the prevention of clotting during haemodialysis and for the treatment of unstable angina and non-Q-wave myocardial infarction.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing nadroparin 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 nadroparin-containing product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the existing contraindication on hypersensitivity to include heparin or its derivatives, including other low molecular weight heparins due to cross-reactivity reactions with nadroparin. Therefore, the current terms of the marketing authorisation(s) should be varied[63].
- In the next PSUR, the MAH should include in the PSUR list of safety concerns serious bullous conditions, osteoporosis and liver injury as important potential risks, as well as use in pregnancy and lactation as missing information.

[63] Update of SmPC section 4.3. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position.

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

6.3.10. Ofloxacin[64] (NAP) - PSUSA/00002203/202104

Applicant(s): various

PRAC Lead: Nikica Mirošević Skvrce

Scope: Evaluation of a PSUSA procedure

Background

Ofloxacin is a quinolone antibiotic of the family of fluoroquinolones indicated for systematic use for the treatment of various bacterial infections including infections of the urogenital tract, community acquired pneumonia, bone and joint infections, complicated skin and soft tissue infections, sinusitis and bronchitis. It is also indicated for the post-exposure prophylaxis and curative treatment of inhaled anthrax.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing ofloxacin for systematic 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 ofloxacin-containing product(s) for systematic use in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include delirium as an undesirable effect with a frequency 'rare'. Therefore, the current terms of the marketing authorisation(s) should be varied[65].
- In the next PSUR, the MAH(s) should include a cumulative review of cases of long-lasting, disabling and potentially irreversible adverse drug reactions (ADRs). The MAH(s) should also include a review of cases of blindness.

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

6.3.11. Oxycodone (NAP) - PSUSA/00002254/202104

Applicant(s): various

PRAC Lead: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

Background

Oxycodone is an opioid analgesic indicated for the management of pain.

[64] For systemic use only
[65] 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.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of oxycodone-containing product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to strengthen the existing warning on opioid use disorder (abuse and dependence). In addition, sleep-related disorders should be added as a warning and central sleep apnoea syndrome as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[66].
- In the next PSUR, the brand leader MAH Mundipharma should provide a detailed follow-up trend analysis of cases reported under 'drug abuse, dependence and withdrawal' and cases reported under 'drug dependence', 'withdrawal syndrome', 'drug withdrawal syndrome', 'drug abuse' and 'overdose' over the past 10 years in the EU. The observed (shifts in) trends and their significance on the safety profile of oxycodone should be discussed together with the need for further action as warranted. The brand leader MAH should also propose routine risk minimisation measures (RMM) to prevent dependence/addiction, including a proposal for an outer packaging warning and a warning including the need for a frequent contact between physicians/patients, a treatment plan for patients and stopping rules. In addition, the brand leader MAH should propose to update the package leaflet to improve patient understanding and identification of symptoms of dependence/opioid use disorder and to instruct patients what to do when experiencing such symptoms. Moreover, the brand leader MAH should include a cumulative review of cases of leukoencephalopathy, encephalopathy, drug-induced encephalopathy and other (leuko)encephalopathy together with a proposal to update the product information as warranted. Furthermore, the brand leader MAH should provide an update on QTc prolongation. Finally, the brand leader MAH, Teva and Novartis/Sandoz should provide a discussion on medication error reported in the EU together with a discussion on whether further risk minimisation measures are 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.

6.3.12. Pholcodine (NAP) - PSUSA/0002396/202105

Applicant(s): various

PRAC Lead: Nathalie Gault

Scope: Evaluation of a PSUSA procedure

Background

[66] 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.

Pholcodine is an opiate with central-acting cough suppressant indicated for the symptomatic treatment of non-productive (dry) cough. It is used alone and in combination with other active substances in preparations to treat the symptoms of common cold.

PRAC is currently reviewing the benefit-risk balance of nationally authorised medicines containing pholcodine, in the framework of the assessment of a PSUR single assessment (PSUSA) procedure due for PRAC recommendation at the January 2022 PRAC meeting.

Summary of conclusions

- The PRAC Rapporteur presented the preliminary assessment of the currently ongoing PSUSA procedure, which is due to complete at the following PRAC meeting.
- Further discussion and adoption of a recommendation is planned at the January 2022 PRAC meeting.

6.3.13. Praziquantel (NAP) - PSUSA/00002503/202104

Applicant(s): various

PRAC Lead: Nathalie Gault

Scope: Evaluation of a PSUSA procedure

Background

Praziquantel is an oral anthelmintic indicated for the treatment of schistosoma infections (e.g. due to *S. haematobium, S. mansoni, S. intercalatum, S. japonicum, S. mekongi*) and in the treatment of infections with liver flukes (e.g. *Clonorchis sinensis, Opisthorchis viverrini*) and lung flukes (e.g. *Paragonimus westermani* and other species).

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing praziquantel 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 praziquantel-containing product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add the drug-drug interaction between praziquantel and efavirenz due to significant decrease in plasma concentrations of praziquantel. Therefore, the current terms of the marketing authorisation(s) should be varied[67].
- In the next PSUR, the MAH(s) should provide a cumulative review of cases of pancytopenia together with a proposal to update the product information as warranted. In addition, the MAH(s) should provide a cumulative safety review on praziquantel toxicity due to the drug-drug interaction with protease inhibitors boosted by ritonavir together with a discussion on the clinical relevance of this effect considering the posology scheme of a single intake of praziquantel for the treatment against trematodes. MAH Bayer should also provide a detailed analysis of medication errors and propose risk minimisation measures as warranted.

[67] Update of SmPC section 4.5. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position.

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

PRAC considered that the interaction between praziquantel and efavirenz is also relevant for medicinal product(s) containing efavirenz alone or in fixed-dose combination(s). Further consideration is to be given at CMDh.

6.3.14. Promestriene[68] (NAP) - PSUSA/00009271/202103

Applicant(s): various

PRAC Lead: Alexandra Maria Spurni

Scope: Evaluation of a PSUSA procedure

Background

Promestriene is a synthetic oestrogen indicated as cream and vaginal capsule(s) for the treatment of vaginal atrophy by oestrogen deficiency and for the treatment of vulvar, vestibular and vaginal atrophy by oestrogen deficiency.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing promestriene[69] 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 promestriene[70]-containing product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to replace allergy by hypersensitivity as an undesirable effect with a frequency 'very rare', and application site pruritus by vulvovaginal pruritus with a frequency 'very rare'. In addition, the product information should be updated to add vulvovaginal burning sensation, vulvovaginal discomfort, vulvovaginal pain, vaginal discharge as undesirable effects with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[71].
- In the next PSUR, the MAH(s) should include a cumulative review of cases of nervous system disorders and 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.

6.3.15. Quinapril (NAP) - PSUSA/00002591/202104

Applicant(s): various

PRAC Lead: Anette Kirstine Stark

[68] Cream and vaginal capsule(s) only
[69] Cream and vaginal capsule(s) only
[70] Cream and vaginal capsule(s) only
[71] 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.

Scope: Evaluation of a PSUSA procedure

Background

Quinapril is an angiotensin-converting enzyme (ACE) inhibitor indicated for the treatment of hypertension alone or in combination with a thiazide diuretic or a beta-blocker. It is also indicated for the treatment of congestive heart failure in combination with a diuretic and/or a cardiac glycoside.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing quinapril 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 quinapril-containing product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include syndrome of inappropriate antidiuretic hormone secretion (SIADH) and subsequent hyponatremia as a warning. In addition, SIADH and hyponatremia should be added as undesirable effects with a frequency 'not known' and 'common' respectively. Finally, psoriasis and psoriasis aggravated should be added as undesirable effects with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[72].

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.

6.3.16. Terlipressin (NAP) - PSUSA/00002905/202104

Applicant(s): various

PRAC Lead: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

Background

Terlipressin is a synthetic vasopressin analogue indicated for the treatment of bleeding oesophageal varices (BOV), hepatorenal syndrome (HRS) and for the treatment of bleeding in connection with surgery particularly from gastrointestinal and urogenital tracts.

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

[72] 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.

- In the next PSUR, the MAHs should maintain 'respiratory failure' as an important identified risk in the PSUR summary 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.

Based on the results of the CONFIRM[73] trial, PRAC considered that a thorough review is needed to assess the impact of these findings on the risk-benefit balance of terlipressin-containing products when used in the indication treatment of HRS.

6.4. Follow-up to PSUR/PSUSA procedures

See Annex 16.4.

6.5. Variation procedure(s) resulting from PSUSA evaluation

See also Annex 16.5.

6.5.1. Emicizumab - HEMLIBRA (CAP) - EMEA/H/C/004406/II/0025

Applicant: Roche Registration GmbH

PRAC Rapporteur: Amelia Cupelli

Scope: Update of sections 4.4, 4.8 and 5.1 of the SmPC concerning immunogenicity and loss of efficacy due to anti-emicizumab antibodies as requested in the conclusions of the latest periodic safety update report single assessment (PSUSA) procedure (PSUSA/00010668/202011) adopted in June 2021, together with a review of haemorrhagic cases as requested in the conclusions of the PSUSA procedure (PSUSA/00010668/202011) finalised in June 2021. The RMP (version 3.0) is updated accordingly.

Background

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

Following the evaluation of the most recently submitted PSUR(s) for the above-mentioned medicine(s), the MAH submitted a variation to EMA to update the product information and the RMP to include new data related to loss of efficacy due to neutralising anti-drug antibodies (ADA) (anti-emicizumab antibodies) in line with the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00010668/202011) finalised in June 2021. PRAC is responsible for adopting an outcome based on the assessment report from the PRAC Rapporteur, to be further considered at the level of CHMP, responsible for adopting an opinion on this variation. For background information, see PRAC minutes June 2021 and PRAC minutes September 2021[74].

Summary of advice/conclusion(s)

[73] Wong F, et al. Terlipressin plus albumin for the treatment of type 1 hepatorenal syndrome. N Engl J Med. 2021 Mar 4;384(9):818-828. doi: 10.1056/NEJMoa2008290
[74] Held 30 August-02 September 2021

- Based on the available data and the Rapporteur's assessment, PRAC considered that the MAH should provide further clarifications and responses before the procedure can be concluded.
- PRAC agreed to request the MAH to remove 'immunogenicity' from the list of safety concerns as an important potential risk and add 'loss of efficacy due to anti-emicizumab antibodies' as an important identified risk. In addition, the important potential risk of 'anaphylaxis, anaphylactoid and systemic hypersensitivity reactions' should be extended to include a description of all types of reactions types 1-4. Moreover, the MAH should revise the proposed updates to the product information on immunogenicity and production of neutralising antibodies possibly associated with a lack of therapeutic efficacy.

6.5.2. Lurasidone - LATUDA (CAP) - EMEA/H/C/002713/II/0036

Applicant: Aziende Chimiche Riunite Angelini Francesco A.C.R.A.F. S.p.A.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of section 4.8 of the SmPC to amend the frequency of adverse drug reactions (ADRs) in adults, as well as to add 'syncope' and 'cerebrovascular accident' as reminded in the conclusions of the last PSUR single assessment (PSUSA) procedure (PSUSA/00010114/202010) adopted in June 2021. The package leaflet is updated accordingly. In addition, the MAH took the opportunity to combine all the dosages in a single version of the product information, to update the list of local representatives in the package leaflet and to bring the product information in line with the latest quality review of documents (QRD) template (version 10.2 Rev. 1)

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 submitted a variation to EMA to update the product information to amend the frequency of ADRs in adults, as well as to add 'syncope' and 'cerebrovascular accident' as reminded in the conclusions of the PSUSA procedure (PSUSA/00010114/202010) finalised in June 2021. PRAC is responsible for adopting an outcome based on the assessment report from the PRAC Rapporteur, to be further considered at the level of CHMP, responsible for adopting an opinion on this variation. For background information, see PRAC minutes June 2021.

Summary of recommendation(s)

- Based on the available data and the Rapporteur's assessment, PRAC agreed to amend[75] the product information with updated frequencies for a large number of ADRs in adult in line with the most recent clinical study data, and to add syncope and cerebrovascular accident with a frequency 'uncommon' and 'rare' respectively.

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

6.5.3. Tozinameran (previously COVID-19 mRNA[76] vaccine (nucleoside modified)) - COMIRNATY (CAP) - EMEA/H/C/005735/II/0080

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Update of section 4.4 of the SmPC in order to amend an existing warning on anxiety-related reactions to add 'numbness' based on the outcome of the ninth monthly summary safety report (MSSR) (MEA 002.8) finalised in October 2021. In addition, the MAH took the opportunity to make minor editorial changes throughout the product information.

Background

Tozinameran is a nucleoside-modified messenger ribonucleic acid (mRNA) vaccine indicated, as Comirnaty, for the active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 12 years of age and older.

Following the evaluation of the MSSR finalised in October 2021 for the above-mentioned medicine(s), the MAH submitted to EMA a variation to amend the existing warning on anxiety-related reactions to add 'numbness' together with a review on hypoesthesia and paraesthesia. For background information, see PRAC minutes October 2021[77]. PRAC is responsible for adopting an outcome based on the assessment report from the PRAC Rapporteur, to be further considered at the level of CHMP, responsible for adopting an opinion on this variation.

Summary of recommendation(s)

- Based on the available data and the Rapporteur's assessment, PRAC considered that the MAH should provide further clarifications and responses before the procedure can be concluded.
- The MAH should provide a proposed updated product information with hypoesthesia and paraesthesia as undesirable effects. PRAC agreed with the addition of 'numbness' to the existing warning on anxiety-related reactions.

6.6. Expedited summary safety reviews[78]

6.6.1. Coronavirus (COVID-19) mRNA[79] vaccine (nucleoside-modified) - SPIKEVAX (CAP) - EMEA/H/C/005791/MEA 011.9

Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Hans Christian Siersted

Scope: Tenth expedited monthly summary safety report (MSSR) for Spikevax (COVID-19 mRNA vaccine (nucleoside-modified)) during the coronavirus disease (COVID-19) pandemic

Background

[76] Messenger ribonucleic acid
[77] Held 27-30 September 2021
[78] 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
[79] Messenger ribonucleic acid

COVID-19 nucleoside-modified messenger ribonucleic acid (mRNA) vaccine is indicated, as Spikevax, for active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 12 years of age and older.

PRAC assessed the tenth monthly summary safety report (MSSR) for Spikevax (COVID-19 mRNA vaccine (nucleoside-modified)) as part of the safety monitoring of the vaccine. At the plenary meeting, PRAC adopted its conclusions.

Summary of advice/conclusion(s)

- In the next MSSR[80], the MAH should provide cumulative reviews and data. In particular, the MAH should include a detailed review of cases of thrombosis with thrombocytopenia syndrome (TTS) with a separate review in the <18-year population. The MAH should also continue to closely monitor cases of multisystem inflammatory syndrome (MIS), with a particular focus on cases with test result for nucleocapsid antibodies. In addition, the MAH should also provide a detailed review of cases of myocarditis/pericarditis with details on any type of sequelae, with a special focus on patterns in the sub-population of 12-17 years old, and younger, if relevant, as well as on cases occurring after the third dose. Finally, the MAH should provide further details on any reported cases of hepatic failure, autoimmune and/or inflammatory disease (AI/ID) and overdose associated to the third/booster dose.
- In the next PSUR, the MAH should provide detailed reviews of cases of encephalitis and of single organ cutaneous vasculitis (SOCV).

6.6.2. Coronavirus (COVID-19) vaccine (Ad26.COV2-S, recombinant) - COVID-19 VACCINE JANSSEN (CAP) – EMEA/H/C/005737/MEA 014.7

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Eighth expedited monthly summary safety report (MSSR) for COVID-19 Vaccine Janssen (COVID-19 vaccine (Ad26.COV2-S, recombinant)) during the coronavirus disease (COVID-19) pandemic

Background

COVID-19 vaccine (Ad26.COV2-S [recombinant]) is a monovalent vaccine composed of a recombinant, replication-incompetent human adenovirus type 26 vector that encodes a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) full-length spike (S) glycoprotein indicated as COVID-19 vaccine Janssen, a centrally authorised vaccine, for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older.

