26 September 2022
EMA/PRAC/780026/2022
Human Medicines Division

Pharmacovigilance Risk Assessment Committee (PRAC)

Minutes of the meeting on 10-13 January 2022

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 meeting highlights once the procedures are finalised.

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

Note on access to documents

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

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1. Introduction

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

The Chairperson opened the meeting by welcoming all participants. Due to the 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 that no restriction in the involvement of meeting participants for agenda topics was identified. Participants were asked to declare any changes, omissions or errors to their declared interests concerning the matters for discussion. No new or additional competing interests were declared. Restrictions applicable to this meeting are captured in the List of participants included in the minutes.

Discussions, deliberations and voting took place in full respect of the restricted involvement of Committee members and experts in line with the relevant provisions of the Rules of Procedure. All decisions, recommendations and advice were agreed by consensus, unless otherwise specified.

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

Finally, the Chair announced the start of the French presidency of the Council of the European Union (EU).

1.2. Agenda of the meeting on 10-13 January 2022

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

1.3. Minutes of the previous meeting on 29 November – 02 December 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 29 November – 02 December 2021 were published on the EMA website on 04 October 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

3.1.1. Terlipressin (NAP) - EMEA/H/A31/1514

Applicant(s): various

PRAC Rapporteur: Krõõt Aab; PRAC Co-rapporteur: Anette Kirstine Stark

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

Action: For adoption of a list of questions (LoQ)

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.

The Danish Medicines Agency (DKMA) sent a letter of notification dated 22 December 2021 of a referral under Article 31 of Directive 2001/83/EC for the review of terlipressin-containing product(s) indicated in the treatment of HRS following the completion of the PSUR single assessment (PSUSA) procedure on terlipressin (PSUSA/00002905/202104) in December 2021. Following the assessment of the results from a large clinical trial CONFIRM[1] involving patients with type 1 HRS, serious safety concerns were raised due to an increased risk of respiratory failure in patients treated with terlipressin, sometimes with fatal outcome, within 90 days after the first dose compared to those who were given a placebo. In addition, the frequency of respiratory failure observed in the study was higher than expected based on frequency stated in the current product information. PRAC considered that such serious concerns had to be further investigated taking into account all available data on the safety and efficacy of terlipressin when used for the treatment of type 1 HRS. For further background, see PRAC minutes December 2021[2].

Based on the results of the CONFIRM trial, a thorough review is considered necessary to assess the impact of these findings on the risk-benefit balance of terlipressin-containing product(s) when used in the indication treatment of HRS. Therefore, in the interest of the Union, DKMA referred the matter to PRAC for further evaluation and requested that it gives

[1] 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
[2] Held 29 November – 02 December 2021

its recommendation as to whether the marketing authorisation(s) for terlipressin-containing product(s) should be maintained, varied, suspended or revoked.

Discussion

PRAC noted the notification letter from DKMA.

PRAC appointed Krõõt Aab as Rapporteur and Anette Kirstine Stark as Co-Rapporteur for the procedure.

PRAC discussed a list of questions (LoQ) to be addressed during the procedure together with a timetable for conducting the review. PRAC also discussed the need for a public hearing.

Summary of recommendation(s)/conclusions

- The Committee adopted a LoQ to the MAHs for terlipressin-containing product(s) indicated in the treatment of HRS (EMA/PRAC/2204/2022) and a timetable for the procedure (EMA/PRAC/2205/2022).
- PRAC agreed on a LoQ inviting the authors of study CONFIRM to address some questions on the study.
- PRAC discussed the option to conduct a public hearing in the context of the current procedure according to the pre-defined criteria set out in the rules of procedure[3] (EMA/363479/2015). It was agreed by the Committee that at this stage in the assessment, in light of the currently available data and the need to determine the appropriate approach to stakeholder engagement, a public hearing would not be appropriate. PRAC can reconsider this at a later stage of the procedure, as needed.

See EMA press release (EMA/8812/2022) entitled 'Review of terlipressin medicines started'.

3.2. Ongoing procedures

None

3.3. Procedures for finalisation

None

3.4. Re-examination procedures[4]

None

3.5. Others

None

[3] Rules of procedure on the organisation and conduct of public hearings at PRAC
[4] Re-examination of PRAC recommendation under Article 32 of Directive 2001/83/EC

4. Signals assessment and prioritisation[5]

4.1. New signals detected from EU spontaneous reporting systems

See Annex 14.1.

4.2. New signals detected from other sources

See Annex 14.2.

4.3. Signals follow-up and prioritisation

4.3.1. Durvalumab – IMFINZI (CAP) - EMEA/H/C/004771/SDA/009

Applicant: AstraZeneca AB

PRAC Rapporteur: David Olsen

Scope: Signal of arthralgia

EPITT 19709 – Follow-up to September 2021[6]

Background

For background information, see PRAC minutes September 2021.

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

Discussion

PRAC considered the available evidence in EudraVigilance, the cumulative review from the MAH together with the Rapporteur's assessment, and agreed that there is reasonable possibility for a causal relationship between durvalumab and arthralgia. Therefore, PRAC concluded that an update of the product information is warranted to add arthralgia as an undesirable effect with a frequency 'very common' when durvalumab is used in monotherapy, and with a frequency 'common' when used in combination with chemotherapy.

Summary of recommendation(s)

- The MAH for Imfinzi (durvalumab) should submit to EMA, within 60 days, a variation to amend[7] the product information.
- In the next PSUR[8], the MAH should include a cumulative review of cases of arthritis.

For the full PRAC recommendation, see EMA/PRAC/13254/2022 published on 07 February 2022 on the EMA website.

[5] Each signal refers to a substance or therapeutic class. The route of marketing authorisation is indicated in brackets (CAP for Centrally Authorised Products; NAP for Nationally Authorised Products including products authorised via Mutual Recognition Procedures and Decentralised Procedure). Product names are listed for reference Centrally Authorised Products (CAP) only. PRAC recommendations will specify the products concerned in case of any regulatory action required.
[6] Held 30 August – 02 September 2021
[7] Update of SmPC section 4.8. The package leaflet is to be updated accordingly
[8] Data lock point (DLP): 30 April 2022

4.3.2. Coronavirus (COVID-19) mRNA[9] vaccine (nucleoside-modified) - SPIKEVAX (CAP) - EMEA/H/C/005791/SDA/052

Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Hans Christian Siersted

Scope: Signal of capillary leak syndrome

EPITT 19743 – Follow-up to November 2021[10]

Background

For background information, see PRAC minutes November 2021[11].

The MAH replied to the request for information on the signal of capillary leak syndrome (CLS) and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence from the review of cases of CLS provided by the MAH together with the Rapporteur's assessment, PRAC agreed on the need to broaden the scope of the signal to Comirnaty (tozinameran). Therefore, PRAC agreed that further assessment of the signal is warranted.

Summary of recommendation(s)

- The MAHs for Spikevax (COVID-19 mRNA vaccine (nucleoside-modified)) and Comirnaty (tozinameran) should submit to EMA, within 30 days, a detailed review of cases of CLS with a discussion on cases reporting a medical history of CLS. The MAHs should also provide an analysis of the publication by *Pineton de Chambrun et al*[12] as well as a discussion on the plausible physio-pathological mechanism leading to CLS as new onset or flare up. Finally, the MAHs should discuss the need for an update the product information and/or RMP as warranted.
- A 30-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.3.3. Pregabalin – LYRICA (CAP); PREGABALIN PFIZER (CAP); NAP - EMEA/H/C/000546/SDA/055

Applicant(s): Upjohn EESV (Lyrica, Pregabalin Pfizer), various

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Signal of toxic epidermal necrolysis (TEN)

EPITT 19723 – Follow-up to September 2021[13]

Background

[9] Messenger ribonucleic acid
[10] Held 25-28 October 2021
[11] Held 25-28 October 2021
[12] Pineton de Chambrun M, Moyon Q, Faguer S, Urbanski G, Mathian A, Zucman N, Werner M, Luyt CE, Verlicchi F, Amoura Z; EurêClark Study Group. The consequences of COVID-19 pandemic on patients with monoclonal gammopathy-associated systemic capillary leak syndrome (Clarkson disease). J Allergy Clin Immunol Pract. 2021 Dec 7:S2213-2198(21)01359-3. doi: 10.1016/j.jaip.2021.11.023. Epub ahead of print. PMID: 34890829; PMCID: PMC8648572
[13] Held 30 August – 02 September 2021

For background information, see PRAC minutes September 2021.

The MAH for Lyrica and Pregabalin Pfizer (pregabalin) replied to the request for information on the signal of toxic epidermal necrolysis (TEN) and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence from preclinical studies, clinical trials, EudraVigilance, the literature, the cumulative review from the MAH together with the Rapporteur's assessment, PRAC considered that in light of the pathophysiological mechanism and the clinical characteristics of TEN, there is sufficient evidence to establish an association between pregabalin and TEN. Therefore, PRAC agreed that an update of the product information is warranted to add toxic epidermal necrolysis as a warning part of severe cutaneous adverse reactions (SCARs) and as an undesirable effect with a frequency 'rare'.

Summary of recommendation(s)

- The MAHs for pregabalin-containing products should submit to EMA, within 60 days, a variation to amend[14] the product information.

For the full PRAC recommendation, see EMA/PRAC/13254/2022 published on 07 February 2022 on the EMA website.

4.3.4. Tocilizumab – ROACTEMRA (CAP) - EMEA/H/C/000955/SDA/059

Applicant: Roche Registration GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Signal of sarcoidosis

EPITT 18860 – Follow-up to September 2021[15]

Background

For background information, see PRAC minutes September 2021.

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

Discussion

Having considered the available evidence, the cumulative review provided by the MAH and the Rapporteur's assessment, PRAC considered that there is insufficient evidence at present to establish a causal association between tocilizumab and sarcoidosis. Therefore, PRAC concluded that no regulatory action is warranted at this stage.

Summary of recommendation(s)

- The MAH for RoActemra (tocilizumab) should continue to monitor cases of sarcoidosis as part of routine safety surveillance.

[14] Update of SmPC sections 4.4 and 4.8. The package leaflet is to be updated accordingly
[15] Held 30 August – 02 September 2021

4.4. Variation procedure(s) resulting from signal evaluation

4.4.1. Coronavirus (COVID-19) vaccine (ChAdOx1-S [recombinant]) - VAXZEVRIA (CAP) - EMEA/H/C/005675/II/0055

Applicant: AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

Scope: Update of section 4.4 of the SmPC in order to update the warning on thrombosis with thrombocytopenia syndrome (TTS) to indicate that the frequency after the second dose is lower than after the first dose based on post-marketing data

Background

Coronavirus (COVID-19) vaccine (ChAdOx1-S [recombinant]) is a monovalent vaccine composed of a single recombinant, replication-deficient chimpanzee adenovirus (ChAdOx1) vector encoding the S glycoprotein of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) indicated, as Vaxzevria, a centrally authorised vaccine, for active immunisation to prevent COVID-19 caused by SARS-CoV-2, in individuals 18 years of age and older.

In relation to previous recommendations on signals on thrombosis with thrombocytopenia syndrome (TTS) and the outcome of the evaluation of summary safety reports (SSR), the MAH submitted to EMA a variation to update the existing warning on TTS to indicate that the frequency after the second dose is lower than after the first dose based on the post-marketing data. 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 November 2021[16].

Summary of outcome(s)

- Based on the available data and the Rapporteur's assessment, PRAC agreed with the update[17] of the product information to specify that fewer cases of TTS have been reported after the second dose compared to after the first dose.

5. Risk management plans (RMPs)

5.1. Medicines in the pre-authorisation phase

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

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

See also Annex 15.1.

[16] Held 25-28 October 2021
[17] Update of SmPC section 4.4. The package leaflet is updated accordingly

5.1.1. Capmatinib - EMEA/H/C/004845

Scope: Treatment of non-small cell lung cancer (NSCLC)

5.1.2. Dimethyl fumarate - EMEA/H/C/006039

Scope: Treatment of multiple sclerosis

5.1.3. Dimethyl fumarate - EMEA/H/C/005956

Scope: Treatment of multiple sclerosis

5.1.4. Dimethyl fumarate - EMEA/H/C/005955

Scope: Treatment of multiple sclerosis

5.1.5. Dimethyl fumarate - EMEA/H/C/006042

Scope: Treatment of multiple sclerosis

5.1.6. Ganaxolone - EMEA/H/C/005825, Orphan

Applicant: Marinus Pharmaceuticals Emerald Limited

Scope (accelerated assessment): Treatment of epileptic seizures associated with cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD)

5.1.7. Leuprorelin - EMEA/H/C/005034

Scope: Treatment of hormone dependent advanced prostate cancer

5.1.8. Mosunetuzumab - EMEA/H/C/005680, Orphan

Applicant: Roche Registration GmbH

Scope (accelerated assessment): Treatment of refractory follicular lymphoma (FL)

5.1.9. PF-07321332, ritonavir - EMEA/H/C/005973

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

At an extraordinary meeting convened remotely on 20 January 2022, PRAC reviewed the proposed RMP in the context of an initial marketing authorisation application procedure. PRAC is responsible for providing advice to CHMP.

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

See Annex 15.2.

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

See also Annex 15.3.

5.3.1. Cladribine - MAVENCLAD (CAP) - EMEA/H/C/004230/II/0020

Applicant: Merck Europe B.V.

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Update of sections 4.4 and 4.8 of the SmPC to add liver injury as a warning and as an undesirable effect with a frequency 'uncommon' based on a review of post-approval data in MAH's safety database, non-clinical and clinical trial data and scientific literature on cladribine and liver injury and epidemiological data on hepatic injury in multiple sclerosis (MS)). The package leaflet is updated accordingly. This includes a proposal for a direct healthcare professional communication (DHPC) and communication plan developed to inform of the risk of serious liver injury and new recommendations about liver function monitoring. The RMP (version 1.7) 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.

CHMP is evaluating a type II variation for Mavenclad, a centrally authorised product containing cladribine, to add liver injury as a warning and as an undesirable effect. PRAC is responsible for providing advice to CHMP on the necessary updates to the RMP to support this variation. For further background, see PRAC minutes June 2021 and PRAC minutes September 2021.

Summary of advice

- The RMP version 1.7 for Mavenclad (cladribine) in the context of the variation procedure under evaluation by PRAC and CHMP is considered acceptable.
- PRAC agreed with the updated prescriber guide and patient guide as educational materials. PRAC also agreed on the content of a direct healthcare professional communication (DHPC) along with a communication plan for its distribution to communicate to healthcare providers on the risk of liver injury and new recommendations on liver function monitoring.