PRAC assessed the eighth MSSR for COVID-19 vaccine Janssen (COVID-19 vaccine (Ad26.COV2-S, [recombinant]) as part of the safety monitoring of the vaccine. At the plenary meeting, PRAC adopted its conclusions.

Summary of advice/conclusion(s)

[80] Submission date on 10 January 2022

- The MAH should submit to EMA, within 60 days, a variation to add small vessel vasculitis with cutaneous manifestations as an undesirable effect with a frequency 'rare'.
- In the next MSSR[81], the MAH should provide cumulative reviews and data. In particular, the MAH should include a cumulative review of cases of acute macular neuroretinopathy as well as detailed reviews of cases of vasculitis and of encephalitis including cases of acute disseminated encephalomyelitis (ADEM).

6.6.3. Tozinameran (previously COVID-19 mRNA[82] vaccine (nucleoside modified)) - COMIRNATY (CAP) - EMEA/H/C/005735/MEA 002.10

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Eleventh expedited monthly summary safety report (MSSR) for Comirnaty (COVID-19 mRNA vaccine (nucleoside-modified)) during the coronavirus disease (COVID-19) pandemic

Background

Tozinameran is a nucleoside-modified messenger ribonucleic acid (mRNA) vaccine indicated, as Comirnaty, for the active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 12 years of age and older.

PRAC assessed the eleventh MSSR for Comirnaty (tozinameran) as part of the safety monitoring of the vaccine. At the plenary meeting, PRAC adopted its conclusions.

Summary of advice/conclusion(s)

- In the next MSSR[83], the MAH should provide cumulative reviews and data. In particular, the MAH should report on handling and dosing errors as a result of the different vaccine formulations on the market and also report on the number of administered dose number three in the EU per country and by age group. In addition, the MAH should provide detailed reviews of cases of rhabdomyolysis and of multisystem inflammatory syndrome (MIS).
- In the next PSUR, the MAH should report on handling and dosing errors as a result of the different vaccine formulations on the market and also report on the number of administered dose number three in the EU per country and by age group.

7. Post-authorisation safety studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)[84]

7.1.1. Evinacumab – EVKEEZA (CAP) – EMEA/H/C/PSP/S/0096

Applicant: Regeneron Ireland Designated Activity Company (DAC)

[81] Submission date on 08 February 2022
[82] Messenger ribonucleic acid
[83] Submission date on 10 January 2022
[84] In accordance with Article 107n of Directive 2001/83/EC

PRAC Rapporteur: Annika Folin

Scope: Protocol for a study to evaluate long-term effects of evinacumab treatment in patients with homozygous familial hypercholesterolemia (HoFH), including safety outcomes in patients with HoFH who are ⩾12 years old, frequency and outcomes of pregnancy in female patients with HoFH, atherosclerosis process over time in patients with HoFH who undergo cardiovascular imaging and frequency of cardiovascular imaging of patients with HoFH.

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 (Annex II-E) imposed in the marketing authorisation(s) of Evkeeza (evinacumab), the MAH Regeneron Ireland Designated Activity Company (DAC) submitted to EMA protocol version 1.0 for a study entitled: 'an observational study to evaluation of the long-term effects of evinacumab treatment in patients with homozygous familial hypercholesterolemia (HoFH)' for review by PRAC. PRAC is responsible for evaluating the PASS protocol.

Endorsement/Refusal of the protocol

- Having considered the draft protocol version 1.0 in accordance with Article 107n of Directive 2001/83/EC, PRAC objected to the draft protocol for the above-listed medicinal product(s). PRAC agreed that the PASS is non-interventional, but the study design does not fulfil the study objectives at this stage.
- The MAH should provide an updated analysis plan together with further clarifications. In particular, the use of a historical cohort vs a contemporaneous cohort should be further discussed and justified. The MAH should also discuss the feasibility of using a concurrent unexposed cohort which would aid in interpretation of any comparative analyses conducted. In addition, the MAH should clarify if patients eligible will be identified throughout the duration of the study in order to include a larger population. Clarification on the validity of the European Atherosclerosis Society (EAS) Familial Hypercholesterolemia Studies Collaboration (FHSC) global FH registry should be also provided. Moreover, the MAH should clarify if development of specific anti-drug antibodies (ADA) could be captured in the registry and whether congenital anomalies will be measured in the study.
- The MAH should submit a revised PASS protocol within 60 days to EMA. A 60 day-assessment timetable will be followed.

7.1.2. Idecabtagene vicleucel – ABECMA (CAP) - EMEA/H/C/PSP/S/0097

Applicant: Bristol-Myers Squibb Pharma EEIG, ATMP[85]

PRAC Rapporteur: Annika Folin

Scope: Protocol for a non-interventional PASS of patients treated with idecabtagene vicleucel (ide-cel, bb2121) for multiple myeloma (MM) in the post-marketing setting to characterize the incidence and severity of selected adverse drug reactions (ADRs), as

[85] Advanced therapy medicinal product

outlined in the product information, in patients treated with ide-cel in the post-marketing setting and to monitor for potential clinically important adverse events (AEs) that have not yet been identified as part of the ide-cel safety profile.

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 (Annex II-E) imposed in the marketing authorisation(s) of Abecma (idecabtagene vicleucel), the MAH Bristol-Myers Squibb Pharma EEIG submitted to EMA protocol version BB2121-MM-006 for a study entitled: 'a non-interventional PASS of patients treated with idecabtagene vicleucel (ide-cel, bb2121) for MM in the post-marketing setting' for review by PRAC. PRAC is responsible for evaluating the PASS protocol.

Endorsement/Refusal of the protocol

- Having considered the draft protocol version BB2121-MM-006 in accordance with Article 107n of Directive 2001/83/EC, PRAC agreed that the PASS is non-interventional and endorsed the protocol.

7.2. Protocols of PASS non-imposed in the marketing authorisation(s)[86]

See Annex 17.2.

7.3. Results of PASS imposed in the marketing authorisation(s)[87]

None

7.4. Results of PASS non-imposed in the marketing authorisation(s)[88]

See also Annex 17.4.

7.4.1. Estrogens conjugated, bazedoxifene - DUAVIVE (CAP) - EMEA/H/C/002314/II/0030

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Martin Huber

Scope: Submission of the final report from study B2311060 (listed as a category 3 study in the RMP): a non-interventional PASS of conjugated oestrogens/bazedoxifene (CE/BZA) in the US, with the aim to monitor the safety profile of Duavive (CE/BZA) in comparison to oestrogen and progestin combination hormone therapy (E+P HT)

Background

[86] 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
[87] In accordance with Article 107p-q of Directive 2001/83/EC
[88] In accordance with Article 61a (6) of Regulation (EC) No 726/2004, in line with the revised variations regulation for any submission as of 04 August 2013

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

As stated in the RMP of Duavive (estrogens conjugated/bazedoxifene (CE/BZA)), the MAH conducted a non-interventional, post-authorisation safety study of CE/BZA in the US in order to monitor the safety profile of Duavive (CE/BZA) in comparison to estrogen and progestin combination hormone therapy (E+P HT). The Rapporteur assessed the MAH's final study report and the responses from the MAH to a request for supplementary information (RSI) adopted in July 2021. For further background, see PRAC minutes July 2021.

Summary of advice

- Based on the available data and the assessment of the Rapporteur, PRAC considered that the ongoing variation assessing the final study report can be recommended for approval.
- PRAC supported the changes to the product information[89] to amend the existing warnings on breast cancer and stroke in light of the study results.

7.4.2. Glycerol phenylbutyrate - RAVICTI (CAP) - EMEA/H/C/003822/II/0038/G, Orphan

Applicant: Immedica Pharma AB

PRAC Rapporteur: Ilaria Baldelli

Scope: Grouped variations consisting of: 1) submission of the final report for study HPN-100-014: a non-interventional registry study - a long-term registry of patients with urea cycle disorders (UCDs) conducted in the US; 2) submission of an updated RMP (version 7) to remove the important potential risks of carcinogenicity and phenylacetic acid (PAA) toxicity. The update to the RMP is based on the review of new and available data including the study report for HPN-100-014 and a new toxicological expert examination of pre-clinical carcinogenicity findings as well as a cumulative review of literature and post marketing data. In accordance with the proposed changes to the RMP, an update of Annex II is requested to waive the imposed condition related to the non-interventional PASS on 'European post-authorisation registry for Ravicti (glycerol phenylbutyrate) oral liquid in partnership with the European registry and network for intoxication type metabolic diseases (E-IMD)'. The SmPC and package leaflet have been updated to delete the information on additional monitoring (including the black triangle).

Background

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

As stated in the RMP and Annex II of Ravicti (glycerol phenylbutyrate), the MAH conducted a non-interventional study as a long-term registry of patients with UCDs conducted in the US (study HPN-100-014). The Rapporteur assessed the MAH's final study report together with the necessary updates to the RMP. The Rapporteur assessed the MAH's final study report and the responses from the MAH to a request for supplementary information (RSI) adopted in July 2021. For further background, see PRAC minutes July 2021.

[89] SmPC section 4.4. The package leaflet is updated accordingly.

Summary of advice

- Based on the available data and the Rapporteur's review, PRAC considered that further information is necessary before the ongoing variation assessing the final study report can be recommended for approval.
- PRAC agreed that 'toxicity due to the active metabolite phenylacetic acid (PAA)' should be retained as an important potential risk in the list of safety concerns for further characterisation. The MAH should implement a follow-up questionnaire (FUQ) to capture any available information on PAA level measurements performed in patients with possible adverse drug reactions related to PAA toxicity. PRAC also supported the removal of 'carcinogenicity' from the list of safety concerns as an important potential risk and supported to continue monitoring via routine pharmacovigilance activities. The MAH should address a further request for RSI before a conclusion can be drawn.

7.4.3. Pegfilgrastim - NEULASTA (CAP) - EMEA/H/C/000420/II/0116

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Submission of the final report from study 20170701 (listed as a category 3 study in the RMP): an observational study to assess the effectiveness of the Neulasta (pegfilgrastim) patient alert card and to measure medication errors related to the use of the on-body injector. The RMP (version 8.0) is updated accordingly.

Background

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

As stated in the RMP of Neulasta (pegfilgrastim), the MAH conducted an observational study (study 20170701) to assess the effectiveness of the patient alert card and to measure medication errors related to the use of the on-body injector (OBI) authorised since 2018. The Rapporteur assessed the MAH's final study report and the responses from the MAH to a request for supplementary information (RSI) adopted in September 2021. For further background, see PRAC minutes September 2021[90].

Summary of advice

- Based on the available data and the assessment of the Rapporteur, PRAC considered that the ongoing variation assessing the final study report can be recommended for approval.
- PRAC agreed with the update of the patient information leaflet to add a warning in the instructions for use of the OBI in case of exposure to water. PRAC also considered that the post-authorisation measure (PAM) is fulfilled and agreed with the update of the RMP.

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.

[90] Held 30 August-02 September 2021

7.6. Others

See Annex 17.6.

7.7. New Scientific Advice

None

7.8. Ongoing Scientific Advice

None

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

None

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

8.1. Annual reassessments of the marketing authorisation

See Annex 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

10.1.1. Idecabtagene vicleucel - ABECMA (CAP) - EMEA/H/C/004662/II/0009, Orphan

Applicant: Celgene Europe B.V., ATMP[91]

PRAC Rapporteur: Annika Folin

Scope: PRAC consultation on an update of sections 4.2 and 4.4 of the SmPC and on Annex II-D on 'Conditions or restrictions with regard to the safe and effective use of the medicinal product' and package leaflet in order to add statements for the use of Abecma (idecabtagene vicleucel) exceptionally during shortage of tocilizumab following the 'CAT recommendation for the use of chimeric antigen receptor (CAR)-T cell-based therapies in EU during shortages of tocilizumab'. The package leaflet is updated accordingly.

Background

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

A type II variation proposing to update the product information of Abecma (idecabtagene vicleucel) to add statements for the use of the medicinal product exceptionally during shortage of tocilizumab following the 'CAT recommendation for the use of chimeric antigen receptor (CAR)-T cell-based therapies in EU during shortages of tocilizumab' is under evaluation at CAT and CHMP. For further background, see PRAC minutes November 2021[92]. PRAC was requested to provide advice on this procedure.

Summary of advice

- Based on the review of the available information and assessment, PRAC supported the changes in the conditions for the safe and effective use in line with the CAT recommendation. PRAC commented that the use of Abecma (idecabtagene vicleucel) in absence of tocilizumab is still unclear and that the safety profile of the medicinal product needs careful monitoring after a change in cytokine release syndrome (CRS) treatment choice. An updated RMP including updated educational materials reflecting the new conditions of use should be submitted to EMA to reflect the relevant amendments.

10.1.2. Tisagenlecleucel - KYMRIAH (CAP) - EMEA/H/C/004090/II/0047, Orphan

Applicant: Novartis Europharm Limited, ATMP[93]

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: PRAC consultation on an update of sections 4.2 and 4.4 of the SmPC and Annex II-D on 'Conditions or restrictions with regard to the safe and effective use of the medicinal product' in order to add statements for the use of Kymriah (tisagenlecleucel) exceptionally during shortage of tocilizumab following the 'CAT recommendation for the use of chimeric antigen receptor (CAR)-T cell-based therapies in EU during shortages of tocilizumab'. The

[91] Advanced therapy medicinal product
[92] Held 25-28 October 2021
[93] Advanced therapy medicinal product

package leaflet is updated accordingly.

Background

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

A type II variation proposing to update the product information of Kymriah (tisagenlecleucel) to add statements for the use of the medicinal product exceptionally during shortage of tocilizumab following the 'CAT recommendation for the use of chimeric antigen receptor (CAR)-T cell-based therapies in EU during shortages of tocilizumab' is under evaluation at CAT and CHMP. For further background, see PRAC minutes November 2021[94]. PRAC was requested to provide advice on this procedure.

Summary of advice

- Based on the review of the available information and assessment, PRAC supported the changes in the conditions for the safe and effective use in line with the CAT recommendation. PRAC commented that the use of Kymriah (tisagenlecleucel) in absence of tocilizumab is still unclear and that the safety profile of the medicinal product needs careful monitoring after a change in cytokine release syndrome (CRS) treatment choice. An updated RMP including updated educational materials reflecting the new conditions of use should be submitted to EMA to reflect the relevant amendments.

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

None

10.3. Other requests

None

10.4. Scientific Advice

None

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

11.1. Safety related variations of the marketing authorisation

None

11.2. Other requests

None

[94] Held 25-28 October 2021

12. Organisational, regulatory and methodological matters

12.1. Mandate and organisation of PRAC

12.1.1. PRAC membership

None

12.1.2. PRAC Training for Assessors 2021 – course overview

The PRAC Secretariat presented to PRAC the final agenda for the yearly PRAC training for assessors 2021 scheduled on 07 December 2021 with an overview of each session together with organisational elements.

12.1.3. 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 ongoing clinical trials and epidemiological studies and initiatives, as well as a summary of medicines in development and medicines authorised for other indications, as potential treatments for COVID-19, and their safety surveillance.

12.5. Cooperation with International Regulators

None

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

None

12.7. PRAC work plan

None

12.8. Planning and reporting

None

12.9. Pharmacovigilance audits and inspections

None

12.9.1. Pharmacovigilance systems and their quality systems

None

12.9.2. Pharmacovigilance inspections

None

12.9.3. Pharmacovigilance audits

None

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

12.10.1. Periodic safety update reports

None

12.10.2. Granularity and Periodicity Advisory Group (GPAG)

PRAC lead: Menno van der Elst, Maia Uusküla

PRAC was updated on the activities of the Granularity and Periodicity Advisory Group (GPAG) focussing on harmonising and streamlining the EURD list and noted the GPAG progress highlights. The presentation included an update on the EURD list tool project and an overview of the draft 2022 GPAG workplan. Regarding the monthly presentation of the EURD list updates, the EMA Secretariat presented criteria for plenary presentation. PRAC endorsed these criteria for implementation as of January 2022.

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 March 2021, reflecting the PRAC's comments impacting on the data lock point (DLP) and PSUR submission frequencies of the substances/combinations. PRAC endorsed the newly allocated Rapporteurs for upcoming PSUSAs in accordance with the principles previously endorsed by PRAC (see PRAC minutes April 2013).

Post-meeting note: following the PRAC meeting of December 2021, the updated EURD list was adopted by CHMP and CMDh at their December 2021 meetings and published on the

EMA website on 22 December 2021, see:

Home> Human Regulatory>Pharmacovigilance>Periodic safety update reports>EURD list> List of Union reference dates and frequency of submission of periodic safety update reports (PSURs)

12.10.5. Periodic safety update reports single assessment (PSUSA) – update to assessment report (AR) template

PRAC lead: Ulla Wändel Liminga, Menno van der Elst, Jana Lukacisinova

At the organisational, regulatory and methodological matters (ORGAM) meeting on 13 December 2021, following input from members and national competent Authorities (NCA)'s assessors and also based on the review of existing EMA guidance and experience gained, the EMA Secretariat presented to PRAC the consolidated proposal for the updated PSUR assessment report templates. PRAC endorsed the revised assessment report templates. The new templates will start to be used for any new periodic safety update reports single assessment (PSUSA) procedures starting in January 2022 and onwards.

12.11. Signal management

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

PRAC lead: Sabine Straus

PRAC was updated on the progress from the signal management review technical (SMART) working group on 'methods'. The presentation focused on the next phase of the pandemic surveillance, COVID-19 internal lessons learnt, an update on observed to expected (O/E) analyses, a template for ad-hoc requests and routine production for detected signals. Further update will be planned in due course.

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

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 on 15 December 2021, see: Home>Human Regulatory>Post-authorisation>Pharmacovigilance>Medicines under additional monitoring>List of medicines under additional monitoring

12.13. EudraVigilance database

12.13.1. Activities related to the confirmation of full functionality

None

12.14. Risk management plans and effectiveness of risk minimisations

12.14.1. Risk management systems

None

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

None

12.15. Post-authorisation safety studies (PASS)

12.15.1. Post-authorisation Safety Studies – imposed PASS

None

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

None

12.16. Community procedures

12.16.1. Referral procedures for safety reasons

None

12.17. Renewals, conditional renewals, annual reassessments

None

12.18. Risk communication and transparency

12.18.1. Public participation in pharmacovigilance

None

12.18.2. Safety communication

None

12.19. Continuous pharmacovigilance

12.19.1. Incident management

None

12.20. Impact of pharmacovigilance activities

12.20.1. Strategy on measuring the impact of pharmacovigilance – PRAC interest group (IG) Impact - Impact research on implementation of EU risk minimisation measures for medicinal products in clinical guidelines

The EMA Secretariat presented to PRAC draft technical specification for tender for an impact study on 'Implementation of EU risk minimisation measures for medicinal products in clinical guidelines'. The purpose is to better understand the roles and responsibilities and processes for updating clinical guidelines (at the national and EU levels), how to engage with healthcare professional (HCP) bodies and other responsible parties to strengthen the role of clinical guidelines for risk minimisation measures (RMM) implementation and to understand which RMM elements trigger(ed) an update of clinical guidelines. PRAC members were invited to send comments by 15 December 2021.

Post-meeting note: On 07 January 2022, PRAC adopted by written procedure the technical specification for tender for the study.

12.20.2. Strategy on measuring the impact of pharmacovigilance – PRAC interest group (IG) Impact - review of the effectiveness of post-authorisation safety studies (PASS) assessed by PRAC between 2016-2019 – final report

The EMA Secretariat presented to PRAC the final report of a review of post-authorisation safety studies (PASS) evaluating the effectiveness of risk minimisation measures (RMMs) assessed by PRAC between 2016-2019. The review is a deliverable of the PRAC interest group (IG) Impact workplan 2021. The objectives include the description of study designs and analytical methods, the types and proportion of successful RMMs and how success was defined, comparison of effective RMMs with non-effective RMMs and identification of factors associated with successful RMMs. PRAC members were invited to send comments by 16 December 2021.

Post-meeting note: PRAC proposed a follow-up review focussing on factors associated with inconclusive PASS, and to gain further insights into factors associated with (in)effective RMMs. This follow-up review based is a deliverable of the PRAC IG Impact work plan 2022.

12.21. Others

12.21.1. End of the year appreciation

The EMA Executive Director thanked PRAC for the work carried out in 2021.

12.21.2. Lifecycle regulatory submissions metadata project (LRSM) - presentation

At the organisational, regulatory and methodological matters (ORGAM) meeting on 13 December 2021, the EMA Secretariat presented to PRAC the lifecycle regulatory submissions meta-data project (LRSM). The purpose of the project is to deliver effective generation of evidence in support of benefit-risk decision making from data-driven interrogation of scientific information within lifecycle regulatory submissions. PRAC noted the project.

12.21.3. Rapid data analytics – project update and initiatives on real world evidence (RWE) analyses to support regulatory assessments

The EMA Secretariat presented to PRAC the new process for rapid data analyses following the pilot phase. The presentation included some use cases, how the pilot is used with other EMA Committees together with the PRAC pilot recommendations. The presentation also included information on real-world data/evidence initiatives, an introduction to 'data analysis and real-world interrogation network (DARWIN EU)' to start in 2022 and how to increase generation of real-world evidence (RWE). PRAC members were invited to request analyses as needed. Further training will be given at PRAC's training to assessors on 07 December 2022. See 12.1.2.

13. Any other business

None

14. Annex I – Signals assessment and prioritisation[95]

14.1. New signals detected from EU spontaneous reporting systems

As per 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[96].

14.1.1. Canakinumab – ILARIS (CAP)

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Signal of interstitial lung disease (ILD) and alveolar proteinosis

EPITT 19736 – New signal

Lead Member State(s): DE

14.1.2. Dabigatran etexilate – PRADAXA (CAP)

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Anette Kirstine Stark

Scope: Signal of autoimmune haemolytic anaemia

EPITT 19745 – New signal

Lead Member State(s): DK

[95] 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.
[96] Either MA(s)'s submission within 60 days followed by a 60 day-timetable assessment or MAH's submission cumulative review within an ongoing or upcoming PSUR/PSUSA procedure (if the DLP is within 90 days), and no disagreement has been raised before the meeting.

14.1.3. Vildagliptin - GALVUS (CAP), JALRA (CAP), XILIARX (CAP); vildagliptin, metformin - EUCREAS (CAP), ICANDRA (CAP), ZOMARIST (CAP)

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Annika Folin

Scope: Signal of cutaneous vasculitis

EPITT 19742 – New signal

Lead Member State(s): SE

14.2. New signals detected from other sources

14.2.1. Abatacept – ORENCIA (CAP)

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Kimmo Jaakkola

Scope: Signal of acute respiratory distress syndrome (ARDS)

EPITT 19751 – New signal

Lead Member State(s): FI

14.2.2. Atezolizumab - TECENTRIQ (CAP)

Applicant: Roche Registration GmbH

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Signal of optic neuritis

EPITT 19747 – New signal

Lead Member State(s): PT

14.2.3. Liraglutide – SAXENDA (CAP), VICTOZA (CAP)

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Menno van der Elst

Scope: Signal of cutaneous amyloidosis

EPITT 19740 – New signal

Lead Member State(s): NL

15. Annex I – Risk management plans

15.1. Medicines in the pre-authorisation phase

As per agreed criteria, PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of the RMP for the below-mentioned medicines 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. Betaine anhydrous - EMEA/H/C/005637

Scope: Treatment of homocystinuria

15.1.2. Ciltacabtagene autoleucel - EMEA/H/C/005095, Orphan

Applicant: Janssen-Cilag International NV, ATMP[97]

Scope: Treatment of multiple myeloma

15.1.3. Enfortumab vedotin - EMEA/H/C/005392

Scope: Treatment of locally advanced (LA) or metastatic urothelial cancer (mUC)

15.1.4. Opicapone - EMEA/H/C/005782

Scope: Treatment of Parkinson's disease and motor fluctuations

15.1.5. Sotrovimab – EMEA/H/C/005676

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

15.1.6. Teriparatide - EMEA/H/C/004932

Scope : Treatment of osteoporosis in postmenopausal women and in men at increased risk of fracture

15.1.7. Teriparatide - EMEA/H/C/005827

Scope: Treatment of osteoporosis

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

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

15.2.1. Coronavirus (COVID-19) mRNA[98] vaccine (nucleoside-modified) - SPIKEVAX (CAP) - EMEA/H/C/005791/II/0022

Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Hans Christian Siersted

Scope: Submission of an updated RMP (version 2.0) to include clinical safety data from study mRNA-1273 P203 (NCT04649151): a phase 2/3, randomised, observer-blind, placebo-controlled study evaluating the safety, reactogenicity and effectiveness of the

[97] Advanced therapy medicinal product
[98] Messenger ribonucleic acid

mRNA-1273 vaccine in healthy adolescents aged ⩾ 12 to < 18 years

15.2.2. Coronavirus (COVID-19) vaccine (ChAdOx1-S [recombinant]) - VAXZEVRIA (CAP) - EMEA/H/C/005675/II/0040

Applicant: AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

Scope: Submission of an updated RMP (version 4.1) in order to add 'thrombosis in combination with thrombocytopenia' as an important potential risk as requested in the outcome of the signal procedure on immune thrombocytopenia (ITP) (EPITT 19678) adopted in July 2021 (SDA/034.1), to add acute macular neuroretinopathy, acute macular outer retinopathy, paracentral acute middle maculopathy, paraesthesia and dysaesthesia in the list of adverse events of special interest (AESI) as requested in the outcome of the signal procedure on acute macular outer retinopathy (EPITT 19703) adopted in July 2021 (SDA/065). In addition, the updated RMP include the removal of the enhanced active surveillance (EAS) studies D8111R00003 [EU], D8110R00001 [US], D8111C00004 [UK], the update of the important potential risk of 'nervous system disorders, including immune-mediated neurological conditions' to reflect the recent product information on Guillain-Barré syndrome (IB/0034) as requested in the outcome of fourth monthly summary safety update (MSSR) (MEA 027.3) adopted in July 2021. Finally, the updated RMP includes the addition of the UK effectiveness study D8111R00007 as per the CHMP conclusion (MEA 010.1) dated June 2021 and the addition of study D8111R00010 to assess the relationship between the exposure to COVID-19 vaccines and the risk of thrombotic thrombocytopenia syndrome.

15.2.3. Dasabuvir - EXVIERA (CAP) - EMEA/H/C/003837/WS2158/0051; ombitasvir, paritaprevir, ritonavir - VIEKIRAX (CAP) - EMEA/H/C/003839/WS2158/0063

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Update of Annex II-D on 'Conditions or restrictions with regard to the safe and effective use of the medicinal product' regarding study B20-146 on the hepatocellular carcinoma (HCC) recurrence PASS to change its milestone due date from 'Q3 2021' to 'Q4 2021', following EMA's recommendation dated July 2021. In addition, the MAH took the opportunity to introduce few minor linguistic and typographical corrections in the product information of Exviera (dasabuvir) for the Hungarian, Latvian and Romanian translations.

15.2.4. Denosumab - PROLIA (CAP) - EMEA/H/C/001120/II/0091/G

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Grouped variations consisting of the submission of an updated RMP (version 28.0) in order to: 1) remove osteonecrosis outside the jaw (OOJ) including external auditory canal (OEAC) as an important potential risk; 2) remove immunogenicity following a significant change to the manufacturing process as missing information; 3) introduce changes study 20190038 (listed as a category 3 study/PASS in the RMP): a retrospective cohort database study to assess the potential increased risk of cardiovascular and cerebrovascular events among women with postmenopausal osteoporosis (PMO) and men with osteoporosis by

adding the study objectives. In addition, the MAH took the opportunity to update the RMP in order to provide the date for the provision of the final study report for study 20190038 and to include the post-marketing exposure data from the last submitted PSUR (#13).

15.2.5. Romosozumab - EVENITY (CAP) - EMEA/H/C/004465/II/0010

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Tiphaine Vaillant

Scope: Submission of an updated RMP (version 2.0) in order to remove 'immunogenicity' as an important identified risk revision 2 of GVP module V on 'Risk management systems', EMA guidance on immunogenicity assessment, and the available non-clinical, clinical and post-marketing data. In addition, the MAH took the opportunity to add 'cardiac arrythmia' as an important potential risk to the RMP and to update the protocol for the ongoing study OP0004: a European non-interventional PASS related to serious cardiovascular events of myocardial infarction and stroke, and all-cause mortality for romosozumab by the EU-ADR Alliance to include cardiac arrhythmias as specific events to monitor, and include a targeted follow-up questionnaire (FUQ) related to cardiac arrhythmias, in line with the outcome of the signal procedure on cardiac arrhythmia (EPITT 19629) adopted in May 2021. The MAH took also the opportunity to introduce minor changes in the PASS protocols of studies OP0004, OP0005: a European non-interventional PASS related to adherence to the risk minimisation measures for romosozumab by the EU-ADR Alliance, and OP0006: European non-interventional PASS related to serious infections for romosozumab by the EU-ADR Alliance

15.2.6. Simoctocog alfa - NUWIQ (CAP) - EMEA/H/C/002813/WS2064/0043; VIHUMA (CAP) - EMEA/H/C/004459/WS2064/0024

Applicant: Octapharma AB

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of an updated RMP (version 11) to remove the following completed studies: 1) study GENA-05: immunogenicity, efficacy and safety of treatment with simoctocog alfa in previously untreated patients with severe haemophilia A; 2) study GENA-15: extension study for patients who completed GENA-05 (NuProtect)- to investigate immunogenicity, efficacy and safety of treatment with simoctocog alfa. As a consequence, 'safety in previously untreated patients', 'children < 2 years' and 'immune tolerance induction' are removed as missing information in the list of safety concerns. Finally, the RMP is brought in line with revision 2 of GVP module V on 'Risk management systems'.

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

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

15.3.1. Adalimumab - IMRALDI (CAP) - EMEA/H/C/004279/II/0048/G

Applicant: Samsung Bioepis NL B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Grouped variations consisting of: 1) introduction of an additional concentration of 40 mg/0.4 mL (same 40 mg strength) for the solution for subcutaneous injection in pre-filled syringe (PFS) and pre-filled pen (PFP) with a shelf life for the active substance of 24 months when stored at or below -60°C and a shelf life and storage conditions for the finished product of 12 months when stored at 5 ± 3°C and up to 31 days at 25°C; 2) change of the composition in excipients for the proposed 40 mg/0.4 mL solution for injection in PFS and PFP; 3) addition of 2 presentations: 1 PFS and 1 PFP with 2 alcohol pads each for the proposed 40 mg/0.4 mL solution for injection; 4) addition of 2 presentations: 2 PFSs and 2 PFPs with 2 alcohol pads each for the proposed 40 mg/0.4 mL solution for injection; 5) addition of 2 presentations: 4 PFSs and 4 PFPs with 4 alcohol pads each for the proposed 40 mg/0.4 mL solution for injection; 6) addition of 2 presentations: 6 PFSs and 6 PFPs with 6 alcohol pads each for the proposed 40 mg/0.4 mL solution for injection. The RMP (version 7.0) is updated accordingly. The MAH took the opportunity to introduce minor updated throughout the product information and implement various editorial changes in Module 3.

15.3.2. Adalimumab - YUFLYMA (CAP) - EMEA/H/C/005188/X/0005

Applicant: Celltrion Healthcare Hungary Kft.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension application to introduce a new strength of 80 mg solution for injection. The RMP (version 1.1) is updated accordingly.