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. Azacitidine - VIDAZA (CAP) - PSUSA/00000274/202105

Applicant: Bristol-Myers Squibb Pharma 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 Vidaza, a centrally authorised medicine containing azacitidine 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 Vidaza (azacitidine) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add differentiation syndrome as a warning and as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[18].
- In the next PSUR, the MAH should closely monitor cases of hearing loss following azacitidine treatment and discuss the plausibility for this to be caused by an infection due to myelosuppressive effects of azacitidine. The MAH should also discuss the publication by *Perino J et al*[19] and provide a cumulative review of cases of cardiac failure, including a discussion on the need for an update of the product information as warranted.

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

6.1.2. Coronavirus (COVID-19) mRNA[20] vaccine (nucleoside-modified) - SPIKEVAX (CAP) - PSUSA/00010897/202106

Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Hans Christian Siersted

Scope: Evaluation of a PSUSA procedure

Background

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

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Spikevax, a centrally authorised medicine containing COVID-19 mRNA vaccine (nucleoside-modified) and issued a recommendation on its marketing authorisation(s).

Summary of recommendation(s) and conclusions

[18] Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion
[19] Perino J, Mottal N, Bohbot Y, et al. Cardiac failure in patients treated with azacitidine, a pyrimidine analogue: case reports and disproportionality analyses in Vigibase. Br J Clin Pharmacol. 2020;86(5):991-998. doi:10.1111/bcp.14211
[20] Messenger ribonucleic acid

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Spikevax (COVID-19 mRNA vaccine (nucleoside-modified)) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include paraesthesia as an undesirable effect with a frequency 'rare'. Therefore, the current terms of the marketing authorisation(s) should be varied[21].
- In the next PSUR, the MAH should provide a detailed review of cases of extensive limb swelling (ELS). The MAH should also provide cumulative reviews of cases of serious hypertension, flare up of immune thrombocytopenia, autoimmune (AI)/inflammatory disease (ID) aggravation, chronic urticaria/worsening of pre-existing chronic urticaria, subacute thyroiditis as well as of polymyalgia rheumatica and exacerbation or flare-up hereof. The MAH should propose to update the product information and/or RMP as warranted. In addition, the MAH should provide a discussion on the safety profile of the vaccine in relation to heterologous COVID-19 vaccines schedule.

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

6.1.3. Dasatinib - SPRYCEL (CAP) - PSUSA/00000935/202106

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Anette Kirstine Stark

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 Sprycel, a centrally authorised medicine containing dasatinib 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 Sprycel (dasatinib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add chylothorax as a warning and as an undesirable effect with a frequency 'uncommon'. Therefore, the current terms of the marketing authorisation(s) should be varied[22].
- In the next PSUR, the MAH should provide an updated cumulative review on the potential association between systemic lupus erythematosus and dasatinib, including

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

spontaneous case reports, literature and clinical trials data. The MAH should also provide a review of cases of drug related hepatic disorders.

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. Opicapone - ONGENTYS (CAP) - PSUSA/00010516/202106

Applicant: Bial - Portela & Cª, S.A.

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

Background

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

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Ongentys, a centrally authorised medicine containing opicapone 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 Ongentys (opicapone) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add nausea as an undesirable effect with a frequency 'common'. Therefore, the current terms of the marketing authorisation(s) should be varied[23].
- In the next PSUR, the MAH should closely monitor cases of dystonia, diarrhoea and rhabdomyolysis.

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

6.1.5. Palivizumab - SYNAGIS (CAP) - PSUSA/00002267/202106

Applicant: AstraZeneca AB

PRAC Rapporteur: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

Background

[23] 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

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 Synagis, a centrally authorised medicine containing palivizumab 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 Synagis (palivizumab) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.

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

6.1.6. Pegvaliase - PALYNZIQ (CAP) - PSUSA/00010761/202105

Applicant: BioMarin International Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

Background

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

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Palynziq, a centrally authorised medicine containing pegvaliase 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 Palynziq (pegvaliase) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include dizziness as a symptom of hypersensitivity reactions. Therefore, the current terms of the marketing authorisation(s) should be varied[24].
- In the next PSUR, the MAH should provide cumulative reviews of cases of diarrhoea and fatigue and discuss the need to update the product information as warranted. In addition, the MAH should provide a detailed analysis of cases of hypersensitivity/increased hypersensitivity to polyethylene glycol (PEG)-containing medicinal products administered via other routes of administration than injection in patients treated with Palynziq (pegvaliase). This should include a discussion on the need to update the product information as warranted.

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

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. Ravulizumab - ULTOMIRIS (CAP) - PSUSA/00010787/202106

Applicant: Alexion Europe SAS

PRAC Rapporteur: Kimmo Jaakkola

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 Ultomiris, a centrally authorised medicine containing ravulizumab 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 Ultomiris (ravulizumab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add urticaria as an undesirable effect with a frequency 'uncommon'. Therefore, the current terms of the marketing authorisation(s) should be varied[25].
- In the next PSUR, the MAH should provide a discussion on the potential risks associated with off-label use of ravulizumab. The MAH should include a discussion on the need for risk minimisation measures to mitigate these risks as warranted.

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

6.1.8. Sildenafil[26] - REVATIO (CAP) - PSUSA/00002700/202105

Applicant: Upjohn EESV

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

Background

[25] 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
[26] Indicated for the treatment of pulmonary hypertension

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 Revatio, a centrally authorised medicine containing sildenafil 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 Revatio (sildenafil) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a warning on increased hypotension in patients treated concomitantly with sildenafil and sacubitril/valsartan. Therefore, the current terms of the marketing authorisation(s) should be varied[27].

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 warning on increased hypotension in patients treated concomitantly with sildenafil and sacubitril/valsartan is also relevant for sildenafil-medicinal products indicated in erectile dysfunction and should be implemented in the relevant product information accordingly. Further consideration will be given at the level of CHMP.

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. Imatinib - GLIVEC (CAP); NAP - PSUSA/00001725/202105

Applicants: Novartis Europharm Limited (Glivec), various

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

Background

Imatinib is a tyrosine kinase inhibitor (TKI) indicated for the treatment of adult and paediatric patients with newly diagnosed Philadelphia chromosome (bcr-abl) positive (Ph+) chronic myeloid leukaemia (CML) for whom bone marrow transplantation is not considered as the first line of treatment; of adult and paediatric patients with Ph+CML in chronic phase after failure of interferon-alpha therapy, or in accelerated phase or blast crisis; of adult and paediatric patients with newly diagnosed Ph+ acute lymphoblastic leukaemia (Ph+ ALL) integrated with chemotherapy; of adult patients with relapsed or refractory Ph+ ALL as monotherapy; for adult patients with myelodysplastic/myeloproliferative diseases (MDS/MPD) associated with platelet-derived growth factor receptor (PDGFR) gene re-arrangements as well as for adult patients with advanced hypereosinophilic syndrome (HES)

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

and/or chronic eosinophilic leukaemia (CEL) with FIP1L1-PDGFRα rearrangement. It is also indicated for the treatment of adult patients with Kit (CD 117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumours (GIST), for the adjuvant treatment of adult patients who are at significant risk of relapse following resection of Kit (CD117)-positive GIST as well as for the treatment of adult patients with unresectable dermatofibrosarcoma protuberans (DFSP) and adult patients with recurrent and/or metastatic DFSP who are not eligible for surgery.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of Glivec, a centrally authorised medicine(s) containing imatinib, and nationally authorised medicine(s) containing imatinib 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 imatinib-containing products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add panniculitis (including erythema nodosum) as an undesirable effect with a frequency 'uncommon'. Therefore, the current terms of the marketing authorisations should be varied[28].
- In the next PSUR, the MAHs should closely monitor cases of hypogammaglobulinaemia, myasthenia gravis, facial paralysis, cerebrovascular events, QT prolongations and thyroid disorders.

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. Benazepril, hydrochlorothiazide (NAP) - PSUSA/00000314/202105

Applicant(s): various

PRAC Lead: Nathalie Gault

Scope: Evaluation of a PSUSA procedure

Background

Benazepril is an angiotensin converting enzyme (ACE) inhibitor and hydrochlorothiazide is a thiazide diuretic. In combination, benazepril/hydrochlorothiazide is indicated for the treatment of hypertension, subject to certain conditions.

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

Summary of recommendation(s) and conclusions

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

- Based on the review of the data on safety and efficacy, the benefit-risk balance of benazepril/hydrochlorothiazide-containing products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add psoriasis aggravation as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[29].

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

6.3.2. Lactulose (NAP) - PSUSA/00001821/202105

Applicant(s): various

PRAC Lead: Ilaria Baldelli

Scope: Evaluation of a PSUSA procedure

Background

Lactulose is a synthetic disaccharide consisting of fructose and galactose. It is indicated for the treatment of constipation, hepatic encephalopathy and hepatic cirrhosis, subject to certain conditions.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing lactulose 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 lactulose-containing products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add hypersensitivity reactions, rash, pruritus and urticaria as undesirable effects with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[30].

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. Levonorgestrel[31] (NAP) - PSUSA/00010828/202105

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

[29] 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
[30] Update of SmPC section 4.8. The package leaflet is updated accordingly. PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position
[31] All indications except emergency contraception

Background

Levonorgestrel is a second-generation progestin (synthetic progesterone) indicated[32] for oral contraception, heavy menstrual bleeding (hypermenorrhoea, idiopathic menorrhagia). It is also indicated for the protection from endometrial hyperplasia during oestrogen replacement therapy.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing levonorgestrel[33] 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 levonorgestrel[34]-containing products in the approved indication(s) remains unchanged.
- Nevertheless, the product information of levonorgestrel-containing intra-uterine device (IUD) should be updated to amend the existing warnings on intra-uterine device expulsion and on masculinisation of female foetus. Therefore, the current terms of the marketing authorisation(s) should be varied[35].
- In the next PSUR, the MAHs of levonorgestrel-containing IUD should provide a discussion on the need for risk minimisation measures to further minimise the risks of inadvertent levonorgestrel-containing intrauterine devices insertion during pregnancy. In addition, the MAHs of levonorgestrel-containing IUD should provide a cumulative review of cases of anxiety categorised as serious adverse events (SAEs) with a de- or re-challenge together with a discussion on a biological plausibility in association with testosterone-derivate levonorgestrel. Furthermore, the MAHs of levonorgestrel-containing IUD should provide cumulative reviews of cases of vascular disorders and a of a potential interaction between levonorgestrel-containing intra-uterine device and lamotrigine. As a consequence, the MAHs should discuss whether updates of the product information are 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 onset of contraceptive efficacy following levonorgestrel IUD insertion and the risk of IUD insertion after conception should be further assessed. Further consideration is to be given at the level of CMDh.

6.3.4. Loperamide (NAP); loperamide, simeticone (NAP) - PSUSA/00010665/202105

Applicant(s): various

PRAC Lead: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

Background

[32] All indications except emergency contraception
[33] All indications except emergency contraception
[34] All indications except emergency contraception
[35] Update of SmPC sections 4.4 and 4.6. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position

Loperamide is a synthetic opioid and simeticone an anti-foaming agent. Loperamide is indicated for the symptomatic treatment of acute diarrhoea under certain conditions. In patients with an ileostomy, loperamide can be used to reduce the number and volume of stools and to harden their consistency. Loperamide oxide is indicated for reducing the volume of stoma discharge and improving anorectal continence. In combination, loperamide/simethicone is indicated for the control of acute diarrhoea of any cause and commonly associated symptoms including abdominal discomfort, bloating, cramping, and flatulence.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing loperamide and loperamide/simethicone 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 loperamide- and loperamide/simeticone-containing products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add acute pancreatitis as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[36].

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

6.3.5. Paracetamol[37] (NAP) - PSUSA/00002311/202105

Applicant(s): various

PRAC Lead: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

Background

Paracetamol is a para-aminophenol derivative indicated, as a solution for infusion, for the short-term treatment of moderate pain.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of paracetamol-containing products for solution for infusion in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add a warning on the risk of high anion gap metabolic acidosis when paracetamol is used concomitantly with

[36] 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
[37] Intravenous (I.V.) formulation only

flucloxacillin. Therefore, the current terms of the marketing authorisation(s) should be varied[38].

- In the next PSUR, the MAHs should provide a cumulative review of cases of renal disorders in the context of paracetamol overdose, including data from spontaneous reports and the literature and discuss the need to update the product information as warranted. The MAHs should also provide cumulative reviews of cases of premature closure/constriction of ductus arteriosus when used in third trimester of pregnancy, and of hepatobiliary disorders and abnormal liver functions. In addition, the MAHs should provide an updated review of the implementation and effectiveness of the existing additional risk minimisation measures (aRMM), including a review of cases of medication error. Moreover, the MAHs should include an updated review of cases of metabolic acidosis with increased anion gap to pyroglutamic acid, at recommended doses (excluding cases of interaction between paracetamol/flucloxacillin). Moreover, the MAHs should provide a detailed cumulative review of cases of drug rash with eosinophilia and systemic symptoms (DRESS) and other serious cutaneous adverse reactions (SCARs). A discussion on the need to update the product information should be included as warranted.

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.

PRAC considered that the risk of high anion gap metabolic acidosis when paracetamol is administered concomitantly with flucloxacillin is also relevant for all other paracetamol-containing products, including paracetamol mono-component products used via other routes of administration as well as all fixed dose combinations including paracetamol. Further consideration is to be given at the level of CMDh.

6.3.6. Pholcodine (NAP) - PSUSA/00002396/202105

Applicant(s): various

PRAC Lead: Nathalie Gault

Scope: Evaluation of a PSUSA procedure

Background

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.

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

[38] 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

- Nevertheless, the product information should be updated to add warnings on drug abuse and on cross-reactivity with neuromuscular blocking agents (NMBAs) that can lead to serious allergic reactions (anaphylaxis). Therefore, the current terms of the marketing authorisation(s) should be varied[39].

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 warnings on drug abuse and on cross-reactivity with NMBAs are also relevant for fixed dose combinations containing pholcodine. Further consideration is to be given at the level of CMDh.

PRAC noted the delay in the submission of the final results of study ALPHO[40], imposed as a condition to the marketing authorisation(s) in the outcome of a referral procedure under Article 31 of Directive 2001/83/EC finalised in 2011 (EMEA/H/A-31/1292) to investigate the role of pholcodine exposure in the onset of peri-anaesthetic NMBA-related-anaphylactic reactions. Further consideration is to be given at the level of CMDh.

6.3.7. Remifentanil (NAP) - PSUSA/00002617/202105

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

Remifentanil is a selective μ-opioid agonist indicated for the induction and/or maintenance of general anaesthesia during surgical procedures including cardiac surgery, for continuation of analgesia into the immediate post-operative period under close supervision, during transition to longer acting analgesia, and for provision of analgesia and sedation in mechanically ventilated intensive care patients.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing remifentanil 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 remifentanil-containing products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add drug withdrawal syndrome and arrhythmia as undesirable effects with a frequency 'not known' and cough with a frequency 'common'. In addition, the existing warning on tolerance and opioid use disorder (abuse and dependence) should be amended. Moreover, warnings should be added to the product information on withdrawal syndrome, on respiratory depression in case remifentanil is administered during labour, on interaction between remifentanil with gabapentinoids (gabapentin and pregabalin) as it can increase the risk of opioid overdose, and on interaction between remifentanil with serotonergic agents as it may

[39] Update of SmPC section 4.4. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position
[40] Allergy/anaphylaxis to neuromuscular blocking agents and pholcodine exposure (ALPHO). Case-control study

increase the risk of serotonin syndrome. Therefore, the current terms of the marketing authorisation(s) should be varied[41].

- In the next PSUR, the MAH(s) should provide detailed reviews of cases of adrenal insufficiency, decreased sex hormone levels, withdrawal syndrome and of chest wall rigidity with or without inability/difficulty to ventilate. The MAH(s) should include a discussion on the need to update the product information as warranted. The MAH(s) should also discuss the need for a contraindication for monoamine oxidase (MAO) inhibitors based on preclinical, clinical and literature data together with a proposal to update the product information as warranted.

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

6.4. 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. 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

Background

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

Following the evaluation of the most recently submitted PSUR(s) for the above-mentioned medicine(s), PRAC requested the MAH to submit a variation to update the product information in line with the conclusions of the PSUR single assessment (PSUSA) procedure. PRAC is responsible for adopting an outcome based on the assessment report from the PRAC Rapporteur, to be further considered at the level of CHMP, responsible for adopting an opinion on this variation. For background information, see PRAC minutes June 2021 and PRAC minutes December 2021[42].

Summary of recommendation(s)

[41] Update of SmPC sections 4.4, 4.5, 4.6 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position
[42] Held 29 November – 02 December 2021

- Based on the available data and the Rapporteur's assessment, PRAC agreed to amend[43] the product information to reflect that women of childbearing potential treated with arsenic trioxide must use effective methods of contraception during treatment with arsenic trioxide and for 6 months following completion of treatment, as well as to add that men should also use effective methods of contraception and be advised to not father a child while receiving arsenic trioxide and for three months following completion of treatment. In addition, PRAC agreed to refine the existing information on breastfeeding to specify that it should not be done while on and until two weeks after the last dose of Trisenox (arsenic trioxide).

6.5.2. Baricitinib - OLUMIANT (CAP) - EMEA/H/C/004085/II/0031

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Update of section 4.4 of the SmPC in order to add a new warning on major adverse cardiac events (MACE) and amend existing warnings on malignancy and venous thromboembolism (VTE) in line with the conclusions of the last PSUR single assessment (PSUSA) procedure (PSUSA/00010578/202102) adopted in October 2021 and based on interim results from study I4V-MC-B023: a retrospective observational study to compare baricitinib relative to the standard of care. The package leaflet is updated accordingly. The RMP (version 13.1) has also been submitted. In addition, the MAH has submitted a proposal for a direct healthcare professional communication (DHPC) and communication plan

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 to EMA a variation to update the product information to add a new warning on major adverse cardiac events (MACE) and amend existing warnings on malignancy and venous thromboembolism (VTE), following requests made in the conclusions of the PSUR single assessment (PSUSA) procedure and based on interim results from study I4V-MC-B023: a retrospective observational study to compare baricitinib relative to the standard of care. PRAC is responsible for adopting an outcome based on the assessment report from the PRAC Rapporteur, to be further considered at the level of CHMP, responsible for adopting an opinion on this variation. For further background, see PRAC minutes October 2021[44].

Summary of recommendation(s)

- Based on the available data and the Rapporteur's assessment, PRAC considered that the MAH should provide further responses before the procedure can be concluded.
- The MAH should provide further characterisation details of study I4V-MC-B023. The MAH should also present an alternative regression model estimating a pooled incidence rate ratio for MACE and VTE from all data sources, taking all exposed person-time into account.

[43] Update of SmPC section 4.6. The package leaflet is updated accordingly
[44] Held 27-30 September 2021

6.5.3. Clofarabine - EVOLTRA (CAP) - EMEA/H/C/000613/II/0075

Applicant: Genzyme Europe BV

PRAC Rapporteur: Tiphaine Vaillant

Scope: Update of section 4.6 of the SmPC as requested in the conclusions of the last PSUR single assessment (PSUSA) procedure (PSUSA/00000805/202012) to revise the section on fertility, pregnancy and lactation considering the recommendations of the Safety Working Party (SWP) as reflected in the 'SWP recommendations on the duration of contraception following the end of treatment with a genotoxic drug' and available data. The package leaflet is updated accordingly. In addition, the MAH took the opportunity 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)

Background

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

Following the evaluation of the most recently submitted PSUR(s) for the above-mentioned medicine(s), PRAC requested the MAH to submit a variation to update the product information in line with the conclusions of the PSUR single assessment (PSUSA) procedure. For background information, see PRAC minutes July 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 recommendation(s)

- Based on the available data and the Rapporteur's assessment, PRAC agreed with the proposed amendments[45] to the product information to reflect that women of childbearing potential treated with clofarabine must use effective methods of contraception during treatment with clofarabine and for 6 months following completion of treatment, as well as to add that men should also use effective methods of contraception and be advised to not father a child while receiving clofarabine and for three months following completion of treatment.

6.5.4. Coronavirus (COVID-19) vaccine (Ad26.COV2-S, recombinant) - COVID-19 VACCINE JANSSEN (CAP) - EMEA/H/C/005737/II/0035

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of section 4.8 of the SmPC in order to add transverse myelitis to the list of adverse drug reactions (ADRs) with a frequency not known based on the PRAC request from the post-authorisation measures MEA 14.5 and MEA 14.6 (sixth and seventh monthly summary safety reports (MSSR) covering August 2021 and September 2021 respectively) and update of section 4.4 of the SmPC in order to amend the wording on thrombosis and thrombocytopenia syndrome (TTS) as requested in the outcome of post-authorisation measure MEA 14.5. The package leaflet is updated accordingly. In addition, the MAH took the opportunity to implement an editorial quality review document (QRD) comment in the

[45] Update of SmPC section 4.6. The package leaflet is updated accordingly

labelling following completion of variation II/0014 in September 2021

Background

Coronavirus (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 in a stabilised conformation. It is indicated, as COVID-19 Vaccine Janssen, for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older.

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 with transverse myelitis as an undesirable effect and update the existing warning on thrombosis and thrombocytopenia syndrome (TTS) as requested in the conclusions of the sixth and seventh monthly summary safety reports (MSSR) finalised in October 2021 and November 2021 respectively. For further background, see PRAC minutes October 2021[46] and PRAC minutes November 2021[47]. 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 agreed to update[48] the product information to add transverse myelitis as a warning and as an undesirable effect with a frequency 'not known'. In addition, PRAC endorsed the refinement made the existing warning on TTS.

6.5.5. 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/00010668/202005) finalised in January 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

[46] Held 27-30 September 2021
[47] Held 25-28 October 2021
[48] Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly

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,PRAC minutes September 2021[49] and PRAC minutes December 2021[50].

Summary of recommendation(s)

- Based on the available data and the Rapporteur's assessment, PRAC considered that the MAH should provide further responses before the procedure can be concluded.
- PRAC supported adding 'therapeutic response decreased' to the product information as an undesirable effect with a frequency 'uncommon', instead of 'neutralising antibodies positive'.

6.6. Expedited summary safety reviews[51]

6.6.1. Coronavirus (COVID-19) vaccine (ChAdOx1-S [recombinant]) - VAXZEVRIA (CAP) - EMEA/H/C/005675/MEA 027.7

Applicant: AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

Scope: Eighth expedited summary safety report (SSR) for Vaxzevria (COVID-19 vaccine (ChAdOx1-S [recombinant])) during the coronavirus disease (COVID-19) pandemic

Background

Coronavirus (COVID-19) vaccine (ChAdOx1-S [recombinant])) is a monovalent vaccine composed of a single recombinant, replication-deficient chimpanzee adenovirus (ChAdOx1) vector encoding the S glycoprotein of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It is indicated, as Vaxzevria, 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 summary safety report (SSR) for Vaxzevria (COVID-19 vaccine (ChAdOx1-S [recombinant]) as part of the safety monitoring of the vaccine. At the plenary meeting, PRAC adopted its conclusions.

Summary of advice/conclusion(s)

- The MAH should submit to EMA, within 14 days, a variation to add transverse myelitis as a warning and as an undesirable effect with a frequency 'not known'.
- In the next PSUR, the MAH should provide cumulative reviews and data. In particular, the MAH should provide an updated review of cases of myocarditis and pericarditis with a discussion on possible mechanisms and a discussion on the need to update the product information as warranted. In addition, the MAH should provide detailed reviews of cases of menstrual disorders, of cases of sarcoidosis, of haemophagocytic lymphohistiocytosis (HLH) and include a discussion on the need to update the product information as warranted. The MAH should also provide reviews of cases of cerebral

[49] Held 30 August-02 September 2021
[50] Held 29 November – 02 December 2021
[51] 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

venous sinus thrombosis (CVST) without thrombocytopenia after vaccination and of capillary leak syndrome (CLS) and discuss a potential biological mechanism. Moreover, the MAH should provide a review of cases of acute macular neuro-retinopathy (AMN)/paracentral acute middle maculopathy (PAMM), and provide a causality assessment as well as an observed/expected analysis. Finally, the MAH should provide a review of cases of pulmonary embolism and venous thromboembolism (VTE) without thrombocytopenia, including an updated observed/expected analysis.

- PRAC agreed that no further SSRs are required.

7. Post-authorisation safety studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)[52]

See Annex 17.1.

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

See also Annex 17.2.

7.2.1. Ponesimod - PONVORY (CAP) - EMEA/H/C/005163/MEA 001

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Anette Kirstine Stark

Scope: Protocol for study PCSNSP004001 (listed as a category 3 study in the RMP): ponesimod pregnancy outcomes enhanced monitoring (POEM) - pregnancy outcomes programme utilising enhanced pharmacovigilance monitoring to evaluate the potential risk of reproductive and embryofetal toxicity in pregnant women exposed to ponesimod (from initial opinion/marketing authorisation)

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 part of the RMP of Ponvory (ponesimod), the MAH is requested to conduct a pregnancy outcomes programme utilising enhanced pharmacovigilance monitoring to evaluate the potential risk of reproductive and embryofoetal toxicity in pregnant women exposed to ponesimod. The MAH Janssen-Cilag International N.V submitted to EMA protocol 1.0 for the study which was assessed by the Rapporteur. PRAC was requested to provide advice to CHMP on the protocol submitted by the MAH.

Summary of advice

- Based on the review of protocol and the assessment from the Rapporteur, PRAC considered the protocol for Ponvory (ponesimod) could be acceptable provided that an

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

updated protocol is submitted to EMA. The MAH should provide further data and clarifications.

- In particular, the MAH should provide further clarifications relating to the intended study design together with a description of the comparator. The MAH should also further characterise the proportion of major congenital malformations as an additional secondary objective. In addition, the MAH should improve the presentation of selection criteria. In terms of study size, the study should apply until a maximum of 10 years from market authorisation or 500 live births whichever occurs first. Moreover, the MAH should include interim analyses in progress reports as well as a statistical analysis plan.

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

7.3.1. Hydroxyethyl starch (HES) (NAP) - EMEA/H/N/PSR/J/0031

Applicant(s): B. Braun Melsungen AG (Tetraspan, Venofundin), Fresenius Kabi Deutschland GmbH (Volulyte, Voluven)

PRAC Rapporteur: Nathalie Gault

Scope: MAH's response to PSR/J/0031 [results for a joint retrospective, multinational, drug utilisation study (DUS) to assess the non-adherence of physicians in hydroxyethyl starch (HES) accredited hospitals to the approved European product information [regarding indication for use, contraindications and posology (dosage)] for HES 130-containing medicinal products in clinical routine after implementation of a set of risk minimisation measures as required in the outcome of the referral procedure under Article 107i of Directive 2001/83/EC for HES completed in 2018 (EMEA/H/A-107i/1457)] as per the request for supplementary information (RSI) adopted in October 2021

Background

Hydroxyethyl starch (HES) is a synthetic colloid indicated for intravenous use for infusion for the treatment of hypovolemia due to acute blood loss when crystalloids alone are not considered sufficient.

In line with the conclusions of the referral procedures under Article 31 of Directive 2001/83/EC (EMEA/H/A-31/1348) and Article 107i of Directive 2001/83/EC (EMEA/H/A-107i/1376) in 2013 for HES-containing medicines as well as a further referral procedure under Article 107i of Directive 2001/83/EC (EMEA/H/A-107i/1457) concluded in 2018, MAHs were required as a condition of the marketing authorisations (Annex IV) to implement additional risk minimisation measures and to demonstrate their effectiveness by means of a drug utilisation study (DUS).

The MAHs Fresenius Kabi Deutschland GmbH and B. Braun Melsungen AG submitted to EMA the results of the required DUS entitled 'a retrospective, multinational, DUS to investigate the routine use of HES-containing infusion solutions in HES-accredited European (EU) hospitals after implementation of a set of risk minimisation measures'. For further background, see PRAC minutes January 2019, PRAC minutes June 2019, PRAC minutes September 2020[55] and PRAC minutes December 2020[56].

[54] In accordance with Article 107p-q of Directive 2001/83/EC
[55] Held 31 August - 03 September 2020
[56] Held 23-26 November 2020

PRAC discussed the final study report of the DUS. PRAC is responsible for evaluating the DUS final results together with the responses from the MAH(s) to the requests for supplementary information (RSI). For further background, see PRAC minutes May 2021 and PRAC minutes October 2021[57].

Summary of recommendation(s) and conclusions

- Based on the review of the final report of the DUS and the assessment from the Rapporteur, PRAC considered that a further RSI is necessary before a final recommendation can be made based on the PASS final report and the responses to the RSI.
- The MAH(s) should provide a detailed discussion whether the newly proposed additional risk minimisation measures (RMMs) are sufficient to improve the adherence to the product information in the EU especially in countries where high non-adherence rate to the conditions of use has been observed. The MAH(s) should also discuss other measures that could be implemented to ensure better adherence and improve effectiveness of the current routine/additional RMMs in place. Considering the observed level and nature of non-adherence to the conditions of use and taking all data on benefits/efficacy and risks/safety into account, the MAH(s) should provide a discussion on the benefit-risk balance of HES-containing products.
- A 30 day-assessment timetable will be followed.

7.4. Results of PASS non-imposed in the marketing authorisation(s)[58]

See Annex 17.4.

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

See Annex 17.5.

7.6. Others

See Annex 17.6.