15.3.3. Anakinra - KINERET (CAP) - EMEA/H/C/000363/II/0086

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Anette Kirstine Stark

Scope: Extension of indication to include treatment of coronavirus disease 2019 (COVID-19) in adult patients with pneumonia who are at risk of developing severe respiratory failure. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 5.7) are updated in accordance.

15.3.4. Apalutamide - ERLEADA (CAP) - EMEA/H/C/004452/II/0017

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Tiphaine Vaillant

Scope: Update of section 5.3 of the SmPC in order to update non-clinical information based on final results from study TOX11338 (in completion of MEA 006): a 2-year study to better characterize the carcinogenic potential of JNJ-56021927-AAA (apalutamide) by oral gavage in rats. The RMP (version 4.1) is updated accordingly. In addition, the MAH took the opportunity to include general information in the RMP regarding study TITAN (PCR3002): a phase 3 randomized, placebo-controlled, double-blind study of apalutamide plus androgen deprivation therapy (ADT) versus ADT in subjects with metastatic hormone-sensitive prostate cancer (mHSPC).

15.3.5. Atezolizumab - TECENTRIQ (CAP) - EMEA/H/C/004143/II/0066

Applicant: Roche Registration GmbH

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Submission of the final report for study WO29635 (listed as a category 3 study activity): a phase 1B/2 study of the safety and pharmacology of atezolizumab administered with or without bacille Calmette-Guérin (BCG) in patients with high-risk non-muscle-invasive bladder cancer. The RMP (version 22.0) is updated accordingly. The RMP also includes a revision of the due date for the submission of the final clinical study report (CSR) for study MO39171 (TAIL): a phase 3/4, single arm, multicentre study of atezolizumab to investigate long-term safety and efficacy in previously treated patients with locally advanced or metastatic non-small cell lung cancer (TAIL).

15.3.6. Baricitinib - OLUMIANT (CAP) - EMEA/H/C/004085/II/0029/G

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Grouped variations consisting of: 1) extension of indication to include treatment of severe alopecia areata in adult patients. 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 and the RMP (version 12.1) are updated in accordance; 2) update of the RMP (version 12.1) regarding study I4V-MC-B011 (listed as a category 3 study in the RMP): a retrospective cohort study to assess the safety of baricitinib compared with other therapies used in the treatment of rheumatoid arthritis in Nordic countries to change the end of data collection for the atopic dermatitis cohort from 'December 2026' to 'December 2027' and the subsequent final study report milestone from 'December 2027' to 'December 2028'.

15.3.7. Bosutinib - BOSULIF (CAP) - EMEA/H/C/002373/II/0050/G

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Martin Huber

Scope: Grouped variations consisting of an update of sections 4.2, 4.4, 4.8 and 5.1 of the SmPC in order to reflect results from: 1) study B1871039 (listed as a specific obligation (SOB) in Annex II): a phase 4 safety and efficacy study of bosutinib in patients with Philadelphia chromosome positive chronic myeloid leukaemia (CML) previously treated with one or more tyrosine kinase inhibitors. As a consequence, the study is removed from Annex II-E on 'Specific obligations to complete post-authorisation measures for the conditional marketing authorisation' of the product information and the MAH requested a switch from the conditional marketing authorisation to a full marketing authorisation; 2) study B1871040 (listed a category 3 study in the RMP): an open-label bosutinib treatment extension study for subjects with CML who have previously participated in bosutinib studies B1871006 or B1871008. The package leaflet is updated accordingly. The RMP (version 6.0) is updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives for Belgium, Luxemburg, Germany and Northern Ireland in the package leaflet. The MAH also requested the deletion of the medicinal product from the additional monitoring list.

15.3.8. Bupivacaine - EXPAREL LIPOSOMAL (CAP) - EMEA/H/C/004586/II/0005

Applicant: Pacira Ireland Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Extension of indication to extend the existing indication of treatment of somatic post-operative pain from small- to medium-sized surgical wounds to children over 6 years old or older. 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 1.1) are updated accordingly.

15.3.9. Burosumab - CRYSVITA (CAP) - EMEA/H/C/004275/II/0023, Orphan

Applicant: Kyowa Kirin Holdings B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include treatment of fibroblast growth factor 23 (FGF23)-related hypophosphataemia in tumour-induced osteomalacia (TIO) associated with phosphaturic mesenchymal tumours that cannot be curatively resected or localised in patients aged 1 year and over, based on data from two ongoing open-label clinical studies, namely: 1) study UX023T-CL201: a phase 2 open-label trial to assess the efficacy and safety of burosumab in subjects with TIO or epidermal nevus syndrome (ENS)-associated osteomalacia, 2) study KRN23-002: a phase 2 open-label trial to assess the efficacy and safety of burosumab in patients with TIO or ENS (144-week data and 88-week data respectively). 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 4.0) are updated accordingly. The MAH also applied for one additional year of market protection.

15.3.10. Dengue tetravalent vaccine (live, attenuated) - DENGVAXIA (CAP) - EMEA/H/C/004171/II/0016/G

Applicant: Sanofi Pasteur

PRAC Rapporteur: Sonja Hrabcik

Scope: Grouped variations consisting of an update of section 4.5 of the SmPC to include co-administration data on Gardasil/Cervarix (human papillomavirus vaccine) and Adacel (tetanus toxoid/reduced diphtheria toxoid and acellular/pertussis vaccine (adsorbed)) based on the final results of studies (listed as category 3 studies in the RMP) dedicated to immunogenicity and safety of the concomitant administration, namely: 1) study CYD66: a phase 3b, randomised, multicentre, open-label study in 688 subjects aged from 9 to 60 years in the Philippines; 2) study CYD67: a phase 3b, randomised, open-label, multicentre study in 528 subjects aged 9 to 13 years in Malaysia; 3) study CD71: a phase 3b, randomised, open-label, multicentre study in 480 female subjects aged 9 to 14 years in Mexico. The package leaflet and the RMP (version 6.1) are updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet.

15.3.11. Dimethyl fumarate - TECFIDERA (CAP) - EMEA/H/C/002601/II/0073

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Martin Huber

Scope: Extension of indication to include treatment of relapsing remitting multiple sclerosis (RRMS) in paediatrics patients from 10 years of age and over based on results from study 109MS306: an open-label, randomized, multicentre, multiple-dose, active-controlled,

parallel-group, efficacy and safety study of dimethyl fumarate in children from 10 to less than 18 years of age with RRMS with optional open-label extension. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.3 of the SmPC are updated. The package leaflet and the RMP (version 11.4) is updated in accordance. The MAH requested an extension of the market protection of one additional year in line with the guidance on elements required to support the significant clinical benefit in comparison with existing therapies of a new therapeutic indication in accordance with Article 14(11) of Regulation (EC) 726/2004.

15.3.12. Empagliflozin - JARDIANCE (CAP) - EMEA/H/C/002677/II/0060

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Eva Segovia

Scope: Extension of indication to add the treatment of patients with heart failure with preserved ejection fraction (HFpEF) based on the results from clinical study 1245.110 (EMPEROR-Preserved): a phase 3 randomised, double-blind trial to evaluate efficacy and safety of once daily empagliflozin 10 mg compared to placebo, in patients with chronic HFpEF. As a consequence, sections 4.1, 4.8 and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 16.0) are updated accordingly. In addition, the statement 'sodium free' was moved from section 2 of the SmPC to section 4.4 in line with the latest quality review of documents (QRD) template (version 10.2 Rev.1). The MAH took the opportunity to include minor linguistic changes to the national translations of the product information. Further, the MAH applied for an additional year of market protection.

15.3.13. Ibrutinib - IMBRUVICA (CAP) - EMEA/H/C/003791/II/0068

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Update of section 4.4 of the SmPC in order to add baseline monitoring in addition to the current warnings for periodic monitoring of cardiac failure and cardiac arrhythmias in patients receiving ibrutinib. The package leaflet and the RMP (version 18.1) are updated accordingly.

15.3.14. Insulin degludec - TRESIBA (CAP) - EMEA/H/C/002498/II/0054

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Annika Folin

Scope: Update of sections 4.6 and 5.1 of the SmPC in order to include new clinical data from the pregnancy trial EXPECT: a trial comparing the effect and safety of insulin degludec versus insulin detemir, both in combination with insulin aspart, in the treatment of pregnant women with type 1 diabetes (T1DM). The package leaflet is updated in accordance. The RMP (version 9.0) is also updated accordingly.

15.3.15. Ixazomib - NINLARO (CAP) - EMEA/H/C/003844/II/0033, Orphan

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Annika Folin

Scope: Submission of the final report for the final analysis of overall survival (OS) for study C16010 (listed as an obligation in Annex II): a phase 3, randomised, double-blind multicentre study comparing ixazomib in combination with lenalidomide and dexamethasone (LenDex) versus placebo plus LenDex in adult patients with relapsed and/or refractory multiple myeloma. Annex II-D on 'Conditions or restrictions with regard to the safe and effective use of the medicinal product' and the RMP (version 7.0) are updated accordingly.

15.3.16. Lanadelumab - TAKHZYRO (CAP) - EMEA/H/C/004806/II/0022, Orphan

Applicant: Takeda Pharmaceuticals International AG

PRAC Rapporteur: Kirsti Villikka

Scope: Update of sections 4.8 and 5.1 of the SmPC to reflect the result of study DX-2930-04 (HELP study extension): an open-label study to evaluate the long-term safety and efficacy of lanadelumab (DX-2930) for prevention against acute attacks of hereditary angioedema (HAE). The RMP (version 2.0) is updated accordingly and in line with revision 2.0.1 of the guidance on the format of RMP in the EU (template). In addition, the MAH took the opportunity to include a refrigeration statement for the multi-pack pre-filled syringe in the product information.

15.3.17. Lomitapide - LOJUXTA (CAP) - EMEA/H/C/002578/II/0046

Applicant: Amryt Pharmaceuticals DAC

PRAC Rapporteur: Menno van der Elst

Scope: Submission of an alternative study: an evaluation of the effect of lomitapide treatment on major adverse cardiovascular events (MACE) in patients with homozygous familial hypercholesterolemia (LILITH) to the currently agreed protocol for study on the effects of lomitapide on carotid and aortic atherosclerosis in patients treated with lomitapide in usual care (CAPTURE) in order to propose an evaluation of the effect of lomitapide treatment on MACE in patients with homozygous familial hypercholesterolemia. As a consequence, Annex II-D on 'Conditions or restrictions with regard to the safe and effective use of the medicinal product' and the RMP (version 6.4) are updated accordingly. In addition, the MAH took the opportunity to bring the product information in line with the latest quality review of documents (QRD) template (version 10.2).

15.3.18. Lorlatinib - LORVIQUA (CAP) - EMEA/H/C/004646/II/0015

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Extension of indication to include the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) previously not treated with an ALK inhibitor based on results from study 1006 (CROWN) (listed as a specific obligation (SOB) in Annex II): a phase 3 randomised open-label study of lorlatinib monotherapy versus crizotinib monotherapy in the first-line treatment of patients with advanced ALK-positive NSCLC. As a consequence, sections 4.1, 4.2 and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 3.0) are updated accordingly. In addition, the applicant proposed to downgrade the SOB to conduct a single arm study in

patients who progressed after alectinib or ceritinib to a recommendation and convert the conditional marketing authorisation to a full marketing authorisation (MA).

15.3.19. Lutetium (^{177}Lu) oxodotreotide - LUTATHERA (CAP) - EMEA/H/C/004123/II/0030, Orphan

Applicant: Advanced Accelerator Applications

PRAC Rapporteur: Adam Przybylkowski

Scope: Update of sections 4.4, 4.8 and 5.1 of the SmPC based on pivotal study NETTER-1: a multicentre, stratified, open, randomized, comparator-controlled, parallel-group phase 3 study comparing treatment with Luthatera ((^{177}Lu) oxodotreotide) to octreotide long-acting release (LAR) in patients with inoperable, progressive, somatostatin receptor positive midgut carcinoid tumours. Additionally, updates are proposed in the product information to correct some information based on currently approved data. The package leaflet and the RMP (version 2.0) are updated accordingly. The MAH took the opportunity to update the details of local representatives in the package leaflet.

15.3.20. Mepolizumab - NUCALA (CAP) - EMEA/H/C/003860/X/0042

Applicant: GlaxoSmithKline Trading Services Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension application to introduce a new strength of 40 mg for Nucala (mepolizumab) solution for injection in a pre-filled syringe for subcutaneous use to be used in children aged 6 to 11 years. The RMP (version 8.0) is updated accordingly.

15.3.21. Octocog alfa - KOVALTRY (CAP) - EMEA/H/C/003825/II/0038

Applicant: Bayer AG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of sections 4.8 and 5.1 of the SmPC to include data from LEOPOLD kids part B: a long-term efficacy open-label programme in severe haemophilia A disease (previously submitted as Art 46; an addendum on biomarker data is included in this submission) and extension study results. In addition, an editorial revision in section 4.2 and a clarification in section 6.5 of the SmPC are proposed. The package leaflet is updated accordingly. The MAH took the opportunity to correct a typo in the Greek product information. The RMP (version 4.1) is updated and brought in line with revision 2.0.1 of the guidance on the format of RMP in the EU (template).

15.3.22. Padeliporfin - TOOKAD (CAP) - EMEA/H/C/004182/II/0013

Applicant: STEBA Biotech S.A

PRAC Rapporteur: Maia Uusküla

Scope: Extension of indication to modify the wording of the existing indication to treatment of adult patients with previously untreated, unilateral, low-risk, adenocarcinoma of the prostate with a life expectancy $\geqslant$ 10 years and clinical stage T1c or T2a, International Society of Urological Pathology (ISUP) grade group $\leqslant$ 2, based on high-resolution biopsy

strategies, prostate-specific antigen (PSA) ⩽ 10 ng/mL, low core positivity. As a consequence, section 4.1 of the SmPC is updated. The RMP (version 6.0) is updated accordingly.

15.3.23. Pandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) - ADJUPANRIX (CAP) - EMEA/H/C/001206/II/0074

Applicant: GlaxoSmithkline Biologicals SA

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication to include use in children from 6 months to <18 years for Adjupanrix (pandemic influenza vaccine (H5N1)) based on the results of the following studies: 1) study H5N1-013: a phase 2, non-randomised, open-label study to evaluate the safety and immunogenicity in children aged 6 to 35 months; 2) study H5N1-032: a phase 3, randomised, open, active-controlled study to evaluate the safety and immunogenicity in children aged 3 to 17 years. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 6.6 of the SmPC are updated. The package leaflet and the RMP (version 13) are updated in accordance. Further, the MAH proposed to update section 4.4 with information on sodium and potassium content in line with the excipient guideline, as well as to add some wording on traceability. 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). Finally, the MAH introduced minor editorial changes throughout the product information.

15.3.24. Patisiran - ONPATTRO (CAP) - EMEA/H/C/004699/II/0022, Orphan

Applicant: Alnylam Netherlands B.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: Update of sections 4.2, 4.8, 5.1 and 5.2 of the SmPC to confirm that the safety profile of pasitiran in liver transplant recipients is comparable to data in patients without liver transplant, based on final results from study ALN-TTR02-008: a global phase 3b, open-label, extension study to evaluate safety, efficacy and pharmacokinetics of patisiran in patients with hereditary transthyretin-mediated amyloidosis (HATTR amyloidosis) with disease progression post-orthotopic liver transplant (OLT). The package leaflet and the RMP (version 1.1) are updated accordingly. In addition, the MAH took the opportunity to make some minor changes to the English product information and to update to local representatives in Cyprus, Malta, and United Kingdom changed to 'United Kingdom [Northern Ireland]' in line with the latest quality review of documents (QRD) template (version 10.2 Rev. 1). Finally, the MAH implemented minor linguistic changes and typographical error corrections in the Italian product information translation.

15.3.25. Pembrolizumab - KEYTRUDA (CAP) - EMEA/H/C/003820/II/0108

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication to include the adjuvant treatment in monotherapy of adults with renal cell carcinoma (RCC) at intermediate-high or high risk of recurrence following nephrectomy or following nephrectomy and resection of metastatic lesions. As a

consequence, sections 4.1, 4.2 and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 35.1) are updated accordingly.