7.7. New Scientific Advice

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

7.8. Ongoing Scientific Advice

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

[57] Held 27-30 September 2021
[58] 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

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

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

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

8.1. Annual reassessments of the marketing authorisation

See Annex 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

9.2. Ongoing or concluded pharmacovigilance inspections

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

9.3. Others

None

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

10.1. Safety related variations of the marketing authorisation

None

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

None

10.3. Other requests

10.3.1. Coronavirus (COVID-19) vaccine (Ad26.COV2-S, recombinant) - COVID-19 VACCINE JANSSEN (CAP) - EMEA/H/C/005737/LEG 038; COVID-19 vaccine

(ChAdOx1-S [recombinant]) - VAXZEVRIA (CAP) - EMEA/H/C/005675/LEG 093; COVID-19 mRNA[59] vaccine (nucleoside-modified) - SPIKEVAX (CAP) - EMEA/H/C/005791/MEA 004.4; COVID-19 vaccine (recombinant, adjuvanted) - NUVAXOVID (CAP) - EMEA/H/C/005808/LEG 015; tozinameran - COMIRNATY (CAP) - EMEA/H/C/005735/LEG 045

Applicants: AstraZeneca AB (Vaxzevria), BioNTech Manufacturing GmbH (Comirnaty), Janssen-Cilag International N.V. (COVID-19 Vaccine Janssen), Moderna Biotech Spain, S.L. (Spikevax), Novavax CZ, a.s (Nuvaxovid)

PRAC Rapporteurs: Jean-Michel Dogné (Vaxzevria), Brigitte Keller-Stanislawski (Nuvaxovid), Hans Christian Siersted (Spikevax), Menno van der Elst (Comirnaty), Ulla Wändel Liminga (COVID-19 Janssen)

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 light of the increasing amount of evidence regarding safety and effectiveness of COVID-19 vaccines in pregnancy, CHMP considered the need for updating COVID-19 vaccines' product information regarding use during pregnancy and lactation, taking into account reviews on vaccination in pregnant women and breastfeeding provided by the MAH(s), a literature review and an assessment of the progress and/or data coming from the relevant RMP measures conducted by the Rapporteurs. CHMP requested PRAC advice on the assessments. At an extraordinary meeting convened remotely on 26 January 2022, PRAC discussed and adopted an advice to CHMP.

Summary of advice

- Based on the review of the available data and relevant assessments, PRAC considered for the mRNA[60] vaccines (Comirnaty and Spikevax) that the available data regarding vaccination in pregnancy is sufficient to justify an amendment of their product information and to align those as much as possible with current guidelines. In addition, PRAC supported to introduce new recommendations to reflect that mRNA vaccines may be used during breast-feeding. Regarding adenovirus vaccines (Covid-19 vaccine Janssen and Vaxzevria), PRAC agreed that based on the currently available data the product information should remain unchanged. With regard to the recombinant, adjuvanted vaccine (Nuvaxovid), PRAC also supported to keep the product information unchanged.

10.4. Scientific Advice

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

[59] Messenger ribonucleic acid
[60] Messenger ribonucleic acid

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

11.2.1. Teriflunomide - DE/H/7257/001/DC

Scope: PRAC consultation on the evaluation of an initial marketing authorisation application under the decentralised procedure for a generic teriflunomide-containing medicinal product in order to consider the need for pharmacovigilance activities, on request of Germany

Background

Teriflunomide is an immunomodulatory agent intended for the treatment of adult patients and paediatric patients aged 10 years and older with relapsing remitting multiple sclerosis and for the treatment of rheumatoid arthritis.

In the context of the evaluation of an initial marketing authorisation application under the decentralised procedure for a generic teriflunomide-containing medicinal product in order to consider the need for further pharmacovigilance activities, Germany requested PRAC advice on its assessment.

Summary of advice

- Based on the review of the available information and assessment, PRAC agreed that applicants/MAH(s) of generic teriflunomide-containing products should not be requested to conduct studies on pregnancy. PRAC supported requesting applicant(s)/MAH(s) to implement follow-up questionnaires in line with the originator teriflunomide-containing product. In addition, applicant(s)/MAH(s) should continuously collect and follow-up on cases of pregnancy with exposure to teriflunomide and prepare regular reports on pregnancy exposure. Moreover, PRAC supported to ensure that generic teriflunomide-containing medicinal products should have some educational material in place for healthcare professionals (HCPs).

12. Organisational, regulatory and methodological matters

12.1. Mandate and organisation of PRAC

12.1.1. PRAC membership

The Chair announced that Georgia Gkegka has been appointed as the new alternate for Greece[61], replacing Sofia Trantza who took over the role of member, replacing Agni Kapou. The Chair thanked Agni Kapou for her contribution to PRAC.

[61] Mandate effective as of 21 December 2021

12.1.2. Vote by proxy

None

12.2. Coordination with EMA Scientific Committees or CMDh-v

None

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

None

12.4. Cooperation within the EU regulatory network

12.4.1. Coronavirus (COVID-19) pandemic - update

The EMA Secretariat updated PRAC on the activities of the COVID-19 EMA pandemic Task Force (ETF), including an overview of ongoing clinical trials and pharmaco-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

12.7.1. PRAC work plan 2022

PRAC lead: Sabine Straus, Martin Huber

The EMA Secretariat presented to PRAC the draft final PRAC work plan 2022, further to previous discussion and comments received. For further background, see PRAC minutes November 2021[62].

Post-meeting note: At the organisational, regulatory and methodological matters (ORGAM) meeting on 26 January 2022, PRAC adopted the work plan 2022. It was published on the EMA website (EMA/PRAC/576527/2021) on 16 March 2022.

[62] Held 25-28 October 2021

12.8. Planning and reporting

12.8.1. Marketing authorisation applications (MAA) forecast for 2022 – planning update dated Q4 2021

At the organisational, regulatory and methodological matters (ORGAM) meeting on 26 January 2022, the EMA Secretariat presented for information to PRAC a quarterly updated report on marketing authorisation applications planned for submission (the business 'pipeline') in 2022. For previous update, see PRAC minutes October 2021[63].

12.8.2. European Commission (EC) report on performance of pharmacovigilance tasks - third three-yearly report

In line with the legislation, the EMA Secretariat presented to PRAC the plan for the preparation of the upcoming report from the European Commission (EC) on the performance of the EU Member States activities relating to the pharmacovigilance (Article 108b of Directive 2001/83/EC and Article 29 of Regulation 726/2004). For further background, see PRAC minutes May 2015, PRAC minutes July 2015 and PRAC minutes July 2018. The presentation included the anticipated timelines as well as a draft structure of the report covering activities completed between 2019 and 2022. The EMA Secretariat informed PRAC that a request for a non-urgent information (NUI) will be sent to the National Competent Authorities in order to collect information on specific activities. Further update will be given in due course.

12.9. Pharmacovigilance audits and inspections

12.9.1. Pharmacovigilance systems and their quality systems

None

12.9.2. Pharmacovigilance inspections

None

12.9.3. Pharmacovigilance audits

None

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

12.10.1. Periodic safety update reports

None

12.10.2. Granularity and Periodicity Advisory Group (GPAG)

None

[63] Held 27-30 September 2021

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

Post-meeting note: following the PRAC meeting of January 2022, the updated EURD list was adopted by CHMP and CMDh at their January 2022 meetings and published on the EMA website on 02 February 2022, 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)

12.11. Signal management

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

None

12.12. Adverse drug reactions reporting and additional monitoring

12.12.1. Management and reporting of adverse reactions to medicinal products

None

12.12.2. Additional monitoring

None

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

PRAC was informed 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 accordingly, see: Home>Human Regulatory>Post-authorisation>Pharmacovigilance>Medicines under additional monitoring>List of medicines under additional monitoring

12.13. EudraVigilance database

12.13.1. Activities related to the confirmation of full functionality

None

12.14. Risk management plans and effectiveness of risk minimisations

12.14.1. Risk management systems

None

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

None

12.15. Post-authorisation safety studies (PASS)

12.15.1. Post-authorisation Safety Studies – imposed PASS

None

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

None

12.16. Community procedures

12.16.1. Referral procedures for safety reasons

None

12.17. Renewals, conditional renewals, annual reassessments

None

12.18. Risk communication and transparency

12.18.1. Public participation in pharmacovigilance

None

12.18.2. Safety communication

None

12.19. Continuous pharmacovigilance

12.19.1. Incident management

None

12.20. Impact of pharmacovigilance activities

None

12.21. Others

12.21.1. EMA guidance on companion diagnostics (CDx) – consultation CHMP/CAT assessment report (AR) CDx template - update

At the organisational, regulatory and methodological matters (ORGAM)[64] meeting on 26 January 2022, the EMA secretariat presented the legislative background (Regulation (EU) 2017/746) covering the companion diagnostics (CDx) consultation procedure, including the EMA guidance on procedural aspects to facilitate the consultation procedure to EMA by Notified bodies on companion diagnostics and the timelines for implementation. The EMA Secretariat also presented the criteria for PRAC involvement in the assessment of such procedures via CHMP requests for PRAC advice.

12.21.2. EU pharmaceutical legislation – revision of Directive 2001/83/EC and Regulation (EC) No 726/2004

PRAC lead: Amelia Cupelli, Maria del Pilar Rayon, Liana Gross-Martirosyan, Martin Huber, Eva Segovia, Sabine Straus, Menno van der Elst, Ulla Wändel Liminga

At the organisational, regulatory and methodological matters (ORGAM)[65] meeting on 26 January 2022, the EMA Secretariat presented an update on the process to revise the EU pharmaceutical legislation, including a summary of the proposed changes and an overview of comments received following the consultation phase on the draft concept papers. For background information, see PRAC minutes November 2021[66]. Further update will be given on a regular basis.

13. Any other business

None

14. Annex I – Signals assessment and prioritisation[67]

14.1. New signals detected from EU spontaneous reporting systems

As per the agreed criteria for new signal(s), PRAC adopted without further plenary discussion the recommendation of the Rapporteur to request MAH(s) to submit a cumulative review following standard timetables[68].

[64] Extended to specific COVID-19-related procedure(s) during EMA business continuity plan (BCP)
[65] Extended to specific COVID-19-related procedure(s) during EMA business continuity plan (BCP)
[66] Held 25-28 October 2021
[67] 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
[68] Either MA(s)'s submission within 60 days followed by a 60 day-timetable assessment or MAH's subm.ission 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

14.1.1. Calcitonin gene-related peptide (CGRP) antagonists: eptinezumab – VYEPTI[69], erenumab – AIMOVIG (CAP), fremanezumab – AJOVY (CAP), galcanezumab – EMGALITY (CAP)

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

PRAC Rapporteur: Kirsti Villikka

Scope: Signal of Raynaud's phenomenon

EPITT 19766 – New signal

Lead Member State(s): FI, NL

14.1.2. Osimertinib – TAGRISSO (CAP)

Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: Signal of aplastic anaemia

EPITT 19769 – New signal

Lead Member State(s): NL

14.1.3. Roxadustat – EVRENZO (CAP)

Applicant: Astellas Pharma Europe

PRAC Rapporteur: Marek Juracka

Scope: Signal of central hypothyroidism

EPITT 19757 – New signal

Lead Member State(s): SK

14.2. New signals detected from other sources

14.2.1. Human normal immunoglobulin[70] – FLEBOGAMMA DIF (CAP), KIOVIG (CAP), PRIVIGEN (CAP); NAP

Applicant(s): Baxter AG (Kiovig), CSL Behring GmbH (Privigen), Instituto Grifols, S.A. (Flebogamma DIF), various

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Signal of thrombocytopenia

EPITT 19764 – New signal

Lead Member State(s): DE

[69] Pending European Commission decision
[70] For intravenous use only

15. Annex I – Risk management plans

15.1. Medicines in the pre-authorisation phase

As per the agreed criteria, PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of the RMP for the 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. Amifampridine - EMEA/H/C/005839

Scope: Treatment of Lambert-Eaton myasthenic syndrome

15.1.2. Budesonide, micronised - EMEA/H/C/005653, Orphan

Applicant: Calliditas Therapeutics AB, Hybrid

Scope: Treatment of primary immunoglobulin A (IgA) nephropathy

15.1.3. Insulin aspart - EMEA/H/C/005635

Scope: Treatment of diabetes mellitus

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

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

15.2.1. Acalabrutinib - CALQUENCE (CAP) - EMEA/H/C/005299/II/0011

Applicant: AstraZeneca AB

PRAC Rapporteur: Željana Margan Koletić

Scope: Submission of an updated RMP (version 3) in order to add hepatotoxicity as an important potential risk to the list of safety concerns

15.2.2. Coronavirus (COVID-19) vaccine (Ad26.COV2-S, recombinant) - COVID-19 VACCINE JANSSEN (CAP) - EMEA/H/C/005737/II/0029

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of an updated RMP (version 2.4) in order to reclassify the important potential risk of venous thromboembolism (VTE) as an important identified risk as an outcome of post-authorisation measure MEA 32 finalised in October 2021, to add clinical trial VAC31518COV3003: a randomised, double-blind, phase 3 study to evaluate 6 dose levels of COVID-19 Vaccine Janssen (Ad26.COV2.S) administered as a two-dose schedule in healthy adults and to update study VAC18193RSV2008: a randomised, observer blind,

phase 1 study to evaluate innate and proinflammatory responses of an Ad26.RSV.preF based vaccine, Ad26.COV2.S vaccine and Ad26.ZEBOV vaccine in adults aged 18 to 59 years as additional pharmacovigilance activities to further characterise the important identified risks of thrombosis with thrombocytopenia syndrome (TTS), immune thrombocytopenia (ITP), and VTE, and the important potential risk thrombocytopenia (excluding ITP and TTS) as an outcome of post-authorisation measure MEA 14.4 (fifth monthly summary safety report (MSSR)) finalised in September 2021. In addition, the MAH took the opportunity to include other minor updates in the RMP

15.2.3. Infliximab - ZESSLY (CAP) - EMEA/H/C/004647/II/0020

Applicant: Sandoz GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of an updated RMP (version 3.0) to remove the German registry Rheumatoide Arthritis: Beobachtung der Biologika-Therapie (RABBIT) registry as an additional pharmacovigilance activity in alignment with the RMP of the reference product and to remove the British Association of Dermatologists Biologic and Immunomodulators Register (BADBIR) registry as an additional pharmacovigilance activity

15.2.4. Inotersen - TEGSEDI (CAP) - EMEA/H/C/004782/II/0026, Orphan

Applicant: Akcea Therapeutics Ireland Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Submission of an updated RMP (version 3.0) to remove carcinogenicity in rats as missing information and to add a targeted questionnaire as routine pharmacovigilance measure and a patient alert card as additional risk minimisation for liver transplant rejection. In addition, the RMP is updated to add 'injection site reactions' and 'immunogenicity' as risks not considered important for inclusion in the list of safety concerns (S.VII.1.1) and to update the patient alert card with additional warnings on hepatic monitoring and ocular toxicity. The MAH took the opportunity to include further minor updates to the RMP

15.2.5. Mercaptamine - CYSTADROPS (CAP) - EMEA/H/C/003769/II/0023, Orphan

Applicant: Recordati Rare Diseases

PRAC Rapporteur: Eva Segovia

Scope: Submission of an updated RMP (version 1.4) in order to bring it in line with revision 2 of GVP module V on 'Risk management systems' and to remove 'patients with other ocular co-morbidities' and 'patients receiving concomitant treatment with ophthalmic products containing benzalkonium chloride' as missing information from the list of safety concerns

15.2.6. Nintedanib - OFEV (CAP) - EMEA/H/C/003821/II/0046

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Submission of an updated RMP (version 11.0) in line with the outcome of the renewal procedure R/0025 finalised in May 2019 to remove the following safety concerns: 1) important identified risks: diarrhoea, liver enzyme and bilirubin elevations including drug-induced liver injury (DILI), bleeding, myocardial infarction; 2) important potential risks: venous thromboembolism, arterial thromboembolism excluding myocardial infarction, perforation, hepatic failure, treatment of pregnant women and teratogenicity, cardiac failure; 3) missing information: treatment of patients with moderate or severe hepatic impairment (Child Pugh B/C), treatment of black patients, treatment of patients with healing wounds, treatment of patients with severe renal impairment or end-stage renal disease, treatment of patients receiving full-dose therapeutic anticoagulation and treatment of breastfeeding women. In addition, the anatomical therapeutic chemical (ATC) code and post-marketing exposure are updated

15.2.7. Sacubitril, valsartan - ENTRESTO (CAP) - EMEA/H/C/004062/WS2185/0041; NEPARVIS (CAP) - EMEA/H/C/004343/WS2185/0039

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Anette Kirstine Stark

Scope: Submission of an updated RMP (version 3.0) as requested in the outcome of variation WS1830 competed in November 2020. In addition, the following changes have been introduced: 1) change to the agreed milestone for study CLCZ696B2320 (listed as a category 3 study in the RMP): a multicentre, randomised, double-blind, active-controlled study to evaluate the effects of sacubitril/valsartan (LCZ696) compared to valsartan on cognitive function as assessed by comprehensive neurocognitive battery and brain amyloid plaque deposition as assessed by positron emission tomography (PET) imaging in patients with chronic heart failure with preserved ejection fraction; 2) update the date for the submission of the final report for study CLCZ696B2320 from 'Q1 2022' to 'Q1 2023', 3) update of the presentation of important identified risks and important potential risks; 4) updated exposure and post-marketing data provided for the data lock point of PSUR#9 (31 July 2021)

15.2.8. Temozolomide - TEMODAL (CAP) - EMEA/H/C/000229/II/0095

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Martin Huber

Scope: Submission of an updated RMP (version 6.1) to bring it in line with revision 2 of GVP module V on 'Risk management systems'. As a consequence, all safety concerns (important identified risks, important potential risks and missing information) are removed

15.2.9. Tozinameran - COMIRNATY (CAP) - EMEA/H/C/005735/II/0087

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Submission of an updated RMP (version 2.6) to include data from the booster/third dose, including data in patients who have undergone a solid organ transplantation, following the outcome of procedures II/0062 (third dose in immunocompromise as part of the primary vaccination) and II/0067 (booster dose) finalised in October 2021. The MAH took

the opportunity to update the RMP regarding the discontinuation of enrolment in study C4591015: a phase 2/3 study to evaluate the safety, tolerability, and immunogenicity in healthy pregnant women 18 years of age and older and the final clinical study report (CSR) milestones

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

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

15.3.1. Alemtuzumab – LEMTRADA (CAP) – EMEA/H/C/003718/II/0038

Applicant: Sanofi Belgium

PRAC Rapporteur: Anette Kirstine Stark

Scope: Update of sections 4.4 and 4.8 of the SmPC to add adult onset Still's disease (AOSD) to the list of adverse drug reactions (ADRs) with a frequency 'not known', based on a signal validated during a routine pharmacovigilance surveillance. The package leaflet is updated accordingly. The MAH took the opportunity to update the list of local representatives in the package leaflet. The RMP (version 9.0) is updated accordingly and reflect the removal of study OBS13436: International Lemtrada (alemtuzumab) pregnancy exposure cohort in multiple sclerosis (pregnancy registry)

15.3.2. Brigatinib - ALUNBRIG (CAP) - EMEA/H/C/004248/II/0037

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Update of section 5.1 of the SmPC in order to update efficacy information based on final results from study AP26113-13-301 (listed as a post-authorisation efficacy study (PAES) in Annex II): a randomised, open-label, multicentre phase 3 study comparing brigatinib versus crizotinib in patients with advanced anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC) who have not previously received ALK-directed therapy. The RMP (version 5.4) is updated in accordance

15.3.3. Brivaracetam - BRIVIACT (CAP) - EMEA/H/C/003898/II/0032/G

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Adam Przybylkowski

Scope: Grouped variations consisting of: 1) extension of indication to include patients from 1 month to 4 years of age for treatment with Briviact (brivaracetam). As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The RMP (version 8.0) is updated accordingly. Furthermore, the product information is brought in line with the latest quality review of documents (QRD) template (version 10.2). The MAH took the opportunity to implement minor editorial updates; 2) extension of the shelf life after the first opening of Briviact (brivaracetam) oral solution (supported by real time data); 3) addition of a 1 mL oral syringe and its adaptor for the paediatric population. The package leaflet and labelling are updated in accordance

15.3.4. Caplacizumab - CABLIVI (CAP) - EMEA/H/C/004426/II/0035, Orphan

Applicant: Ablynx NV

PRAC Rapporteur: Jan Neuhauser

Scope: Update of sections 4.4 and 4.8 of the SmPC in order to amend an existing warning on increased risk of bleeding and add blood and lymphatic system disorders to the list of adverse drug reactions (ADRs) with a frequency not known based on a safety evaluation report. The package leaflet and the RMP (version 2.0) are updated accordingly

15.3.5. Delamanid - DELTYBA (CAP) - EMEA/H/C/002552/II/0053, Orphan

Applicant: Otsuka Novel Products GmbH

PRAC Rapporteur: Laurence de Fays

Scope: Update of section 4.8 of the SmPC in order to update the list of adverse drug reactions (ADRs) following the development of an improved methodology to identify relevant ADRs likely attributable to delamanid. The package leaflet and the RMP (version 3.6) are updated accordingly

15.3.6. Dimethyl fumarate - TECFIDERA (CAP) - EMEA/H/C/002601/II/0069/G

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Martin Huber

Scope: Grouped variations consisting of: 1) update of section 4.8 of the SmPC in order to add rhinorrhoea to the list of adverse drug reactions (ADRs) with a frequency not known based on a systematic review of information from clinical and non-clinical studies, post-marketing data and scientific literature. The package leaflet is updated accordingly; 2) update of sections 4.4, 4.8 and 5.1 of the SmPC in order to update efficacy and safety information based on final results from study 109MS303 (ENDORSE) (listed as a category 3 study in the RMP): a dose-blind, multicentre, extension study to determine the long-term safety and efficacy of two doses of dimethyl fumarate (BG00012) monotherapy in subjects with relapsing-remitting multiple sclerosis. The RMP (version 11.1) is updated accordingly

15.3.7. 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

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

Applicant: Roche Registration GmbH

PRAC Rapporteur: Amelia Cupelli

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

15.3.9. Eptacog alfa (activated) - NOVOSEVEN (CAP) - EMEA/H/C/000074/II/0116

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication to include treatment of severe postpartum haemorrhage for NovoSeven (eptacog alfa). As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 8.0) are updated accordingly

15.3.10. Etanercept - ENBREL (CAP) - EMEA/H/C/000262/II/0246

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Eva Segovia

Scope: Update of section 5.1 of the SmPC in order to update clinical information based on final results obtained from the clinical paediatric study B1801023 (CLIPPER 2): an open label extension study to assess the long-term safety of etanercept in children and adolescents with extended oligoarticular juvenile idiopathic arthritis, enthesitis related arthritis, or psoriatic arthritis who were previously enrolled in protocol 0881A1 3338 WW(B1801014). The RMP (version 7.5) is updated accordingly

15.3.11. Galsulfase - NAGLAZYME (CAP) - EMEA/H/C/000640/II/0086

Applicant: BioMarin International Limited

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Submission of the final report from the mucopolysaccharidosis (MPS VI clinical surveillance programme (CSP) (listed as a specific obligation (SOB002) in Annex II): an observational CSP to characterise the natural progression of MPS VI; to evaluate the long-term safety and efficacy data from Naglazyme (galsulfase) treatment; to collect information on the effect of Naglazyme (galsulfase) treatement on lactation, growth and development of infants of Naglazyme (galsulfase) treated mothers and to evaluate the effects of Naglazyme (galsulfase) treatment on children under 5 years of age. The RMP (version 6.4) is updated accordingly to remove gastrointestinal haemorrhage, hepatic impairment and thrombocytopenia from the list of important potential risks

15.3.12. Givosiran - GIVLAARI (CAP) - EMEA/H/C/004775/II/0006, PRIME, Orphan

Applicant: Alnylam Netherlands B.V.

PRAC Rapporteur: Martin Huber

Scope: Update of section 4.8 of the SmPC to add 'blood homocysteine increase' as a new adverse drug reaction (ADR) and update of section 4.4 of the SmPC to add a related warning. The package leaflet and the RMP (version 1.1) are updated accordingly. In addition, the MAH took the opportunity to make editorial changes to the product information and to update the local representative details for Malta and Cyprus

15.3.13. Guselkumab - TREMFYA (CAP) - EMEA/H/C/004271/II/0031

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of sections 4.8 and 5.1 of the SmPC based on 2-year data from study CNTO1959PSA3002: a phase 3, multicentre, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of guselkumab administered subcutaneously in subjects with active psoriatic arthritis. The RMP (version 8.2) is updated accordingly

15.3.14. Ibrutinib - IMBRUVICA (CAP) - EMEA/H/C/003791/II/0069

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Update of section 4.4 of the SmPC to include information on fatal and serious cardiac arrythmias and cardiac failure, relevant warnings and periodical monitoring of patients- following a safety assessment for increased risk of sudden death/cardiac death with the use of ibrutinib. The MAH took the opportunity to correct typographical errors throughout the product information. The package leaflet and the RMP (version 11) are updated accordingly

15.3.15. Idecabtagene vicleucel - ABECMA (CAP) - EMEA/H/C/004662/II/0010, PRIME, Orphan

Applicant: Bristol-Myers Squibb Pharma EEIG, ATMP[71]

PRAC Rapporteur: Annika Folin

Scope: Update of section 5.1 of the SmPC in order to update efficacy information based on 24 month follow up data from the pivotal study submitted during the initial procedure, namely study BB2121-MM-001 (listed as a specific obligation in Annex II and in the RMP): a phase 2, multicentre study to determine the efficacy and safety of idecabtagene vicleucel (bb2121) in subjects with relapsed and refractory multiple myeloma. Annex II and the RMP (version 1.1) are updated accordingly

[71] Advanced therapy medicinal product

15.3.16. Lacosamide - LACOSAMIDE UCB (CAP) - EMEA/H/C/005243/WS2049/0009/G; VIMPAT (CAP) - EMEA/H/C/000863/WS2049/0091/G

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Grouped applications consisting of: 1) extension of indication to include patients from 1 month to 4 years of age for treatment of partial-onset seizures with or without secondary generalisation as monotherapy and adjunctive therapy. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The RMP (version 16.0) is updated accordingly; 2) change of a measuring or administration device; 3) extension of the shelf-life of the finished product. The package leaflet and labelling are updated in accordance

15.3.17. Luspatercept - REBLOZYL (CAP) - EMEA/H/C/004444/II/0009, Orphan

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Laurence de Fays

Scope: Extension of indication in β-thalassaemia to include adult patients with non-transfusion dependent β-thalassaemia (NTDT) for Reblozyl (luspatercept). As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 1.1) are updated in accordance. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet

15.3.18. Olaparib - LYNPARZA (CAP) - EMEA/H/C/003726/II/0051/G

Applicant: AstraZeneca AB

PRAC Rapporteur: Amelia Cupelli

Scope: Extension of indication to include adjuvant treatment of breast cancer for Lynparza (for tablets). As a consequence, sections 4.1, 4.2, 4.5, 4.8 and 5.1 of the SmPC are updated. In addition, section 4.8 of the SmPC for Lynparza (olaparib) hard capsules is revised based on the updated safety data analysis. The package leaflet and the RMP (version 23) are updated accordingly

15.3.19. Pembrolizumab - KEYTRUDA (CAP) - EMEA/H/C/003820/II/0117

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication to include a new indication in combination with chemotherapy with or without bevacizumab, for the treatment of persistent, recurrent, or metastatic cervical cancer in adults. As a consequence, sections 4.1 and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 38.1) are updated accordingly

15.3.20. Ponatinib - ICLUSIG (CAP) - EMEA/H/C/002695/II/0061, Orphan

Applicant: Incyte Biosciences Distribution B.V.

PRAC Rapporteur: Annika Folin

Scope: Update of sections 4.2, 4.4, 4.8 and 5.1 of the SmPC based on results from OPTIC study (AP24534-14-203) (listed as a specific obligation (SOB002) in Annex II): a randomised, open-label, phase 2 trial of ponatinib in patients with chronic myeloid leukaemia to characterise the efficacy and safety of ponatinib over a range of doses. The package leaflet and the RMP (version 21.0) are updated accordingly. The RMP (version 21.0) is updated as a response to the request for supplementary information (RSI)

15.3.21. Secukinumab - COSENTYX (CAP) - EMEA/H/C/003729/II/0079

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Eva Segovia

Scope: Extension of indication to include treatment of juvenile idiopathic arthritis (enthesitis-related arthritis and juvenile psoriatic arthritis) in patients 2 years and older whose disease has responded inadequately to, or who cannot tolerate conventional therapy. 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 10.0) are updated in accordance

15.3.22. Semaglutide - OZEMPIC (CAP) - EMEA/H/C/004174/WS2141/0024; RYBELSUS (CAP) - EMEA/H/C/004953/WS2141/0018

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Annika Folin

Scope: Submission of the final report from study NN9535-4386 (SUSTAIN-11) (listed as a category 3 study in the RMP): a 52-week, multicentre, multinational, open-label, active controlled, two armed, parallel, randomised trial undertaken to investigate the effect on glycaemic control, body weight, safety and health-related quality of life of once-weekly semaglutide subcutaneous (sc) vs insulin aspart three times daily, both as add-on to metformin and optimised insulin glargine U100 treatment in subjects with inadequately controlled type 2 diabetes mellitus (T2DM). The RMP (version 7.0) is updated accordingly

15.3.23. Setmelanotide - IMCIVREE (CAP) - EMEA/H/C/005089/II/0002/G, PRIME, Orphan

Applicant: Rhythm Pharmaceuticals Netherlands B.V.