15.3.26. Pyronaridine, artesunate - PYRAMAX (Art 58[99]) - EMEA/H/W/002319/II/0023/G

Applicant: Shin Poong Pharmaceutical Co., Ltd.

PRAC Rapporteur: Nathalie Gault

Scope: Grouped variations consisting of the submission of the final clinical study reports (CSR) of two completed studies: 1) study SP-C-021-15 (listed as a category 3 study in the RMP): a phase 3b/4 cohort event monitoring study conducted in Central Africa to evaluate the safety in patients after the local registration of Pyramax (pyronaridine/artesunate) (CANTAM study); 2) study SP-C-026-18: a randomized open-label exploratory study to determine the efficacy of different treatment regimens of Pyramax (pyronaridine/artesunate) in asymptomatic carriers of Plasmodium falciparum mono-infections. This non-imposed study was conducted in Gambia and Zambia and compared asymptomatic subjects with parasitaemia dosed according to the approved label of 3-day dosing with 2-day and 1-day dosing. As a consequence, sections 4.2, 4.4, 4.6, 4.8 and 5.1 are updated. The package leaflet is updated in accordance. The RMP (version 17) is also updated accordingly and in line with revision 2.0.1 of the guidance on the format of RMP in the EU (template).

15.3.27. Remdesivir - VEKLURY (CAP) - EMEA/H/C/005622/II/0016

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Eva Jirsová

Scope: Extension of indication to include treatment of adults with pneumonia not requiring supplemental oxygen (moderate coronavirus-19 (COVID-19)) based on: 1) part A of study GS-US-540-5774: a phase 3, randomized, open-label, multicentre study comparing 2 remdesivir (RDV) regimens (5 days and 10 days) versus standard of care in 584 participants with moderate COVID 19; 2) study CO-US-540-5776 (adaptive COVID-19 treatment trial (ACTT)): a National Institute of Allergy and Infectious Diseases (NIAID)-sponsored phase 3, multicentre, adaptive, randomized, double blind, placebo controlled trial on the safety and efficacy study of investigational therapeutics for the treatment of COVID-19. As a consequence, sections 4.1 and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 1.2) are updated in accordance.

15.3.28. Ruxolitinib - JAKAVI (CAP) - EMEA/H/C/002464/II/0053

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Annika Folin

Scope: Extension of indication to include treatment of patients with graft versus host disease (GvHD) aged 12 years and older who have inadequate response to corticosteroids or other systemic therapies. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8. 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 13.0) are updated in

[99] 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)

accordance. In addition, the MAH took the opportunity to update the list of local representatives for the Netherlands in the package leaflet.

15.3.29. Saxagliptin - ONGLYZA (CAP) - EMEA/H/C/001039/WS2098/0053; saxagliptin, metformin hydrochloride - KOMBOGLYZE (CAP) - EMEA/H/C/002059/WS2098/0051

Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: Submission of the final report from study D1680C00016 (MEASURE HF) (listed as a category 3 study in the RMP): a 24-week, multicentre, randomised, double-blind, parallel group, placebo-controlled study to investigate the effects of saxagliptin and sitagliptin on cardiac dimensions and function in patients with type 2 diabetes mellitus (T2DM) and heart failure. The RMP (version 16) is updated accordingly.

15.3.30. Secukinumab - COSENTYX (CAP) - EMEA/H/C/003729/II/0076

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Eva Segovia

Scope: Update of sections 4.2 and 5.1 of the SmPC in order to introduce a new posology regimen for adult plaque psoriasis patients and psoriatic arthritis patients with concomitant moderate to severe plaque psoriasis based on the final results of study CAIN457A2324 (and exposure-response modelling): a randomised, double-blind, multicentre study assessing short (16 weeks) and long-term efficacy (up to 1 year), safety, and tolerability of sub-cutaneous secukinumab in subjects of body weight 90 kg or higher with moderate to severe chronic plaque-type psoriasis. The package leaflet and the RMP (version 9.0) are updated accordingly.

15.3.31. Selexipag - UPTRAVI (CAP) - EMEA/H/C/003774/II/0034

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Nathalie Gault

Scope: Update of section 4.8 of the SmPC to add 'dyspepsia' as a new adverse drug reaction (ADR) and to include further information on the frequency of 'dyspepsia' and 'anaemia' specific to initial 2-step triple combination therapy, based on: 1) study AC-065A308 (TRITON) : a randomised, double-blind, placebo-controlled, parallel-group, phase 3b, efficacy and safety study comparing triple oral combination therapy (selexipag, macitentan, tadalafil) with double oral combination therapy (placebo, macitentan, tadalafil) in newly diagnosed, treatment-naïve participants with pulmonary arterial hypertension (PAH); 2) study AC-065A404 (TRACE): a randomised, double-blind, placebo-controlled, parallel-group, exploratory phase 4 study in participants with PAH to assess the effect of selexipag on daily life physical activity and participant's self-reported symptoms and their impacts. The package leaflet and the RMP (version 9.2) are updated accordingly.

15.3.32. Selinexor - NEXPOVIO (CAP) - EMEA/H/C/005127/II/0001/G

Applicant: Karyopharm Europe GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Grouped variations consisting of: 1) extension of indication for Nexpovio (selinexor) in combination with bortezomib and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least one prior therapy; 2) addition of a new pack size (8 tablets) to align with the dose modification guidance for the new indication. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 6.5 of the SmPC are updated accordingly. Annex II is updated to reflect the completion of the specific obligation. The labelling, package leaflet and RMP (version 1.1) are updated in accordance.

15.3.33. Siponimod - MAYZENT (CAP) - EMEA/H/C/004712/X/0007

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Extension application to add a new strength of 1 mg film-coated tablet. The RMP (version 3.0) is updated in accordance.

15.3.34. Sugammadex - BRIDION (CAP) - EMEA/H/C/000885/II/0042

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Kirsti Villikka

Scope: Update of sections 4.2, 4.8, 5.1 and 5.2 of the SmPC in order to change posology recommendations and update safety, efficacy and pharmacokinetic information in children and adolescents (2-17 years) following P46/025 and based on final results from study P089MK8616: a phase 4 double-blind, randomised, active comparator-controlled clinical trial to study the efficacy, safety and pharmacokinetics of sugammadex (MK-8616) for reversal of neuromuscular blockade in paediatric participants. In addition, the MAH took the opportunity to implement some minor editorial changes throughout the product information. The package leaflet is updated in accordance and the MAH took the opportunity to update the list of local representatives. The RMP (version 7.2) is also updated accordingly and in line with revision 2.0.1 of the guidance on the format of RMP in the EU (template).

15.3.35. Ticagrelor - BRILIQUE (CAP) - EMEA/H/C/001241/II/0049

Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication to include, in co-administration with acetylsalicylic acid (ASA), the prevention of stroke in adult patients with acute ischaemic stroke or transient ischaemic attack (TIA), based on the final results of study D5134C00003 (THALES): a phase 3, international, multicentre, randomised, double-blind, placebo-controlled study to investigate the efficacy and safety of ticagrelor and ASA compared with ASA in the prevention of stroke and death in patients with acute ischaemic stroke or transient ischaemic attack. As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 13.0) are updated in accordance.

15.3.36. Tisagenlecleucel - KYMRIAH (CAP) - EMEA/H/C/004090/II/0044, Orphan

Applicant: Novartis Europharm Limited, ATMP[100]

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include treatment of adult patients with follicular lymphoma (FL) after two or more lines of therapy who are refractory, or relapsed during or within 6 months after completion of anti-CD[101]20 antibody maintenance, or relapsed after autologous haematopoietic stem cell transplantation (HSCT). 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 4.0) are updated accordingly. The MAH took the opportunity to introduce minor editorial corrections throughout the product information to bring in line with the latest quality review of documents (QRD) template (version 10.2). Module 3 is also updated to include the incoming FL material characterisation, final product characterisation and FL batch analyses data.

15.3.37. Tocilizumab - ROACTEMRA (CAP) - EMEA/H/C/000955/II/0101

Applicant: Roche Registration GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include the treatment of coronavirus disease 2019 (COVID-19) in hospitalised adults who are receiving systemic corticosteroids and require supplemental oxygen or mechanical ventilation. As a consequence, sections 4.1, 4.2, 4.3, 4.4, 4.8, 5.1 and 5.2 of the SmPC for RoActemra (tocilizumab) 20 mg/mL concentrate for solution for infusion are updated. The package leaflet and the RMP (version 27.0) are updated in accordance. Furthermore, the product information is brought in line with the latest quality review of documents (QRD) template (version 10.2 Rev. 1).

15.3.38. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/II/0039

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Extension of indication to include treatment of active ankylosing spondylitis for Xeljanz (tofacitinib) prolonged release. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet is updated in accordance. The RMP (version 18.1) is updated accordingly.

15.3.39. Trametinib - MEKINIST (CAP) - EMEA/H/C/002643/II/0051

Applicant: Novartis Europharm Limited

PRAC Rapporteur: David Olsen

Scope: Update of sections 4.2 and 5.2 of the SmPC in order to change posology recommendations in hepatic impairment and update pharmacokinetic information based on final results from study MEC116354 (listed as a category 3 study in the RMP): a phase 1 trial of single agent trametinib (GSK1120212) in advanced cancer patients with hepatic

[100] Advanced therapy medicinal product
[101] Cluster of differentiation

dysfunction. The RMP (version 18) is updated accordingly.

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 below-mentioned medicines 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 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. Abiraterone - ZYTIGA (CAP) - PSUSA/00000015/202104

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

16.1.2. Acalabrutinib - CALQUENCE (CAP) - PSUSA/00010887/202104

Applicant: AstraZeneca AB

PRAC Rapporteur: Željana Margan Koletić

Scope: Evaluation of a PSUSA procedure

16.1.3. Andexanet alfa - ONDEXXYA (CAP) - PSUSA/00010764/202104

Applicant: Alexion Europe SAS

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.4. Avatrombopag - DOPTELET (CAP) - PSUSA/00010779/202105

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

16.1.5. Axicabtagene ciloleucel - YESCARTA (CAP) - PSUSA/00010703/202104

Applicant: Kite Pharma EU B.V. ATMP[102]

[102] Advanced therapy medicinal product

PRAC Rapporteur: Anette Kirstine Stark

16.1.6. Basiliximab - SIMULECT (CAP) - PSUSA/00000301/202104

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.7. Brigatinib - ALUNBRIG (CAP) - PSUSA/00010728/202104

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Evaluation of a PSUSA procedure

16.1.8. Cerliponase alfa - BRINEURA (CAP) - PSUSA/00010596/202104

Applicant: BioMarin International Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.9. Conestat alfa - RUCONEST (CAP) - PSUSA/00000873/202104

Applicant: Pharming Group N.V

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.1.10. Crizanlizumab - ADAKVEO (CAP) - PSUSA/00010888/202105

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Laurence de Fays

Scope: Evaluation of a PSUSA procedure

16.1.11. Ebola Zaire vaccine (live, attenuated) - ERVEBO (CAP) - PSUSA/00010834/202105

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.12. Erenumab - AIMOVIG (CAP) - PSUSA/00010699/202105

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

16.1.13. Epoetin theta - BIOPOIN (CAP); EPORATIO (CAP) - PSUSA/00001240/202104

Applicant(s): ratiopharm GmbH (Eporatio), Teva GmbH (Biopoin)

PRAC Rapporteur: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

16.1.14. Everolimus[103] - AFINITOR (CAP) - PSUSA/00010268/202103

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.15. Everolimus[104] - VOTUBIA (CAP) - PSUSA/00001343/202103

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.16. Febuxostat - ADENURIC (CAP) - PSUSA/00001353/202104

Applicant: Menarini International Operations Luxembourg S.A.

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.1.17. Fenofibrate, pravastatin - PRAVAFENIX (CAP) - PSUSA/00001363/202104

Applicant: Laboratoires SMB s.a.

PRAC Rapporteur: Nathalie Gault

Scope: Evaluation of a PSUSA procedure

16.1.18. Fluticasone furoate - AVAMYS (CAP) - PSUSA/00009154/202104

Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.19. Fostamatinib - TAVLESSE (CAP) - PSUSA/00010819/202104

Applicant: Instituto Grifols, S.A.

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

[103] Indicated for advanced renal cell carcinoma, advanced breast cancer, advanced neuroendocrine tumours (gastrointestinal, lung, pancreatic cancers) (NET)
[104] Indicated for subependymal giant cell astrocytoma (SEGA), renal angiomyolipoma, refractory seizures

16.1.20. Gemtuzumab ozogamicin - MYLOTARG (CAP) - PSUSA/00010688/202105

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Evaluation of a PSUSA procedure

16.1.21. Givosiran - GIVLAARI (CAP) - PSUSA/00010839/202105

Applicant: Alnylam Netherlands B.V.

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.22. Glasdegib - DAURISMO (CAP) - PSUSA/00010859/202105

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.23. Glycopyrronium bromide, formoterol - BEVESPI AEROSPHERE (CAP) - PSUSA/00010739/202104

Applicant: AstraZeneca AB

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.1.24. Hepatitis B surface antigen - HEPLISAV B (CAP) - PSUSA/00010919/202105

Applicant: Dynavax GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.25. Insulin lispro - HUMALOG (CAP); INSULIN LISPRO SANOFI (CAP); LIPROLOG (CAP); LYUMJEV (CAP) - PSUSA/00001755/202104

Applicant(s): Eli Lilly Nederland B.V. (Humalog, Liprolog, Lyumjev), Sanofi-aventis groupe (Insulin lispro Sanofi)

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

16.1.26. Ivacaftor, tezacaftor, elexacaftor - KAFTRIO (CAP) - PSUSA/00010868/202104

Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.27. Lumacaftor, ivacaftor - ORKAMBI (CAP) - PSUSA/00010455/202105

Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

16.1.28. Lumasiran - OXLUMO (CAP) - PSUSA/00010884/202105

Applicant: Alnylam Netherlands B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.29. Ozanimod - ZEPOSIA (CAP) - PSUSA/00010852/202105

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

16.1.30. Padeliporfin - TOOKAD (CAP) - PSUSA/00010654/202105

Applicant: STEBA Biotech S.A

PRAC Rapporteur: Maia Uusküla

Scope: Evaluation of a PSUSA procedure

16.1.31. Pandemic influenza vaccine (H5N1) (live attenuated, nasal) - PANDEMIC INFLUENZA VACCINE H5N1 ASTRAZENECA (CAP) - PSUSA/00010501/202105

Applicant: AstraZeneca AB

PRAC Rapporteur: Sonja Hrabcik

Scope: Evaluation of a PSUSA procedure

16.1.32. Parathyroid hormone - NATPAR (CAP) - PSUSA/00010591/202104

Applicant: Takeda Pharmaceuticals International AG

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

16.1.33. Pemigatinib - PEMAZYRE (CAP) - PSUSA/00010923/202104

Applicant: Incyte Biosciences Distribution B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.34. Prasterone[105] - INTRAROSA (CAP) - PSUSA/00010672/202105

Applicant: Endoceutics S.A.

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.35. Radium (Ra^{223}) dichloride - XOFIGO (CAP) - PSUSA/00010132/202105

Applicant: Bayer AG

PRAC Rapporteur: Rugile Pilviniene

Scope: Evaluation of a PSUSA procedure

16.1.36. Regadenoson - RAPISCAN (CAP) - PSUSA/00002616/202104

Applicant: GE Healthcare AS

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

16.1.37. Remdesivir - VEKLURY (CAP) - PSUSA/00010840/202105

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Eva Jirsová

Scope: Evaluation of a PSUSA procedure

16.1.38. Rurioctocog alfa pegol - ADYNOVI (CAP) - PSUSA/00010663/202105

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.39. Sotagliflozin - ZYNQUISTA (CAP) - PSUSA/00010766/202104

Applicant: Guidehouse Germany GmbH

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.40. Susoctocog alfa - OBIZUR (CAP) - PSUSA/00010458/202105

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

[105] Pessary, vaginal use only

16.1.41. Tafamidis - VYNDAQEL (CAP) - PSUSA/00002842/202105

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

16.1.42. Temsirolimus - TORISEL (CAP) - PSUSA/00002887/202103

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.43. Thiotepa[106] - TEPADINA (CAP); THIOTEPA RIEMSER (CAP) - PSUSA/00002932/202103

Applicant(s): Adienne S.r.l. S.U. (Tepadina), Riemser Pharma GmbH (Thiotepa Riemser)

PRAC Rapporteur: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

16.1.44. Tolvaptan[107] - JINARC (CAP) - PSUSA/00010395/202105

Applicant: Otsuka Pharmaceutical Netherlands B.V.