PRAC Rapporteur: Marek Juracka

Scope: Grouped variations consisting of: 1) addition of a new therapeutic indication for the treatment of obesity and the control of hunger associated with genetically confirmed Bardet-Biedl syndrome (BBS). As a consequence, sections 4.1, 4.2, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The package leaflet and the RMP (version 1.0) are updated accordingly; 2) addition of a new therapeutic indication for the treatment of obesity and the control of hunger associated with genetically confirmed Alström syndrome (AS). As a consequence, sections 4.1, 4.2, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated accordingly. The package leaflet and the RMP (version 1.0) are updated in accordance

15.3.24. Tagraxofusp - ELZONRIS (CAP) - EMEA/H/C/005031/II/0009, Orphan

Applicant: Stemline Therapeutics B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Submission of the final report from study 20255431 (CRL-263114) (listed as a category 3 study in the RMP): a non-interventional, post-authorisation study on blood brain barrier (BBB) models in order to determine a potential toxicity biomarker to further investigate the risk of choroid plexus lesions - a characterisation of fixed choroid plexus samples from primate study MPI-2231-007 by immunohistochemistry with diphtheria toxin (DT), interleukin-3 receptor (CD123), interleukin-3 (IL-3) and immunoglobulin G (IgG) (in fulfilment of MEA 002). The RMP (version 2.0) is updated accordingly

15.3.25. Trastuzumab deruxtecan - ENHERTU (CAP) - EMEA/H/C/005124/II/0012

Applicant: Daiichi Sankyo Europe GmbH

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Extension of indication to include monotherapy treatment of adult patients with locally advanced or metastatic epidermal growth factor receptor 2 (HER2)-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma who have received a prior anti-HER2-based regimen for Enhertu (trastuzumab deruxtecan) based on final results from: 1) study DS8201-A-J202 (DESTINY Gastric01): a phase 2, multicentre, open-label study of trastuzumab deruxtecan (DS-8201a) in subjects with HER2-expressing advanced gastric or gastroesophageal junction adenocarcinoma; 2) study DS8201-A-U205 (DESTINY Gastric02): a phase 2, open-label, single-arm trial of trastuzumab deruxtecan (DS 8201a) in HER2-positive, unresectable or metastatic gastric or GEJ adenocarcinoma subjects who have progressed on or after a trastuzumab-containing regimen. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 1.1) are updated accordingly. In addition, changes regarding the dosing recommendation for corticosteroid treatment and the protection of the infusion bag from light have been introduced

15.3.26. Upadacitinib - RINVOQ (CAP) - EMEA/H/C/004760/X/0012/G

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Grouped applications consisting of: 1) extension application to add a new strength (45 mg) of the prolonged-release tablets; 2) include the treatment of adults with moderately to severely active ulcerative colitis who had an inadequate response, lost response or were intolerant to either conventional therapy or a biologic agent. As a consequence, sections 4.1, 4.2, 4.5, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The package leaflet, labelling and the RMP (version 6.) are updated in accordance

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 the agreed criteria, the procedures listed below were finalised at the PRAC level without further plenary discussion.

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

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

16.1.1. Afamelanotide - SCENESSE (CAP) - PSUSA/00010314/202106

Applicant: Clinuvel Europe Limited

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.2. Alpelisib - PIQRAY (CAP) - PSUSA/00010871/202105

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.3. Angiotensin II - GIAPREZA (CAP) - PSUSA/00010785/202106

Applicant: Paion Deutschland GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.4. Atidarsagene autotemcel - LIBMELDY (CAP) - PSUSA/00010899/202106

Applicant: Orchard Therapeutics (Netherlands) BV, ATMP[72]

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.5. Berotralstat - ORLADEYO (CAP) - PSUSA/00010930/202106

Applicant: BioCryst Ireland Limited

PRAC Rapporteur: Julia Pallos

Scope: Evaluation of a PSUSA procedure

16.1.6. Betibeglogene autotemcel - ZYNTEGLO (CAP) - PSUSA/00010769/202105

Applicant: bluebird bio (Netherlands) B.V., ATMP[73]

PRAC Rapporteur: Brigitte Keller-Stanislawski

[72] Advanced therapy medicinal product
[73] Advanced therapy medicinal product

Scope: Evaluation of a PSUSA procedure

16.1.7. Binimetinib - MEKTOVI (CAP) - PSUSA/00010717/202106

Applicant: Pierre Fabre Medicament

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Evaluation of a PSUSA procedure

16.1.8. Bromfenac - YELLOX (CAP) - PSUSA/00000436/202105

Applicant: Bausch Health Ireland Limited

PRAC Rapporteur: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

16.1.9. Buprenorphine[74] - SIXMO (CAP) - PSUSA/00010778/202105

Applicant: L. Molteni & C. dei Fratelli Alitti Societa di Esercizio S.p.A.

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.10. Cannabidiol[75] - EPIDYOLEX (CAP) - PSUSA/00010798/202106

Applicant: GW Pharma (International) B.V.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.1.11. Cholera vaccine, oral, live - VAXCHORA (CAP) - PSUSA/00010862/202106

Applicant: Emergent Netherlands B.V.

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

16.1.12. Coronavirus (COVID-19) vaccine (ChAdOx1-S [recombinant]) - VAXZEVRIA (CAP) - PSUSA/00010912/202106

Applicant: AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

16.1.13. Crisaborole - STAQUIS (CAP) - PSUSA/00010842/202106

Applicant: Pfizer Europe MA EEIG

[74] Implant(s) only
[75] Centrally authorised product(s) only

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

16.1.14. Delafloxacin - QUOFENIX (CAP) - PSUSA/00010822/202106

Applicant: A. Menarini Industrie Farmaceutiche Riunite s.r.l.

PRAC Rapporteur: Željana Margan Koletić

Scope: Evaluation of a PSUSA procedure

16.1.15. Dengue tetravalent vaccine (live, attenuated) - DENGVAXIA (CAP) - PSUSA/00010740/202106

Applicant: Sanofi Pasteur

PRAC Rapporteur: Sonja Hrabcik

Scope: Evaluation of a PSUSA procedure

16.1.16. Efmoroctocog alfa - ELOCTA (CAP) - PSUSA/00010451/202106

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Sonja Hrabcik

Scope: Evaluation of a PSUSA procedure

16.1.17. Encorafenib - BRAFTOVI (CAP) - PSUSA/00010719/202106

Applicant: Pierre Fabre Medicament

PRAC Rapporteur: Rugile Pilviniene

Scope: Evaluation of a PSUSA procedure

16.1.18. Entrectinib - ROZLYTREK (CAP) - PSUSA/00010874/202106

Applicant: Roche Registration GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.19. Fenfluramine - FINTEPLA (CAP) - PSUSA/00010907/202106

Applicant: Zogenix ROI Limited

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.20. Fluticasone furoate, vilanterol - RELVAR ELLIPTA (CAP); REVINTY ELLIPTA (CAP) - PSUSA/00010099/202105

Applicant(s): GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

16.1.21. Formoterol fumarate dihydrate, glycopyrronium bromide, budesonide - TRIXEO AEROSPHERE (CAP) - PSUSA/00010908/202106

Applicant: AstraZeneca AB

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.1.22. Galsulfase - NAGLAZYME (CAP) - PSUSA/00001515/202105

Applicant: BioMarin International Limited

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.1.23. Glibenclamide[76] - AMGLIDIA (CAP) - PSUSA/00010690/202105

Applicant: Ammtek

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

16.1.24. Human papillomavirus 9-valent vaccine (recombinant, adsorbed) - GARDASIL 9 (CAP) - PSUSA/00010389/202106

Applicant: MSD Vaccins

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

16.1.25. Hydroxycarbamide[77] - SIKLOS (CAP); XROMI (CAP) - PSUSA/00001692/202106

Applicant(s): Addmedica S.A.S. (Siklos), Nova Laboratories Ireland Limited (Xromi)

PRAC Rapporteur: Laurence de Fays

Scope: Evaluation of a PSUSA procedure

16.1.26. Imiglucerase - CEREZYME (CAP) - PSUSA/00001727/202105

Applicant: Genzyme Europe BV

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

[76] Centrally authorised product(s) only
[77] Centrally authorised product(s) only

16.1.27. Inclisiran - LEQVIO (CAP) - PSUSA/00010904/202106

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

16.1.28. Indacaterol, mometasone furoate - ATECTURA BREEZHALER (CAP); BEMRIST BREEZHALER (CAP) - PSUSA/00010850/202105

Applicant(s): Novartis Europharm Limited

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.1.29. Interferon beta-1a[78] - AVONEX (CAP) - PSUSA/00010725/202105

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

16.1.30. Interferon beta-1a[79] - REBIF (CAP) - PSUSA/00010726/202105

Applicant: Merck Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.31. Larotrectinib - VITRAKVI (CAP) - PSUSA/00010799/202105

Applicant: Bayer AG

PRAC Rapporteur: Rugile Pilviniene

Scope: Evaluation of a PSUSA procedure

16.1.32. Latanoprost, netarsudil - ROCLANDA (CAP) - PSUSA/00010905/202106

Applicant: Aerie Pharmaceuticals Ireland Limited

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.33. Levodopa - INBRIJA (CAP) - PSUSA/00107800/202106

Applicant: Acorda Therapeutics Ireland Limited

PRAC Rapporteur: Nikica Mirošević Skvrce

[78] Intramuscular use only
[79] Subcutaneous use only

Scope: Evaluation of a PSUSA procedure

16.1.34. Linagliptin - TRAJENTA (CAP); linagliptin, metformin - JENTADUETO (CAP) - PSUSA/00010427/202105

Applicant(s): Boehringer Ingelheim International GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.35. Luspatercept - REBLOZYL (CAP) - PSUSA/00010860/202106

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Laurence de Fays

Scope: Evaluation of a PSUSA procedure

16.1.36. Migalastat - GALAFOLD (CAP) - PSUSA/00010507/202105

Applicant: Amicus Therapeutics Europe Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.37. Netarsudil - RHOKIINSA (CAP) - PSUSA/00107812/202106

Applicant: Aerie Pharmaceuticals Ireland Limited

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

16.1.38. Nevirapine - VIRAMUNE (CAP) - PSUSA/00002147/202105

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.1.39. Nonacog beta pegol - REFIXIA (CAP) - PSUSA/00010608/202105

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.40. Nusinersen - SPINRAZA (CAP) - PSUSA/00010595/202105

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.41. Obeticholic acid - OCALIVA (CAP) - PSUSA/00010555/202105

Applicant: Intercept Pharma International Limited

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

16.1.42. Onasemnogene abeparvovec - ZOLGENSMA (CAP) - PSUSA/00010848/202105

Applicant: Novartis Gene Therapies EU Limited, ATMP[80]

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.43. Pandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) - ADJUPANRIX (CAP) - PSUSA/00002281/202105

Applicant: GlaxoSmithkline Biologicals SA

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.44. Pentosan polysulfate sodium[81] - ELMIRON (CAP) - PSUSA/00010614/202106

Applicant: bene-Arzneimittel GmbH

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.1.45. Pertuzumab - PERJETA (CAP) - PSUSA/00010125/202106

Applicant: Roche Registration GmbH

PRAC Rapporteur: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

16.1.46. Pertuzumab, trastuzumab - PHESGO (CAP) - PSUSA/00010906/202106

Applicant: Roche Registration GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.47. Polatuzumab vedotin - POLIVY (CAP) - PSUSA/00010817/202106

Applicant: Roche Registration GmbH

PRAC Rapporteur: Annika Folin

[80] Advanced therapy medicinal product
[81] Centrally authorised product(s) only

Scope: Evaluation of a PSUSA procedure

16.1.48. Propranolol[82] - HEMANGIOL (CAP) - PSUSA/00010250/202104

Applicant: Pierre Fabre Dermatologie

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

16.1.49. Rilpivirine[83] - EDURANT (CAP) - PSUSA/00009282/202105

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

16.1.50. Semaglutide - OZEMPIC (CAP); RYBELSUS (CAP) - PSUSA/00010671/202105

Applicant(s): Novo Nordisk A/S

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

16.1.51. Sofosbuvir, velpatasvir - EPCLUSA (CAP) - PSUSA/00010524/202106

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.1.52. Sonidegib - ODOMZO (CAP) - PSUSA/00010408/202106

Applicant: Sun Pharmaceutical Industries Europe B.V.

PRAC Rapporteur: Željana Margan Koletić

Scope: Evaluation of a PSUSA procedure

16.1.53. Tozinameran - COMIRNATY (CAP) - PSUSA/00010898/202106

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.54. Trametinib - MEKINIST (CAP) - PSUSA/00010262/202105

Applicant: Novartis Europharm Limited

PRAC Rapporteur: David Olsen

[82] Centrally authorised product(s) only
[83] Oral use only

Scope: Evaluation of a PSUSA procedure

16.1.55. Trastuzumab deruxtecan - ENHERTU (CAP) - PSUSA/00010894/202106

Applicant: Daiichi Sankyo Europe GmbH

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Evaluation of a PSUSA procedure

16.1.56. Treosulfan[84] - TRECONDI (CAP) - PSUSA/00010777/202106

Applicant: medac Gesellschaft fur klinische Spezialpraparate mbH

PRAC Rapporteur: Julia Pallos

Scope: Evaluation of a PSUSA procedure

16.1.57. Turoctocog alfa pegol - ESPEROCT (CAP) - PSUSA/00010782/202106

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Brigitte Keller-Stanislawski

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. Capsaicin - QUTENZA (CAP); NAP - PSUSA/00000533/202105

Applicants: Grunenthal GmbH (Qutenza), various

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.2.2. Measles, mumps, rubella vaccines (live, attenuated) - M-M-RVAXPRO (CAP); NAP - PSUSA/00001937/202105

Applicants: MSD Vaccins (M-M-RVAXPRO), various

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.2.3. Treprostinil - TREPULMIX (CAP); NAP - PSUSA/00003013/202105

Applicants: SciPharm Sarl (Trepulmix), various

PRAC Rapporteur: Zane Neikena

Scope: Evaluation of a PSUSA procedure

[84] Centrally authorised product(s) only

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

16.3.1. 5 fluorouracil, salicylic acid (NAP) - PSUSA/00000008/202105

Applicant(s): various

PRAC Lead: Marek Juracka

Scope: Evaluation of a PSUSA procedure

16.3.2. Acipimox (NAP) - PSUSA/00000050/202105

Applicant(s): various

PRAC Lead: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

16.3.3. Amino acid combinations, glucose, triglyceride combinations[85], with or without electrolytes, mineral compounds (NAP) [86] [87] - PSUSA/00010565/202106

Applicant(s): various

PRAC Lead: Melinda Palfi

Scope: Evaluation of a PSUSA procedure

16.3.4. Amino acid combinations, glucose, with or without electrolytes, mineral compounds[88] (NAP) - PSUSA/00010566/202106

Applicant(s): various

PRAC Lead: Polona Golmajer

Scope: Evaluation of a PSUSA procedure

16.3.5. Bismuth subcitrate potassium, metronidazole, tetracycline (NAP) - PSUSA/00010199/202105

Applicant(s): various

PRAC Lead: Nikica Mirošević Skvrce

Scope: Evaluation of a PSUSA procedure

16.3.6. Cidofovir (NAP) - PSUSA/00010558/202106

Applicant(s): various

PRAC Lead: Rugilė Pilvinienė

Scope: Evaluation of a PSUSA procedure

[85] E.g. olive oil, soya bean oil, fish oil
[86] Intravenous (I.V.) application only
[87] Except for the combination with nationally authorised product Numeta
[88] Intravenous (I.V.) application only

16.3.7. Clevidipine (NAP) - PSUSA/00010288/202105

Applicant(s): various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.3.8. Daunorubicin (NAP) - PSUSA/00000936/202106

Applicant(s): various

PRAC Lead: Sonja Hrabcik

Scope: Evaluation of a PSUSA procedure

16.3.9. Flunarizine (NAP) - PSUSA/00001416/202105

Applicant(s): various

PRAC Lead: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.3.10. Goserelin (NAP) - PSUSA/00001562/202105

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.3.11. Human hemin (NAP) - PSUSA/00001629/202105

Applicant(s): various

PRAC Lead: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

16.3.12. Iodine (^{131}I) iobenguane (NAP) - PSUSA/00001764/202105

Applicant(s): various

PRAC Lead: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

16.3.13. Lanreotide (NAP) - PSUSA/00001826/202105

Applicant(s): various

PRAC Lead: Zane Neikena

Scope: Evaluation of a PSUSA procedure

16.3.14. Levofloxacin, dexamethasone[89] (NAP) - PSUSA/00010881/202106

Applicant(s): various

PRAC Lead: Ilaria Baldelli

Scope: Evaluation of a PSUSA procedure

16.3.15. Milnacipran (NAP) - PSUSA/00002063/202104

Applicant(s): various

PRAC Lead: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

16.3.16. Misoprostol[90] (NAP) - PSUSA/00010291/202106

Applicant(s): various

PRAC Lead: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

16.3.17. Misoprostol[91] (NAP) - PSUSA/00010353/202105

Applicant(s): various

PRAC Lead: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

16.3.18. Moxifloxacin[92] (NAP) - PSUSA/00002094/202105

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.3.19. Nadifloxacin (NAP) - PSUSA/00002102/202105

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.3.20. Olodaterol, tiotropium (NAP) - PSUSA/00010489/202105

Applicant(s): various

PRAC Lead: Menno van der Elst

[89] Formulation(s) for ocular use only
[90] Gastrointestinal indication(s) only
[91] Gynaecological indication(s) only - labour induction
[92] Topical ophthalmic use only

Scope: Evaluation of a PSUSA procedure

16.3.21. Pamidronate (NAP) - PSUSA/00002269/202105

Applicant(s): various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.3.22. Phenylpropanolamine (NAP) - PSUSA/00010483/202106

Applicant(s): various

PRAC Lead: Eva Jirsová

Scope: Evaluation of a PSUSA procedure

16.3.23. Ranitidine (NAP) - PSUSA/00002610/202105

Applicant(s): various

PRAC Lead: Ilaria Baldelli

Scope: Evaluation of a PSUSA procedure

16.3.24. Triglyceride combinations[93], with or without mineral compounds, electrolytes[94] (NAP) - PSUSA/00010648/202106

Applicant(s): various

PRAC Lead: Nikica Mirošević Skvrce

Scope: Evaluation of a PSUSA procedure

16.4. Follow-up to PSUR/PSUSA procedures

16.4.1. Pregabalin - LYRICA (CAP) - EMEA/H/C/000546/LEG 056

Applicant: Upjohn EESV

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Review of Northern Ireland (NI) Health and Social Care Board letter to prescribers on the removal of pregabalin from NI formulary for neuropathic pain, as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00002511/202101) adopted in September 2021

16.4.2. Pregabalin - PREGABALIN PFIZER (CAP) - EMEA/H/C/003880/LEG 008

Applicant: Upjohn EESV

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Review of Northern Ireland (NI) Health and Social Care Board letter to prescribers

[93] E.g. olive oil, soya bean oil, fish oil
[94] Intravenous (I.V.) application only

on the removal of pregabalin from NI formulary for neuropathic pain, as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00002511/202101) adopted in September 2021

16.4.3. Tenofovir disoproxil - VIREAD (CAP) - EMEA/H/C/000419/LEG 278

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Nathalie Gault

Scope: Detailed analysis of cases of neural tube defects following exposure to tenofovir disoproxil fumarate (TDF) in pregnancy including information on concomitant treatment, as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00002892/202003) adopted in November 2020

16.5. Variation procedure(s) resulting from PSUSA evaluation

16.5.1. Tozinameran - 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

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

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

17.1. Protocols of PASS imposed in the marketing authorisation(s)[95]

17.1.1. Lenalidomide - REVLIMID (CAP) - EMEA/H/C/PSA/S/0075.1

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Tiphaine Vaillant

Scope: MAH's response to PSA/S/0075 [substantial amendment to a protocol previously agreed in December 2017 (PSA/S/0016.2) for study CC-5013-MDS-012: a post-authorisation, non-interventional, retrospective, drug-utilisation study (DUS) to describe the pattern of use of lenalidomide in patients with myelodysplastic syndromes (MDS)] as per the request for supplementary information (RSI) adopted in September 2021

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

17.1.2. Parathyroid hormone – NATPAR (CAP) - EMEA/H/C/PSA/S/0053.4

Applicant: Takeda Pharmaceuticals International AG

PRAC Rapporteur: Rhea Fitzgerald

Scope: MAH's response to PSA/S/0053.3 [substantial amendment to a protocol previously agreed in March 2018 (PSA/S/0026) for study PARADIGHM (physicians advancing disease knowledge in hypoparathyroidism): a registry for subjects with chronic hypoparathyroidism to explore physicians advancing disease knowledge in hypoparathyroidism] as per the request for supplementary information (RSI) adopted in September 2021

17.1.3. Selumetinib - KOSELUGO (CAP) - EMEA/H/C/PSP/S/0095.1

Applicant: AstraZeneca AB

PRAC Rapporteur: Annika Folin

Scope: MAH's response to PSA/S/0053.3 [protocol for a PASS of paediatric patients initiating selumetinib: a multiple-country prospective cohort study] as per the request for supplementary information (RSI) adopted in November 2021

17.1.4. Tisagenlecleucel - KYMRIAH (CAP) - EMEA/H/C/PSA/S/0080

Applicant: Novartis Europharm Limited, ATMP[96]

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Substantial amendment to a protocol previously agreed in November 2019 (PSP/S/0066.3) for registry study CCTL019B2401 to assess the long-term safety of patients with B lymphocyte malignancies treated with tisagenlecleucel

17.1.5. Valproate[97] (NAP) - EMEA/H/N/PSP/J/0074.4

Applicant: Sanofi-Aventis Recherche & Développement (on behalf of a consortium)

PRAC Rapporteur: Jean-Michel Dogné

Scope: Interim report for a joint observational study to evaluate and identify the best practices for switching of valproate in clinical practice, as required in the outcome of the referral procedure under Article 31 of Directive 2001/83/EC on valproate-containing products completed in February 2018 (EMEA/H/A-31/1454)]

17.1.6. Valproate[98] (NAP) - EMEA/H/N/PSA/J/0077

Applicant: Sanofi-Aventis Recherche & Développement (on behalf of a consortium)

PRAC Rapporteur: Jean-Michel Dogné

Scope: Substantial amendment to a protocol previously agreed in July 2020 (PSP/0074.3) for an observational study to evaluate and identify the best practices for switching of

[96] Advanced therapy medicinal product
[97] Valproic acid, sodium valproate, valproate pivoxil, valproate semisodium, valpriomide, valproate bismuth, calcium valproate, valproate magnesium
[98] Valproic acid, sodium valproate, valproate pivoxil, valproate semisodium, valpriomide, valproate bismuth, calcium valproate, valproate magnesium

valproate in clinical practice

17.1.7. Voretigene neparvovec - LUXTURNA (CAP) - EMEA/H/C/PSA/S/0081

Applicant: Novartis Europharm Ltd, ATMP[99]

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Substantial amendment to a protocol previously agreed in March 2021 (PSA/S/0066) for a post-authorisation multicentre, multinational, longitudinal, observational safety registry study to collect long-term safety information associated with voretigene neparvovec (vector and/or transgene), its subretinal injection procedure, the concomitant use of corticosteroids, or a combination of these procedures and products

17.2. Protocols of PASS non-imposed in the marketing authorisation(s)[100]

17.2.1. Alpelisib - PIQRAY (CAP) - EMEA/H/C/004804/MEA 003.1

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to MEA 003.1 [protocol for study CBYL719C2005: a survey among healthcare professionals treating patients with metastatic breast cancer in selected European countries to evaluate their knowledge on management of hyperglycaemia when using Piqray (alpelisib) as included in the educational material] as per the request for supplementary information (RSI) adopted in September 2021

17.2.2. Cabotegravir - VOCABRIA (CAP) - EMEA/H/C/004976/MEA 004.2

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Martin Huber

Scope: MAH's response to MEA 004.1 [protocol for study 215162 (listed as a category 3 study in the RMP): a prospective observational cohort study to monitor for hepatotoxicity and regimen discontinuation due to liver related adverse events among patients initiating cabotegravir-containing antiretroviral regimen [final clinical study report (CSR): expected in March 2027]] as per the request for supplementary information (RSI) adopted in September 2021

17.2.3. Cabotegravir - VOCABRIA (CAP) - EMEA/H/C/004976/MEA 005.2

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Martin Huber

Scope: MAH's response to MEA 005.1 [protocol for study 215163: a study on pregnancy and neonatal outcomes following prenatal exposure to cabotegravir long acting (CAB LA) – data from the European Pregnancy and Paediatric human immunodeficiency virus (HIV) Cohort Collaboration (EPPICC)] as per the request for supplementary information (RSI)

[99] Advanced therapy medicinal product
[100] 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

adopted in September 2021

17.2.4. Cabotegravir - VOCABRIA (CAP) - EMEA/H/C/004976/MEA 006.2

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Martin Huber

Scope: MAH's response to MEA 006.1 [protocol for study 215325: a study on pregnancy and neonatal outcomes following prenatal exposure to cabotegravir – data from the Antiretroviral Pregnancy Registry (APR)] as per the request for supplementary information (RSI) adopted in September 2021

17.2.5. Coronavirus (COVID-19) mRNA[101] vaccine (nucleoside-modified) - SPIKEVAX (CAP) - EMEA/H/C/005791/MEA 004.4

Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Hans Christian Siersted

Scope: MAH's response to MEA 004.3 [protocol for study mRNA-1273-P904 (study 1) (listed as a category 3 study in the RMP): a post-authorisation active surveillance safety study using secondary data to monitor real-world safety of Spikevax (COVID-19 mRNA-1273 vaccine) in Europe - an enhanced pharmacovigilance study to provide additional evaluation of adverse events of special interest (AESI) and emerging validated safety signals in European populations and electronic database assessment of use in pregnant women [final clinical study report (CSR) expected in December 2023]] as per the request for supplementary information (RSI) adopted in July 2021 together with the first study progress report for study mRNA-1273-P904

17.2.6. Isatuximab - SARCLISA (CAP) - EMEA/H/C/004977/MEA 002.2

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Eva Segovia

Scope: MAH's response to MEA 002.1 [protocol for study SARSAC09715: a non-interventional PASS survey to evaluate the effectiveness of isatuximab educational materials to minimise the risk of interference for blood typing (minor antigen) (positive indirect Coombs' test)] as per the request for supplementary information (RSI) adopted in September 2021

17.2.7. Patisiran - ONPATTRO (CAP) - EMEA/H/C/004699/MEA 003.2

Applicant: Alnylam Netherlands B.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: Update to a previously agreed protocol and interim study report for study ALN-TTR02-010: patisiran- lipid nanoparticle (LNP) pregnancy surveillance programme (PSP) to collect primary data on pregnant women from the US, the United Kingdom (UK), France, Spain, Italy, Portugal and Germany, and other potential countries, who have been exposed to patisiran during the exposure window, defined as 12 weeks prior to their last menstrual

[101] Messenger ribonucleic acid

period (LMP), or at any time during pregnancy as well as to collect and analyse information pertaining to pregnancy complications and birth outcomes in women exposed to patisiran during pregnancy

17.2.8. Risankizumab - SKYRIZI (CAP) - EMEA/H/C/004759/MEA 001.4

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Substantial amendment to a protocol previously agreed in January 2021 for study P19-633: a post-marketing registry-based prospective cohort study of long-term safety of risankizumab in real world setting in Denmark and Sweden [final study report expected in December 2031] together with a statistical analysis plan (SAP)

17.2.9. Sacubitril, valsartan - ENTRESTO (CAP) - EMEA/H/C/004062/MEA 002.7

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Anette Kirstine Stark

Scope: Substantial amendment to a previously agreed protocol for study CLCZ696B2014 (PASS 1) (listed as a category 3 study in the RMP): a non-interventional post-authorisation European multi-database safety study to characterise the risk of angioedema and other specific safety events of interest in association with the use of Entresto/Neparvis (sacubitril/valsartan) in adult patients with heart failure [final report expected in Q4 2022] together with a statistical analysis plan (SAP)

17.2.10. Sacubitril, valsartan - NEPARVIS (CAP) - EMEA/H/C/004343/MEA 002.4

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Anette Kirstine Stark

Scope: Substantial amendment to a previously agreed protocol for study CLCZ696B2014 (PASS 1) (listed as a category 3 study in the RMP): a non-interventional post-authorisation European multi-database safety study to characterise the risk of angioedema and other specific safety events of interest in association with the use of Entresto/Neparvis (sacubitril/valsartan) in adult patients with heart failure [final report expected in Q4 2022] together with a statistical analysis plan (SAP)

17.2.11. Somapacitan - SOGROYA (CAP) - EMEA/H/C/005030/MEA 002.1

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Martin Huber

Scope: MAH's response to MEA 002 [protocol for study NN8640-4515: a multinational, multicentre, prospective, open label, single-arm, observational, non-interventional PASS to investigate long-term safety of somapacitan in adults with growth hormone deficiency (AGHD) under normal clinical practice conditions (from initial marketing authorisation/opinion)] as per the request for supplementary information (RSI) adopted in September 2021

17.2.12. Trastuzumab deruxtecan - ENHERTU (CAP) - EMEA/H/C/005124/MEA 003.1

Applicant: Daiichi Sankyo Europe GmbH

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: MAH's response to MEA 003 [protocol for an EU survey of relevant healthcare professionals on the understanding of key risk minimisation measures pertaining to interstitial lung disease (ILD)/pneumonitis with trastuzumab deruxtecan treatment (from initial marketing authorisation/opinion)] as per the request for supplementary information (RSI) adopted in September 2021