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.1.45. Tolvaptan[108] - SAMSCA (CAP) - PSUSA/00002994/202105

Applicant: Otsuka Pharmaceutical Netherlands B.V.

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.1.46. Vedolizumab - ENTYVIO (CAP) - PSUSA/00010186/202105

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.47. Volanesorsen - WAYLIVRA (CAP) - PSUSA/00010762/202105

Applicant: Akcea Therapeutics Ireland Limited

PRAC Rapporteur: Martin Huber

[106] Centrally authorised product(s) only
[107] Indicated for adults with autosomal dominant polycystic kidney disease (ADPKD)
[108] Indicated for adults with hyponatraemia secondary to syndrome of inappropriate antidiuretic hormone secretion (SIADH)

Scope: Evaluation of a PSUSA procedure

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

16.2.1. Capecitabine - CAPECITABINE ACCORD (CAP); CAPECITABINE MEDAC (CAP); ECANSYA (CAP); XELODA (CAP); NAP - PSUSA/00000531/202104

Applicants: Accord Healthcare S.L.U. (Capecitabine Accord), KRKA, d.d., Novo mesto (Ecansya), medac Gesellschaft fur klinische Spezialpraparate mbH (Capecitabine medac), Roche Registration GmbH (Xeloda), various

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.2.2. Olopatadine - OPATANOL (CAP); NAP - PSUSA/00002211/202104

Applicants: Novartis Europharm Limited (Opatanol), various

PRAC Rapporteur: Ronan Grimes

Scope: Evaluation of a PSUSA procedure

16.2.3. Tacrolimus[109] - PROTOPIC (CAP); NAP - PSUSA/00002840/202103

Applicants: LEO Pharma A/S (Protopic), various

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

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

16.3.1. Amlodipine besilate, ramipril (NAP); amlodipine, hydrochlorothiazide, ramipril (NAP); hydrochlorothiazide, ramipril (NAP) - PSUSA/00010774/202103

Applicant(s): various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.3.2. Argipressin (NAP) - PSUSA/00010749/202103

Applicant(s): various

PRAC Lead: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

16.3.3. Bacterial lysate of haemophilus influenzae, klebsiella pneumoniae, moraxella catarrhalis, staphylococcus aureus, streptococcus mitis, streptococcus pneumoniae,

[109] Topical formulation(s) only

streptococcus pyogenes (NAP); bacterial lysate of haemophilus influenzae, klebsiella pneumoniae, moraxella catarrhalis, staphylococcus aureus, streptococcus pneumoniae, streptococcus pyogenes (NAP); streptococcus pneumoniae, streptococcus agalactiae, staphylococcus aureus, haemophilus influenzae (NAP) - PSUSA/00002786/202103

Applicant(s): various

PRAC Lead: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.3.4. Budesonide[110] (NAP) - PSUSA/00000449/202104

Applicant(s): various

PRAC Lead: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

16.3.5. Captopril, hydrochlorothiazide (NAP) - PSUSA/00000536/202104

Applicant(s): various

PRAC Lead: Nathalie Gault

Scope: Evaluation of a PSUSA procedure

16.3.6. Carmustine[111] (NAP) - PSUSA/00010349/202104

Applicant(s): various

PRAC Lead: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

16.3.7. Cytarabine (NAP) - PSUSA/00000911/202103

Applicant(s): various

PRAC Lead: Melinda Palfi

Scope: Evaluation of a PSUSA procedure

16.3.8. Deoxycholic acid (NAP) - PSUSA/00010525/202104

Applicant(s): various

PRAC Lead: Annika Folin

Scope: Evaluation of a PSUSA procedure

16.3.9. Dexamethasone, netilmicin (NAP) - PSUSA/00010854/202104

Applicant(s): various

[110] Nationally authorised product(s) only
[111] Powder and solvent for solution for infusion only

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.3.10. Dexamethasone, tobramycin[112] (NAP) - PSUSA/00000979/202103

Applicant(s): various

PRAC Lead: Ilaria Baldelli

Scope: Evaluation of a PSUSA procedure

16.3.11. Dihydroergotamine (NAP) - PSUSA/00001075/202104

Applicant(s): various

PRAC Lead: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.3.12. Docosanol (NAP) - PSUSA/00010092/202104

Applicant(s): various

PRAC Lead: Nikica Mirošević Skvrce

Scope: Evaluation of a PSUSA procedure

16.3.13. Human anti-d immunoglobulin (NAP) - PSUSA/00001614/202103

Applicant(s): various

PRAC Lead: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.3.14. Human prothrombin complex (NAP) - PSUSA/00001638/202104

Applicant(s): various

PRAC Lead: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.3.15. Ivermectin[113] (NAP) - PSUSA/00010376/202104

Applicant(s): various

PRAC Lead: Nathalie Gault

Scope: Evaluation of a PSUSA procedure

16.3.16. Metformin (NAP) - PSUSA/00002001/202104

Applicant(s): various

[112] Ophthalmic and otic use only
[113] For topical use only

PRAC Lead: Nathalie Gault

Scope: Evaluation of a PSUSA procedure

16.3.17. Methoxyflurane (NAP) - PSUSA/00010484/202105

Applicant(s): various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.3.18. Nitrendipine (NAP) - PSUSA/00002171/202103

Applicant(s): various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.3.19. Ofloxacin[114] (NAP) - PSUSA/00002204/202104

Applicant(s): various

PRAC Lead: Nikica Mirošević Skvrce

Scope: Evaluation of a PSUSA procedure

16.3.20. Oxaliplatin (NAP) - PSUSA/00002229/202104

Applicant(s): various

PRAC Lead: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

16.3.21. Ozenoxacin (NAP) - PSUSA/00010651/202105

Applicant(s): various

PRAC Lead: Eva Segovia

Scope: Evaluation of a PSUSA procedure

16.3.22. Pholcodine, biclotymol, chlorphenamine maleate (NAP) - PSUSA/00010437/202104

Applicant(s): various

PRAC Lead: Rugilė Pilvinienė

Scope: Evaluation of a PSUSA procedure

16.3.23. Plasma protein fraction (NAP) - PSUSA/00002449/202104

Applicant(s): various

[114] For topical use only

PRAC Lead: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.3.24. Risedronate (NAP) - PSUSA/00002648/202103

Applicant(s): various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.3.25. Tafluprost (NAP) - PSUSA/00002843/202104

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.3.26. Tobramycin[115] (NAP) - PSUSA/00009317/202103

Applicant(s): various

PRAC Lead: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Evaluation of a PSUSA procedure

16.3.27. Triamcinolone[116] (NAP) - PSUSA/00010292/202103

Applicant(s): various

PRAC Lead: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Evaluation of a PSUSA procedure

16.3.28. Valganciclovir (NAP) - PSUSA/00003089/202103

Applicant(s): various

PRAC Lead: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

16.4. Follow-up to PSUR/PSUSA procedures

16.4.1. Arsenic trioxide - TRISENOX (CAP) - EMEA/H/C/000388/LEG 051

Applicant: Teva B.V.

PRAC Rapporteur: Tiphaine Vaillant

Scope: Cumulative review including all available data of cases of paresis, bone marrow necrosis, deafness, melanoma, pancreatic cancer, squamous cell carcinoma and toxic epidermal necrolysis following the addition of these adverse drug reactions (ADRs) in the

[115] Ophthalmic and otic use only
[116] Intraocular formulation(s) only

US product information at the FDA's request, as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00000235/202009) adopted in June 2021.

16.4.2. Leflunomide - ARAVA (CAP) - EMEA/H/C/000235/LEG 058.1

Applicant: Sanofi-Aventis Deutschland GmbH

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: MAH's response to LEG 058 [cumulative review of cases of skin ulcer in line with the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00001837/202009) adopted in May 2021] as per the request for supplementary information (RSI) adopted in October 2021.

16.4.3. Tolvaptan - JINARC (CAP) - EMEA/H/C/002788/LEG 008.1

Applicant: Otsuka Pharmaceutical Netherlands B.V.

PRAC Rapporteur: Amelia Cupelli

Scope: MAH's response to LEG 008 [review of cases of rapid correction of hyponatremia and neurological sequelae as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00010395/202005) adopted in January 2021] as per the request for supplementary information (RSI) adopted in June 2021.

16.5. Variation procedure(s) resulting from PSUSA evaluation

16.5.1. Arsenic trioxide - TRISENOX (CAP) - EMEA/H/C/000388/II/0076

Applicant: Teva B.V.

PRAC Rapporteur: Tiphaine Vaillant

Scope: Update of section 4.6 of the SmPC in order to update information on pregnancy and contraception in male patients as requested in the conclusions of the last PSUR single assessment (PSUSA) procedure (PSUSA/00000235/202009) adopted in June 2021. The package leaflet is updated accordingly.

16.6. Expedited summary safety reviews[117]

None

17. Annex I – Post-authorisation safety studies (PASS)

Based on the assessment of the following PASS protocol(s), result(s), interim result(s) or feasibility study(ies), and following endorsement of the comments received, PRAC adopted the conclusion of the Rapporteurs on their assessment for the medicines listed below without further plenary discussion.

[117] 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

17.1. Protocols of PASS imposed in the marketing authorisation(s)[118]

None

17.2. Protocols of PASS non-imposed in the marketing authorisation(s)[119]

17.2.1. Autologous peripheral blood T cells CD[120]4 and CD8 selected and CD3 and CD28 activated transduced with retroviral vector expressing anti-CD19 CD28/CD3-zeta chimeric antigen receptor and cultured - TECARTUS (CAP) - EMEA/H/C/005102/MEA 005.1

Applicant: Kite Pharma EU B.V., ATMP[121]

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to MEA 005 [protocol for study KT-EU-472-5966: a prescriber survey to assess prescribers' understanding of the risks of Tecartus (KTE-X19) to evaluate the effectiveness of risk minimisation activities, namely healthcare professional (HCP) educational materials and patient alert card (PAC) [final study report expected in September 2023] (from initial opinion/marketing authorisation(s) (MA))] as per the request for supplementary information (RSI) adopted in July 2021.

17.2.2. Beclometasone, formoterol, glycopyrronium bromide - TRIMBOW (CAP) - EMEA/H/C/004257/MEA 002.1

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Jan Neuhauser

Scope: MAH's response to MEA 002 [protocol for study CLI-05993BA1-05 (TRIBE): a multinational database cohort study to assess adverse cardiovascular and cerebrovascular outcomes in patients with chronic obstructive pulmonary disease initiating a fixed triple therapy containing beclometasone dipropionate, formoterol fumarate and glycopyrronium administered via dry powder inhaler (DPI) compared to pressurised metered dose inhaler (pMDI)] as per the request for supplementary information (RSI) adopted in July 2021.

17.2.3. Berotralstat - ORLADEYO (CAP) - EMEA/H/C/005138/MEA 002.1

Applicant: BioCryst Ireland Limited

PRAC Rapporteur: Julia Pallos

Scope: MAH's response to MEA 002 [protocol for study BCX7353-401: a non-interventional post-authorisation study to evaluate safety, tolerability and effectiveness of berotralstat for patients with hereditary angioedema in a real-world setting (from initial opinion/marketing authorisation (MA))] as per the request for supplementary information (RSI) adopted in October 2021.

[118] In accordance with Article 107n of Directive 2001/83/EC
[119] 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
[120] Cluster of differentiation
[121] Advanced therapy medicinal product

17.2.4. Canagliflozin - INVOKANA (CAP) - EMEA/H/C/002649/MEA 009.4

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Martin Huber

Scope: MAH's response to MEA 009.3 [amended protocol for a drug utilisation study (DUS) to evaluate the drug utilisation patterns of canagliflozin-containing medicines including off-label usage in type 1 diabetes mellitus (T1DM) and the risk of diabetic ketoacidosis (DKA) using EU databases on market uptake and exposure within the European Union] as per the request for supplementary information (RSI) adopted in July 2021.

17.2.5. Canagliflozin, metformin - VOKANAMET (CAP) - EMEA/H/C/002656/MEA 008.4

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to MEA 008.3 [amended protocol for a drug utilisation study (DUS) to evaluate the drug utilisation patterns of canagliflozin-containing medicines including off-label usage in type 1 diabetes mellitus (T1DM) and the risk of diabetic ketoacidosis (DKA) using EU databases on market uptake and exposure within the European Union] as per the request for supplementary information (RSI) adopted in July 2021.

17.2.6. Coronavirus (COVID-19) vaccine (Ad26.COV2-S, recombinant) - COVID-19 VACCINE JANSSEN (CAP) - EMEA/H/C/005737/MEA 008.1

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: MAH's response to MEA 008 [protocol for study VAC31518COV4003 (listed as a category 3 study in the RMP): a post-authorisation, observational study to assess the safety of Ad26.COV2.S using electronic health record (EHR) database(s) in Europe (from initial opinion/marketing authorisation(s) (MA))] as per the request for supplementary information (RSI) adopted in July 2021.

17.2.7. Coronavirus (COVID-19) vaccine (Ad26.COV2-S, recombinant) - COVID-19 VACCINE JANSSEN (CAP) - EMEA/H/C/005737/MEA 010.1

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: MAH's response to MEA 010 [protocol for study VAC31518COV4001 (listed as a category 3 study in the RMP): a post-authorisation, observational study to assess the safety of Ad26.COV2.S (COVID-19 Vaccine Janssen) using health insurance claims and/or electronic health record (EHR) database(s) in the United States [final study report expected in December 2024]] as per the request for supplementary information (RSI) adopted in October 2021.

17.2.8. Crizanlizumab - ADAKVEO (CAP) - EMEA/H/C/004874/MEA 004

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Laurence de Fays

Scope: Protocol for study CSEG101A2405 (listed as a category 3 study in the RMP): a non-interventional PASS - Registry-based study to assess long-term safety and pregnancy outcomes in patients with Sickle cell disease (SCD) using crizanlizumab.

17.2.9. Fentanyl - INSTANYL (CAP) - EMEA/H/C/000959/MEA 029.2

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Tiphaine Vaillant

Scope: Updated protocol for study Instanyl-5002 (listed as a category 3 study in the RMP): a non-interventional study to assess the effectiveness of updated educational materials on prescribers' knowledge and behaviour with respect to risks associated with Instanyl (fentanyl) off-label use [final clinical study report (CSR) expected in Q3 2023].

17.2.10. Filgotinib - JYSELECA (CAP) - EMEA/H/C/005113/MEA 003.1

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: MAH's response to MEA 003 [protocol for study GS-EU-417-9047: a non-interventional PASS of filgotinib in the treatment of patients with moderate to severe active rheumatoid arthritis within the Anti-Rheumatic Treatment in Sweden (ARTIS) register [final report expected in Q2 2030]] as per the request for supplementary information (RSI) adopted in June 2021.

17.2.11. Infliximab - REMSIMA (CAP) - EMEA/H/C/002576/MEA 020.4

Applicant: Celltrion Healthcare Hungary Kft.

PRAC Rapporteur: Kimmo Jaakkola

Scope: MAH's response to MEA 020.3 [protocol for study CT-P13 4.8: an observational, prospective cohort study to evaluate the safety of Remsima (infliximab) subcutaneous in patients with rheumatoid arthritis (RA)] as per the request for supplementary information (RSI) adopted in June 2021.

17.2.12. Lutetium (^{177}Lu) oxodotreotide - LUTATHERA (CAP) - EMEA/H/C/004123/MEA 001.8

Applicant: Advanced Accelerator Applications

PRAC Rapporteur: Adam Przybylkowski

Scope: Substantial amendment to a protocol previously agreed in September 2018 for study A-LUT-T-E02-402 (SALUS study) (listed as a category 3 study in the RMP):: an international, non-interventional, post-authorisation long-term safety study of Lutathera (lutetium (^{177}Lu) oxodotreotide) in patients with unresectable or metastatic, well-differentiated, somatostatin receptor positive, gastro-enteropancreatic neuroendocrine tumours, together with the third quarterly progress report for study A-LUT-T-E02-402.

17.2.13. Ofatumumab - KESIMPTA (CAP) - EMEA/H/C/005410/MEA 002

Applicant: Novartis Ireland Limited

PRAC Rapporteur: Amelia Cupelli

Scope: Protocol for study OMB157G2407 (listed as category 3 study in the RMP): pregnancy outcomes intensive monitoring (PRIM) to evaluate pregnancy and infant outcomes in patients taking Kesimpta (ofatumumab).

17.2.14. Ponesimod - PONVORY (CAP) - EMEA/H/C/005163/MEA 004

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Anette Kirstine Stark

Scope: Protocol for study PCSNSP003693 (listed as a category 3 study in the RMP): a survey among healthcare professionals (neurologists treating patients with multiple sclerosis (MS) along with MS specialist nurses) in selected European countries to evaluate knowledge and behaviours required for the safe use of ponesimod.

17.2.15. Satralizumab - ENSPRYNG (CAP) - EMEA/H/C/004788/MEA 002

Applicant: Roche Registration GmbH

PRAC Rapporteur: Jan Neuhauser

Scope: Protocol for study WN42856: a global observational 10-year single arm prospective study to assess the frequency of maternal, foetal, and infant adverse outcomes among women with neuromyelitis optica spectrum disorder (NMOSD) exposed to satralizumab during the 6 months prior to the last menstrual period or at any time during pregnancy (from initial opinion/marketing authorisation(s) (MA)).

17.2.16. Selexipag - UPTRAVI (CAP) - EMEA/H/C/003774/MEA 003.4

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Nathalie Gault

Scope: MAH's response to MEA 003.3 [amendment to a protocol previously agreed in May 2017 for study AC-065A403: a PASS to evaluate risk minimisation measures for mEDication errors with Uptravi (selexipag) during the titration phase in patients with pulmonary arterial hypertension (PAH) in Clinical prAcTicE (EDUCATE)] as per the request for supplementary information (RSI) adopted in June 2021.

17.2.17. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/MEA 008.4

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Updated protocol for study A3921312 (listed as a category 3 study in the RMP): a prospective non-interventional comparative active surveillance PASS of serious infection, malignancy, cardiovascular and other safety events of interest among patients treated with tofacitinib for moderately to severely active rheumatoid arthritis (RA) within the British

Society for Rheumatology Biologics Register-Rheumatoid Arthritis (BSRBR-RA) following on the recommendation of the signal on major adverse cardiovascular events (MACE) and malignancies excluding non-melanoma skin cancer (NMSC) (EPITT 19382) finalised in June 2021.

17.2.18. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/MEA 009.4

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Updated protocol for study A3921314 (listed as a category 3 study in the RMP): a prospective non-interventional comparative active surveillance PASS of serious infection, malignancy, cardiovascular and other safety events of interest among patients treated with tofacitinib for moderately to severely active rheumatoid arthritis (RA) within the Swedish (ARTIS) register following on the recommendation of the signal on major adverse cardiovascular events (MACE) and malignancies excluding non-melanoma skin cancer (NMSC) (EPITT 19382) finalised in June 2021.

17.2.19. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/MEA 010.4

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Updated protocol for study A3921316 (listed as a category 3 study in the RMP): a prospective non-interventional comparative active surveillance PASS of serious infection, malignancy, cardiovascular and other safety events of interest among patients treated with Xeljanz (tofacitinib) for moderately to severely active rheumatoid arthritis (RA) within the Spanish registry of adverse events of biological therapies and biosimilars in rheumatoid diseases (BIOBADASER) following on the recommendation of the signal on major adverse cardiovascular events (MACE) and malignancies excluding non-melanoma skin cancer (NMSC) (EPITT 19382) finalised in June 2021.

17.2.20. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/MEA 011.4

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

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

17.2.21. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/MEA 013.3

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: MAH's response to MEA 013.2 [protocol for study A3921344 (listed as a 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 (UC) in the real-world setting using data from the Swedish Quality Register for Inflammatory Bowel Disease (SWIBREG) registry] as per the request for supplementary information (RSI) adopted in February 2021 and based on the recommendation of the signal on major adverse cardiovascular events (MACE) and malignancies excluding non-melanoma skin cancer (NMSC) (EPITT 19382) finalised in June 2021.

17.2.22. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/MEA 014.4

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: MAH's response to MEA 014.3 [protocol for study A3921321: a drug utilisation study (DUS) on the utilisation and prescribing patterns of Xeljanz (tofacitinib) in two European countries using administrative claims databases and national registries for assessment, as requested in the conclusions of the referral procedure under Article 20 of Regulation (EC) No 726/2004 (EMEA/H/A-20/1485) finalised in November 2019] as per the request for supplementary information (RSI) adopted in July 2021.

17.2.23. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/MEA 047.3

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Rhea Fitzgerald

Scope: MAH's response to MEA 047.2 [protocol for study SWIBREG-UST UC: an observational PASS to describe the safety of ustekinumab and other ulcerative colitis treatments in a cohort of patients with ulcerative colitis using the Swedish Inflammatory Bowel Disease Register (SWIBREG) as requested in the conclusions of variation II/071 finalised in July 2019 [final clinical study report (CSR) expected in May 2027]] as per the request for supplementary information (RSI) adopted in July 2021.

17.2.24. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/MEA 048.3

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Rhea Fitzgerald

Scope: MAH's response to MEA 048.2 [protocol for study SNDS-UST UC: an observational PASS to describe the safety of ustekinumab and other ulcerative colitis treatments in a cohort of patients with ulcerative colitis using the French administrative healthcare database (SNDS) as requested in the conclusions of variation II/071 finalised in July 2019 [final clinical study report (CSR) expected in May 2027]] as per the request for supplementary information (RSI) adopted in July 2021.

17.2.25. Vosoritide - VOXZOGO (CAP) - EMEA/H/C/005475/MEA 005

Applicant: BioMarin International Limited

PRAC Rapporteur: Zane Neikena

Scope: Protocol for study 111-603: a multicentre, non-interventional study to evaluate long-term safety in patients with achondroplasia treated with Voxzogo (vosoritide) (from initial opinion/marketing authorisation(s) (MA)).

17.3. Results of PASS imposed in the marketing authorisation(s)[122]

None

17.4. Results of PASS non-imposed in the marketing authorisation(s)[123]

17.4.1. Daunorubicin, cytarabine - VYXEOS LIPOSOMAL (CAP) - EMEA/H/C/004282/II/0017, Orphan

Applicant: Jazz Pharmaceuticals Ireland Limited

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Submission of the final clinical study report (CSR) for a post-marketing observational study to assess the nature, incidence and severity of infusion-related reactions in adult patients treated with Vyxeos liposomal (daunorubicin/cytarabine).

17.4.2. Denosumab - PROLIA (CAP) - EMEA/H/C/001120/II/0092

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of the final report for study 20190038 (listed as a category 3 study in the RMP): an observational retrospective cohort study assessing the incidence of cardiovascular and cerebrovascular events among postmenopausal women and men with osteoporosis who initiated treatment with denosumab or zoledronic acid.

17.4.3. Emicizumab - HEMLIBRA (CAP) - EMEA/H/C/004406/II/0028

Applicant: Roche Registration GmbH

PRAC Rapporteur: Amelia Cupelli

Scope: Submission of the final study report for BO40853 (listed as a category 3 study in the RMP): a survey to prescribers and patients/carers to evaluate awareness, knowledge, and compliance to additional risk minimisation measures. The RMP (version 4.0) is updated accordingly.

17.4.4. Influenza vaccine surface antigen inactivated prepared in cell cultures - FLUCELVAX TETRA (CAP) - EMEA/H/C/004814/II/0023

Applicant: Seqirus Netherlands B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of section 4.6 of the SmPC in order to update information on pregnancy registry 130_110B (listed as a category 3 study in the RMP) on use in pregnant and

[122] In accordance with Article 107p-q of Directive 2001/83/EC
[123] In accordance with Article 61a (6) of Regulation (EC) No 726/2004, in line with the revised variations regulation for any submission as of 04 August 2013

breastfeeding women to evaluate pregnancy outcomes. The package leaflet and the RMP (version 3.1) are updated accordingly.

17.4.5. Loxapine - ADASUVE (CAP) - EMEA/H/C/002400/II/0033

Applicant: Ferrer Internacional s.a.

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Update of sections 4.2, 4.4 and 4.8 of the SmPC in order to update safety information on bronchospasm based on final results from study AMDC-204-401 EU PASS (listed as a category 3 study in the RMP): a post-authorisation observational study to evaluate the safety of Adasuve (loxapine for inhalation) in agitated persons in routine clinical care (assessed in variation II/0032 finalised in May 2021). The package leaflet and labelling are updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet.

17.4.6. Teriflunomide - AUBAGIO (CAP) - EMEA/H/C/002514/II/0038

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Martin Huber

Scope: Submission of the final study report for study OBS12753 (listed as a category 3 study in the RMP): a prospective cohort study of long-term safety of teriflunomide in multiple sclerosis patients in Europe. The RMP (version 7.1) is updated accordingly.

17.4.7. Velaglucerase alfa - VPRIV (CAP) - EMEA/H/C/001249/II/0049, Orphan

Applicant: Takeda Pharmaceuticals International AG

PRAC Rapporteur: Martin Huber

Scope Submission of final physician data study results for study EUPASS 14255: an evaluation of the effectiveness of risk minimisation measures - a survey among healthcare professionals (HCPs) and patient/caregivers to assess their knowledge and attitudes on prescribing and home administration conditions of velaglucerase alfa (Vpriv) in 6 European countries.

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

17.5.1. Ataluren - TRANSLARNA (CAP) - EMEA/H/C/002720/MEA 002.8

Applicant: PTC Therapeutics International Limited

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: MAH's response to MEA 002.7 [five-year interim report for study PTC124-GD-0250-DMD (listed as a category 3 study in the RMP): a post-approval registry observational study exploring the long-term of ataluren safety and effectiveness in usual care setting [final clinical study report (CSR) expected in April 2023]] as per the request for supplementary information (RSI) adopted in July 2021.

17.5.2. Axicabtagene ciloleucel - YESCARTA (CAP) - EMEA/H/C/004480/ANX 002.2

Applicant: Kite Pharma EU B.V., ATMP[124]

PRAC Rapporteur: Anette Kirstine Stark

Scope: First annual interim report for study KT-EU-471-0117: a long-term, non-interventional study of recipients of Yescarta (axicabtagene ciloleucel) to evaluate the incidence rate and severity of adverse drug reactions (ADRs) and further evaluate and characterise the identified risks, potential risks and missing information (EU PAS EUPAS32539).

17.5.3. Benralizumab - FASENRA (CAP) - EMEA/H/C/004433/MEA 004.4

Applicant: AstraZeneca AB

PRAC Rapporteur: David Olsen

Scope: First interim report for study D3250R00042: a descriptive study of the incidence of malignancy in patients with severe asthma overall and among those receiving benralizumab and other therapies in real-world settings.

17.5.4. Nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/MEA 008.9

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Fifth 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].

17.5.5. Semaglutide - OZEMPIC (CAP) - EMEA/H/C/004174/MEA 002.4

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Annika Folin

Scope: Second study progress report for study NN9535-4447: an epidemiological database study to estimate the risk of pancreatic cancer in patients with type 2 diabetes mellitus (T2DM) taking semaglutide - a cohort study based on Nordic registry data [final clinical study report (CSR) expected in Q3 2025].

17.5.6. Semaglutide - RYBELSUS (CAP) - EMEA/H/C/004953/MEA 002.2

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Annika Folin

Scope: First study progress report for study NN9535-4447: an epidemiological database study to estimate the risk of pancreatic cancer in patients with type 2 diabetes mellitus (T2DM) taking semaglutide - a cohort study based on Nordic registry data [final clinical study report (CSR) expected in Q3 2025].

[124] Advanced therapy medicinal product

17.6. Others

17.6.1. Alemtuzumab - LEMTRADA (CAP) - EMEA/H/C/003718/ANX 010.1

Applicant: Sanofi Belgium

PRAC Rapporteur: Anette Kirstine Stark

Scope: Feasibility report for a drug utilisation study (DUS) to assess compliance with the therapeutic indication and effectiveness of measures to minimise the risk of cardiovascular and cerebrovascular adverse events in close temporal association with Lemtrada (alemtuzumab) infusion and immune-mediated adverse reactions, as requested in the conclusions of the referral procedure under Article 20 of Regulation (EC) No 726/2004 (EMEA/H/A-20/1483) finalised in 2019.

17.6.2. Natalizumab - TYSABRI (CAP) - EMEA/H/C/000603/MEA 071

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Feasibility assessment 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 (from X/0116).

17.7. New Scientific Advice

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

17.8. Ongoing Scientific Advice

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

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

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

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

Based on the review of the available pharmacovigilance data for the medicines 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 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/0056 (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/0035 (without RMP)

Applicant: BioMarin International Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Annual reassessment of the marketing authorisation

18.1.3. Lomitapide - LOJUXTA (CAP) - EMEA/H/C/002578/S/0048 (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/0070 (without RMP)

Applicant: Ipsen Pharma

PRAC Rapporteur: Kirsti Villikka

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) - COVID-19 VACCINE JANSSEN (CAP) - EMEA/H/C/005737/R/0023 (without RMP)

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Conditional renewal of the marketing authorisation

18.2.2. Bosutinib - BOSULIF (CAP) - EMEA/H/C/002373/R/0051 (without RMP)

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Martin Huber

Scope: Conditional renewal of the marketing authorisation

18.2.3. Delamanid - DELTYBA (CAP) - EMEA/H/C/002552/R/0052 (without RMP)

Applicant: Otsuka Novel Products GmbH

PRAC Rapporteur: Laurence de Fays

Scope: Conditional renewal of the marketing authorisation

18.2.4. Dostarlimab - JEMPERLI (CAP) - EMEA/H/C/005204/R/0004 (without RMP)

Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Conditional renewal of the marketing authorisation

18.2.5. Parathyroid hormone - NATPAR (CAP) - EMEA/H/C/003861/R/0034 (without RMP)

Applicant: Takeda Pharmaceuticals International AG

PRAC Rapporteur: Rhea Fitzgerald

Scope: Conditional renewal of the marketing authorisation

18.2.6. Pemigatinib - PEMAZYRE (CAP) - EMEA/H/C/005266/R/0003 (without RMP)

Applicant: Incyte Biosciences Distribution B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Conditional renewal of the marketing authorisation

18.2.7. Volanesorsen - WAYLIVRA (CAP) - EMEA/H/C/004538/R/0016 (without RMP)

Applicant: Akcea Therapeutics Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: Conditional renewal of the marketing authorisation

18.3. Renewals of the marketing authorisation

18.3.1. Beclometasone, formoterol, glycopyrronium bromide - TRIMBOW (CAP) - EMEA/H/C/004257/R/0025 (without RMP)

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Jan Neuhauser

Scope: 5-year renewal of the marketing authorisation

18.3.2. Ceritinib - ZYKADIA (CAP) - EMEA/H/C/003819/R/0042 (with RMP)

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Annika Folin

Scope: 5-year renewal of the marketing authorisation

18.3.3. Dimethyl fumarate - SKILARENCE (CAP) - EMEA/H/C/002157/R/0030 (with RMP)

Applicant: Almirall S.A

PRAC Rapporteur: Annika Folin

Scope: 5-year renewal of the marketing authorisation

18.3.4. Febuxostat - FEBUXOSTAT MYLAN (CAP) - EMEA/H/C/004374/R/0011 (without RMP)

Applicant: Mylan Pharmaceuticals Limited

PRAC Rapporteur: Jan Neuhauser

Scope: 5-year renewal of the marketing authorisation

18.3.5. Fluciclovine (^{18}F) - AXUMIN (CAP) - EMEA/H/C/004197/R/0027 (without RMP)

Applicant: Blue Earth Diagnostics Ireland Limited

PRAC Rapporteur: Rugile Pilviniene

Scope: 5-year renewal of the marketing authorisation

18.3.6. Inotuzumab ozogamicin - BESPONSA (CAP) - EMEA/H/C/004119/R/0023 (without RMP)

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: 5-year renewal of the marketing authorisation

18.3.7. Ivabradine - IVABRADINE ACCORD (CAP) - EMEA/H/C/004241/R/0010 (with RMP)

Applicant: Accord Healthcare S.L.U.

PRAC Rapporteur: Menno van der Elst

Scope: 5-year renewal of the marketing authorisation

18.3.8. Ivacaftor - KALYDECO (CAP) - EMEA/H/C/002494/R/0106 (without RMP)

Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Maria del Pilar Rayon

Scope: 5-year renewal of the marketing authorisation

18.3.9. Nonacog beta pegol - REFIXIA (CAP) - EMEA/H/C/004178/R/0025 (with RMP)

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: 5-year renewal of the marketing authorisation

18.3.10. Patiromer - VELTASSA (CAP) - EMEA/H/C/004180/R/0028 (without RMP)

Applicant: Vifor Fresenius Medical Care Renal Pharma France

PRAC Rapporteur: Kirsti Villikka

Scope: 5-year renewal of the marketing authorisation

18.3.11. Rituximab - RIXATHON (CAP) - EMEA/H/C/003903/R/0053 (without RMP)

Applicant: Sandoz GmbH

PRAC Rapporteur: Anette Kirstine Stark

Scope: 5-year renewal of the marketing authorisation

18.3.12. Rituximab - RIXIMYO (CAP) - EMEA/H/C/004729/R/0054 (without RMP)

Applicant: Sandoz GmbH

PRAC Rapporteur: Anette Kirstine Stark

Scope: 5-year renewal of the marketing authorisation

18.3.13. Sarilumab - KEVZARA (CAP) - EMEA/H/C/004254/R/0029 (with RMP)

Applicant: sanofi-aventis groupe

PRAC Rapporteur: Eva Segovia

Scope: 5-year renewal of the marketing authorisation

18.3.14. Spheroids of human autologous matrix-associated chondrocytes - SPHEROX (CAP) - EMEA/H/C/002736/R/0024 (with RMP)

Applicant: CO.DON AG, ATMP[125]

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: 5-year renewal of the marketing authorisation

18.3.15. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/R/0040 (without RMP)

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

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 plenary meeting held 29 November – 02 December 2021 (marked as "a"), and for the 'Extraordinary PRAC – ORGAM meeting held

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13 December 2021 (marked as "b").

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Sabine Straus [a, b]	Chair	Netherlands	No interests declared	Full involvement
Jan Neuhauser [a, b]	Member	Austria	No interests declared	Full involvement
Sonja Hrabcik [a]	Alternate	Austria	No interests declared	Full involvement
Jean-Michel Dogné [a]	Member	Belgium	No interests declared	Full involvement
Laurence de Fays [a, b]	Alternate	Belgium	No interests declared	Full involvement
Maria Popova-Kiradjieva [a, b]	Member	Bulgaria	No interests declared	Full involvement
Nikica Mirošević Skvrce [a, b]	Member	Croatia	No interests declared	Full involvement
Željana Margan Koletić [a]	Alternate	Croatia	No interests declared	Full involvement
Elena Kaisis [a, b]	Member	Cyprus	No interests declared	Full involvement
Panagiotis Psaras [a, b]	Alternate	Cyprus	No interests declared	Full involvement
Eva Jirsová [a]	Member	Czechia	No interests declared	Full involvement
Jana Lukacisinová [a, b]	Alternate	Czechia	No interests declared	Full involvement
Anette Kirstine Stark [a]	Member	Denmark	No interests declared	Full involvement
Hans Christian Siersted [a, b]	Alternate	Denmark	No participation in discussion, final deliberations and voting on:	15.3.20. Mepolizumab - NUCALA (CAP) - EMEA/H/C/003860/X/0042
Maia Uusküla [a, b]	Member	Estonia	No interests declared	Full involvement
Krõõt Aab [a, b]	Alternate	Estonia	No interests declared	Full involvement
Kirsti Villikka [a, b]	Member	Finland	No interests declared	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Kimmo Jaakkola [a, b]	Alternate	Finland	No interests declared	Full involvement
Tiphaine Vaillant [a, b]	Member	France	No interests declared	Full involvement
Nathalie Gault [a, b]	Alternate	France	No interests declared	Full involvement
Martin Huber [a, b]	Member (Vice-Chair)	Germany	No interests declared	Full involvement
Brigitte Keller-Stanislawski [a, b]	Alternate	Germany	No interests declared	Full involvement
Sofia Trantza [a, b]	Alternate	Greece	No interest declared	Full involvement
Melinda Palfi [a, b]	Member	Hungary	No interests declared	Full involvement
Julia Pallos [a, b]	Alternate	Hungary	No participation in final deliberations and voting on:	4.3.2. Olmesartan (NAP); olmesartan, amlodipine (NAP); olmesartan, hydrochlorothiazide (NAP); olmesartan medoxomil, amlodipine besilate, hydrochlorothiazide (NAP) 16.3.6. Metformin (NAP) - PSUSA/00002001/202104
Guðrún Stefánsdóttir [a]	Member	Iceland	No participation in discussions, final deliberations and voting on:	7.4.3. Pegfilgrastim - NEULASTA (CAP) - EMEA/H/C/000420/II/0116 15.2.4. Denosumab - PROLIA (CAP) - EMEA/H/C/001120/II/0091/G 17.4.2. Denosumab - PROLIA (CAP) - EMEA/H/C/001120/II/0092
Ronan Grimes [a, b]	Alternate	Ireland	No interests declared	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Amelia Cupelli [a, b]	Member	Italy	No interests declared	Full involvement
Ilaria Baldelli [a, b]	Alternate	Italy	No interests declared	Full involvement
Zane Neikena [a, b]	Member	Latvia	No interests declared	Full involvement
Rugile Pilviniene [a, b]	Member	Lithuania	No interests declared	Full involvement
Nadine Petitpain [a]	Member	Luxembourg	No participation in final deliberations and voting on:	6.3.12. Pholcodine (NAP) - PSUSA/0002396/202105 16.3.22. Pholcodine, biclotymol, chlorphenamine maleate (NAP) - PSUSA/00010437/202104
Anne-Cécile Vuillemin [a, b]	Alternate	Luxembourg	No interests declared	Full involvement
John Joseph Borg [a, b]	Member	Malta	No interests declared	Full involvement
Menno van der Elst [a]	Member	Netherlands	No interests declared	Full involvement
Liana Gross-Martirosyan [a, b]	Alternate	Netherlands	No interests declared	Full involvement
David Olsen [a, b]	Member	Norway	No participation in final deliberations and voting on:	4.3.2. Olmesartan (NAP); olmesartan, amlodipine (NAP); olmesartan, hydrochlorothiazide (NAP); olmesartan medoxomil, amlodipine besilate, hydrochlorothiazide (NAP) 6.3.1. Chloroquine (NAP) - PSUSA/00000685/202104 6.3.13. Praziquantel (NAP) -

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				PSUSA/00002503/202104 15.3.21. Octocog alfa - KOVALTRY (CAP) - EMEA/H/C/003825/II/0038 16.1.35. Radium (Ra223) dichloride - XOFIGO (CAP) - PSUSA/00010132/202105 16.3.18. Nitrendipine (NAP) - PSUSA/00002171/202103
Karen Pernille Harg [a, b]	Alternate	Norway	No interests declared	Full involvement
Adam Przybylkowski [a]	Member	Poland	No interests declared	Full involvement
Katarzyna Ziolkowska [b]	Alternate	Poland	No interests declared	Full involvement
Ana Diniz Martins [a, b]	Member	Portugal	No interests declared	Full involvement
Marcia Sofia Sanches de Castro Lopes Silva [a, b]	Alternate	Portugal	No interests declared	Full involvement
Roxana Dondera [a, b]	Member	Romania	No interests declared	Full involvement
Alexandra - Maria Spurni [a, b]	Alternate	Romania	No interests declared	Full involvement
Marek Juracka [a, b]	Member	Slovakia	No interests declared	Full involvement
Anna Mareková [a]	Alternate	Slovakia	No interests declared	Full involvement
Polona Golmajer [a, b]	Member	Slovenia	No interests declared	Full involvement
Eva Segovia [a]	Member	Spain	No interests declared	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Maria del Pilar Rayon [a, b]	Alternate	Spain	No interests declared	Full involvement
Ulla Wändel Liminga [a, b]	Member	Sweden	No interests declared	Full involvement
Annika Folin [a, b]	Alternate	Sweden	No interests declared	Full involvement
Annalisa Capuano [a, b]	Member	Independent scientific expert	No interests declared	Full involvement
Milou Daniel Drici [a, b]	Member	Independent scientific expert	No restrictions applicable to this meeting	Full involvement
Maria Teresa Herdeiro [a, b]	Member	Independent scientific expert	No interests declared	Full involvement
Patricia McGettigan [a]	Member	Independent scientific expert	No interests declared	Full involvement
Daniel Morales [a, b]	Member	Independent scientific expert	No interests declared	Full involvement
Raymond Anderson [a]	Member	Healthcare Professionals' Representative	No interests declared	Full involvement
Roberto Frontini [a, b]	Alternate	Healthcare Professionals' Representative	No participation in final deliberations and voting on:	15.2.6. Simoctocog alfa - NUWIQ (CAP) - EMEA/H/C/002813/WS2064/0043; VIHUMA (CAP) - EMEA/H/C/004459/WS2064/0024 16.3.14. Human prothrombin complex (NAP) - PSUSA/00001638/202104
Virginie Hivert [a]	Alternate	Patients' Organisation Representative	No restrictions applicable to this meeting	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Els Beghein [a]	Expert – via Webex*	Belgium	No interests declared	Full involvement
Jamila Hamdani [a]	Expert - via Webex*	Belgium	No interests declared	Full involvement
Melita Dumančić [a]	Expert - via Webex*	Croatia	No restrictions applicable to this meeting	Full involvement
Nina Lalić [a]	Expert - via Webex*	Croatia	No restrictions applicable to this meeting	Full involvement
Petra Kaftanová [a]	Expert - via Webex*	Czechia	No interests declared	Full involvement
Ane Blicher Schelde [a]	Expert - via Webex*	Denmark	No restrictions applicable to this meeting	Full involvement
Alexander Braathen [a]	Expert - via Webex*	Denmark	No interests declared	Full involvement
Kirsten Egebjerg Juul [a]	Expert - via Webex*	Denmark	No interests declared	Full involvement
Karin Erneholm [a]	Expert - via Webex*	Denmark	No restrictions applicable to this meeting	Full involvement
Helle Gerda Olsen [a]	Expert - via Webex*	Denmark	No interests declared	Full involvement
Rasmus Heje Thomsen [a]	Expert - via Webex*	Denmark	No restrictions applicable to this meeting	Full involvement
Marian Hjortlund Allon [a]	Expert - via Webex*	Denmark	No interests declared	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Peter Horskjær Rose [a]	Expert - via Webex*	Denmark	No interests declared	Full involvement
Kristina Laursen [a]	Expert - via Webex*	Denmark	No interests declared	Full involvement
Astrid Munch Hestbæk [a]	Expert - via Webex*	Denmark	No restrictions applicable to this meeting	Full involvement
Emma Louise Nautrup Ravn Stadsbjerg [a]	Expert - via Webex*	Denmark	No interests declared	Full involvement
Moritz Sander [a]	Expert - via Webex*	Denmark	No interests declared	Full involvement
Aynur Sert [a]	Expert - via Webex*	Denmark	No interests declared	Full involvement
Per Sindahl [a]	Expert - via Webex*	Denmark	No restrictions applicable to this meeting	Full involvement
Helene Stenbæk Hansen [a]	Expert - via Webex*	Denmark	No restrictions applicable to this meeting	Full involvement
Josiane Uwera [a]	Expert - via Webex*	Denmark	No restrictions applicable to this meeting	Full involvement
Sarah Bendahou [a]	Expert - via Webex*	France	No restrictions applicable to this meeting	Full involvement
Benjamin Burrus [a]	Expert - via Webex*	France	No interests declared	Full involvement
Samuel Crommelynck [a]	Expert - via Webex*	France	No restrictions applicable to this meeting	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Rosemary Dray-Spira [a]	Expert - via Webex*	France	No interests declared	Full involvement
Vincent Gazin [a]	Expert - via Webex*	France	No interests declared	Full involvement
Stéphanie Hueber [a]	Expert – via Webex*	France	No restrictions applicable to this meeting	Full involvement
Léo Lambart [b]	Expert – via Webex*	France	No restrictions applicable to this meeting	Full involvement
Stéphane Le-Vu [a]	Expert - via Webex*	France	No restrictions applicable to this meeting	Full involvement
Dina Sanctussy [a]	Expert - via Webex*	France	No interests declared	Full involvement
Mahmoud Zureik [a]	Expert - via Webex*	France	No interests declared	Full involvement
Dennis Lex [a]	Expert - via Webex*	Germany	No restrictions applicable to this meeting	Full involvement
Jan Mueller-Berghaus [a]	Expert – via Webex*	Germany	No interests declared	Full involvement
Eamon O'Murchu [a]	Expert - via Webex*	Ireland	No interests declared	Full involvement
Sara Galluzzo [a]	Expert – via Webex*	Italy	No interests declared	Full involvement
Armando Genazzani [a]	Expert – via Webex*	Italy	No interests declared	Full involvement
Marloes Bazelier [a]	Expert - via Webex*	Netherlands	No interests declared	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Marianne Klanker [a]	Expert - via Webex*	Netherlands	No interests declared	Full involvement
Marcel Kwa [a]	Expert – via Webex*	Netherlands	No interests declared	Full involvement
Petrus Luijsterburg [a]	Expert – via Webex*	Netherlands	No interests declared	Full involvement
Lotte Minnema [a]	Expert – via Webex*	Netherlands	No interests declared	Full involvement
Paul ten Berg [a]	Expert – via Webex*	Netherlands	No interests declared	Full involvement
Maria Vanenburg [a]	Expert – via Webex*	Netherlands	No interests declared	Full involvement
Anita Volkers [a]	Expert – via Webex*	Netherlands	No interests declared	Full involvement
Inge Zomerdijk [a]	Expert – via Webex*	Netherlands	No interests declared	Full involvement
Rune Kjeken [a]	Expert – via Webex*	Norway	No restrictions applicable to this meeting	Full involvement
Irina Sandu [a]	Expert – via Webex*	Romania	No interests declared	Full involvement
Eva Cantarero [a]	Expert – via Webex*	Spain	No interests declared	Full involvement
Rebeca Gonzalez [a]	Expert – via Webex*	Spain	No interests declared	Full involvement
Luz Medrano de Dios [a]	Expert – via Webex*	Spain	No interests declared	Full involvement
Miguel del Rey [a]	Expert – via Webex*	Spain	No interests declared	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Charlotte Backman [a, b]	Expert – via Webex*	Sweden	No interests declared	Full involvement
Karin Bolin [a]	Expert – via Webex*	Sweden	No restrictions applicable to this meeting	Full involvement
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:
http://www.ema.europa.eu/ema/