17.3. Results of PASS imposed in the marketing authorisation(s)[102]

None

17.4. Results of PASS non-imposed in the marketing authorisation(s)[103]

17.4.1. Apremilast - OTEZLA (CAP) - EMEA/H/C/003746/II/0039

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Eva Segovia

Scope: Submission of the final study report (CSR) from the UK Clinical Practice Research Database (CPRD) (listed as a category 3 study in the RMP): an observational study to assess the long-term data of apremilast in patients with psoriasis and psoriatic arthritis. The RMP (version 14.0) is updated accordingly

17.4.2. 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

17.4.3. Infliximab - REMICADE (CAP) - EMEA/H/C/000240/II/0231

Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of the final report of the Remicade (infliximab) Anti-Rheumatic Therapy in Sweden (ARTIS) register study. The RMP (version 20.1) is updated accordingly and with revisions agreed in previous procedures

[102] In accordance with Article 107p-q of Directive 2001/83/EC
[103] 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

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

17.4.5. Insulin glargine, lixisenatide - SULIQUA (CAP) - EMEA/H/C/004243/II/0024

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Menno van der Elst

Scope: Submission of the final clinical study report (CSR) of study INSLIC08571 (listed as a category 3 study in the RMP): a survey to evaluate the knowledge and understanding of the key safety messages in the healthcare professional guide and the patient guide (in fulfilment of MEA 002). The RMP (version 6.0) is updated accordingly

17.4.6. Naloxegol - MOVENTIG (CAP) - EMEA/H/C/002810/II/0034

Applicant: Kyowa Kirin Holdings B.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: Submission of the final report from study D3820R00006 (listed as a category 3 study in the RMP): an observational drug utilisation in selected European populations. The RMP (version 7.0) is updated accordingly

17.4.7. Susoctocog alfa - OBIZUR (CAP) - EMEA/H/C/002792/II/0043

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Submission of the final report from study US PASS 241302 (EUPAS36659) (listed as a category 3 study in the RMP): a post-marketing non-interventional safety evaluation of Obizur (susoctocog alfa) in the treatment of bleeding episodes for patients with acquired haemophilia A (AHA) to determine the incidence of therapy-related serious adverse events (SAEs) in patients with AHA who are prescribed and treated with Obizur (susoctocog alfa) in routine clinical practice. The RMP (version 5.0) is updated accordingly

17.4.8. 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

17.4.9. Trastuzumab - ONTRUZANT (CAP) - EMEA/H/C/004323/II/0036

Applicant: Samsung Bioepis NL B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Submission of the final report from clinical study SB3-G31-BC-E (listed as a category 3 study in the RMP): an observational cohort study assessing the long-term cardiac safety (for cardiac safety and survival cohort) and survival (survival only cohort and cardiac safety and survival cohort) in patients who received treatment with trastuzumab. The RMP (version 5.0) is updated accordingly

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

17.5.1. Aclidinium - BRETARIS GENUAIR (CAP) - EMEA/H/C/002706/ANX 001.10

Applicant: AstraZeneca AB

PRAC Rapporteur: Adam Przybylkowski

Scope: MAH's response to ANX 001.9 [third interim report for study D6560R00004, formerly M/34273/44, (listed as a category 1 in Annex II and the RMP): an observational study evaluating the risk of cardiovascular endpoints of aclidinium bromide-containing products versus other chronic obstructive pulmonary disease (COPD) medications in COPD patients - sub-study report addressing the acute myocardial infarction (AMI) report and stroke components of the PASS programme] as per the request for supplementary information (RSI) adopted in September 2021

17.5.2. Aclidinium - EKLIRA GENUAIR (CAP) - EMEA/H/C/002211/ANX 001.10

Applicant: AstraZeneca AB

PRAC Rapporteur: Adam Przybylkowski

Scope: MAH's response to ANX 001.9 [third interim report for study D6560R00004, formerly M/34273/44, (listed as a category 1 in Annex II and the RMP): an observational study evaluating the risk of cardiovascular endpoints of aclidinium bromide-containing products versus other chronic obstructive pulmonary disease (COPD) medications in COPD patients - sub-study report addressing the acute myocardial infarction (AMI) report and stroke components of the PASS programme] as per the request for supplementary information (RSI) adopted in September 2021

17.5.3. Aclidinium, formoterol fumarate dihydrate - BRIMICA GENUAIR (CAP) - EMEA/H/C/003969/ANX 003.7

Applicant: AstraZeneca AB

PRAC Rapporteur: Adam Przybylkowski

Scope: MAH's response to ANX 003.6 [third interim report for study D6560R00004, formerly M/34273/44, (listed as a category 1 in Annex II and the RMP): an observational study evaluating the risk of cardiovascular endpoints of aclidinium bromide-containing products versus other chronic obstructive pulmonary disease (COPD) medications in COPD

patients - sub-study report addressing the acute myocardial infarction (AMI) report and stroke components of the PASS programme] as per the request for supplementary information (RSI) adopted in September 2021

17.5.4. Aclidinium, formoterol fumarate dihydrate - DUAKLIR GENUAIR (CAP) - EMEA/H/C/003745/ANX 003.7

Applicant: AstraZeneca AB

PRAC Rapporteur: Adam Przybylkowski

Scope: MAH's response to ANX 003.6 [third interim report for study D6560R00004, formerly M/34273/44, (listed as a category 1 in Annex II and the RMP): an observational study evaluating the risk of cardiovascular endpoints of aclidinium bromide-containing products versus other chronic obstructive pulmonary disease (COPD) medications in COPD patients - sub-study report addressing the acute myocardial infarction (AMI) report and stroke components of the PASS programme] as per the request for supplementary information (RSI) adopted in September 2021

17.5.5. Burosumab - CRYSVITA (CAP) - EMEA/H/C/004275/MEA 004.3

Applicant: Kyowa Kirin Holdings B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: First interim report for study 2019-36-EU-CRY (EUPAS32190): a non-interventional study in the treatment of children >1 year of age and adolescents with X-linked hypophosphataemia (XLH) to assess the long-term safety of Crysvita (burosumab) during routine clinical care using data collected in a European disease registry for XLH [final report expected in December 2028]

17.5.6. Cangrelor - KENGREXAL (CAP) - EMEA/H/C/003773/MEA 002.4

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Amelia Cupelli

Scope: Second interim report for study DFIDM-1801 (ARCANGELO (itAlian pRospective study on CANGrELOr)): a multicentre prospective observational study of acute coronary syndrome patients undergoing percutaneous coronary intervention (PCI) who receive cangrelor and transition to either clopidogrel, prasugrel or ticagrelor

17.5.7. Cladribine - MAVENCLAD (CAP) - EMEA/H/C/004230/MEA 002.2

Applicant: Merck Europe B.V.

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: First interim report for study MS 700568-0002 (listed as a category 3 study in the RMP): a prospective, observational cohort study evaluating the safety profile, in terms of incidence of adverse events of special interest, in patients with highly active relapsing multiple sclerosis (RMS) newly started on oral cladribine [final report expected in Q2 2034]

17.5.8. Coronavirus (COVID-19) vaccine (ChAdOx1-S [recombinant]) - VAXZEVRIA (CAP) - EMEA/H/C/005675/MEA 005.2

Applicant: AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

Scope: First interim report for study D8111R00003: a phase 4 non-interventional enhanced active surveillance study of adults vaccinated with Vaxzevria (AZD1222 – COVID-19 vaccine)

17.5.9. Coronavirus (COVID-19) vaccine (ChAdOx1-S [recombinant]) - VAXZEVRIA (CAP) - EMEA/H/C/005675/MEA 006.2

Applicant: AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

Scope: First quarterly report for study C-VIPER: a pregnancy registry of women exposed to Vaxzevria (AZD1222 – COVID-19 vaccine) immediately before or during pregnancy (from initial opinion/marketing authorisation(s) (MA))

17.5.10. Coronavirus (COVID-19) vaccine (ChAdOx1-S [recombinant]) - VAXZEVRIA (CAP) - EMEA/H/C/005675/MEA 007.3

Applicant: AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

Scope: First progress report for study D8111R00006: a post-authorisation/post-marketing observational study using existing secondary health data sources to evaluate the association between exposure to Vaxzevria (AZD1222) and safety concerns.

17.5.11. Coronavirus (COVID-19) mRNA[104] vaccine (nucleoside-modified) - SPIKEVAX (CAP) - EMEA/H/C/005791/MEA 003.4

Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Hans Christian Siersted

Scope: Third Interim report for a study (listed as a category 3 study in the RMP): a post authorisation safety of Spikevax (SARS-CoV-2 mRNA-1273 vaccine) in the US - an enhanced pharmacovigilance study (listed as a category 3 study in the RMP) to provide additional evaluation of adverse events of special interest (AESI) and emerging validated safety signals [final clinical study report (CSR) expected in June 2023] (from initial opinion/marketing authorisation (MA))

17.5.12. Ketoconazole - KETOCONAZOLE HRA (CAP) - EMEA/H/C/003906/ANX 002.8

Applicant: HRA Pharma Rare Diseases

PRAC Rapporteur: Željana Margan Koletić

Scope: Fourth interim annual report for a prospective, multi-country, observational registry

[104] Messenger ribonucleic acid

study to collect clinical information on patients with endogenous Cushing's syndrome exposed to ketoconazole using the existing European registry on Cushing's syndrome (ERCUSYN) to assess drug utilisation pattern and to document the safety (e.g. hepatotoxicity, QT prolongation) and effectiveness of ketoconazole

17.5.13. Romosozumab - EVENITY (CAP) - EMEA/H/C/004465/MEA 001.3

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Tiphaine Vaillant

Scope: Second interim report for study OP0005: a European non-interventional PASS to study the adherence to the risk minimisation measures (RMMs) in the product information by estimating the compliance with contraindications and target indication(s) amongst incident romosozumab users, and analysing the utilisation pattern using the EU-adverse drug reactions (EU-ADR) Alliance [final study results expected in March 2026]

17.5.14. Romosozumab - EVENITY (CAP) - EMEA/H/C/004465/MEA 002.3

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Tiphaine Vaillant

Scope: Second interim report for study OP0004: a European non-interventional PASS to evaluate potential differences in terms of serious cardiovascular adverse events between romosozumab and currently available therapies used in comparable patients in real-world conditions using the EU-adverse drug reactions (EU-ADR) Alliance [final study results expected in December 2026]

17.5.15. Romosozumab - EVENITY (CAP) - EMEA/H/C/004465/MEA 003.2

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Tiphaine Vaillant

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

17.5.16. Sacubitril, valsartan - ENTRESTO (CAP) - EMEA/H/C/004062/MEA 004.11

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Anette Kirstine Stark

Scope: Fourth interim results for study CLCZ696B2015 (PASS 3) (listed as a category 3 study in the RMP): a non-interventional post-authorisation European multi-database safety study to assess the risk of myotoxicity, hepatotoxicity and acute pancreatitis in statin-exposed heart failure patients with or without concomitant use of Entresto/Neparvis (sacubitril/valsartan) [final study report expected in December 2022]

17.5.17. Sacubitril, valsartan - NEPARVIS (CAP) - EMEA/H/C/004343/MEA 003.8

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Anette Kirstine Stark

Scope: Fourth interim results for study CLCZ696B2015 (PASS 3) (listed as a category 3 study in the RMP): a non-interventional post-authorisation European multi-database safety study to assess the risk of myotoxicity, hepatotoxicity and acute pancreatitis in statin-exposed heart failure patients with or without concomitant use of Entresto/Neparvis (sacubitril/valsartan) [final study report expected in December 2022]

17.5.18. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/MEA 045.7

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Rhea Fitzgerald

Scope: MAH’s response to MEA 045.6 [second interim report for study RRA-20745: an observational PASS to describe the safety of ustekinumab and other Crohn’s disease treatments in a cohort of patients with Crohn’s disease] as per the request for supplementary information (RSI) adopted in September 2021

17.6. Others

17.6.1. Cabazitaxel - CABAZITAXEL ACCORD (CAP) - EMEA/H/C/005178/MEA 001.1

Applicant: Accord Healthcare S.L.U.

PRAC Rapporteur: Tiphaine Vaillant

Scope: Second six-monthly review of cases of ‘medication error’ for cabazitaxel reported during routine signal management activities

17.6.2. Fentanyl - INSTANYL (CAP) - EMEA/H/C/000959/LEG 028.4

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Tiphaine Vaillant

Scope: Fifth six-monthly update on the development of the child-resistant multi-dose nasal spray DoseGuard as requested in the conclusions of procedure R/0049 finalised in April 2019

17.6.3. Insulin human - INSUMAN (CAP) - EMEA/H/C/000201/MEA 041.5

Applicant: Sanofi-Aventis Deutschland GmbH

PRAC Rapporteur: Jean-Michel Dogné

Scope: MAH's request of early termination of study HUBIN-C-06380: a European observational cohort of patients with type 1 diabetes treated via intraperitoneal route with Insuman Implantable 400 IU/mL in Medtronic MiniMed implantable pump

17.6.4. Lopinavir, ritonavir - KALETRA (CAP) - EMEA/H/C/000368/LEG 121.4

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Nathalie Gault

Scope: Fourth annual safety review of the PENTA - European Pregnancy and Paediatric human immunodeficiency virus (HIV) Cohort Collaboration (EPPICC) cohort study conducted in children from 14 days to 2 years of age as regards to chronic exposure to propylene glycol and ethanol and toxicity, medication errors and lack of efficacy/resistance in relation to potentially suboptimal pharmacokinetic (PK) parameters

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 the agreed criteria, the procedures were finalised at the PRAC level without further plenary discussion.

18.1. Annual reassessments of the marketing authorisation

18.1.1. Idebenone - RAXONE (CAP) - EMEA/H/C/003834/S/0029 (with RMP)

Applicant: Santhera Pharmaceuticals (Deutschland) GmbH

PRAC Rapporteur: Amelia Cupelli

Scope: Annual reassessment of the marketing authorisation

18.1.2. Metreleptin - MYALEPTA (CAP) - EMEA/H/C/004218/S/0023 (without RMP)

Applicant: Amryt Pharmaceuticals DAC

PRAC Rapporteur: Adam Przybylkowski

Scope: Annual reassessment of the marketing authorisation

18.2. Conditional renewals of the marketing authorisation

18.2.1. Andexanet alfa - ONDEXXYA (CAP) - EMEA/H/C/004108/R/0025 (without RMP)

Applicant: Alexion Europe SAS

PRAC Rapporteur: Menno van der Elst

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. Lorlatinib - LORVIQUA (CAP) - EMEA/H/C/004646/R/0019 (without RMP)

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Conditional renewal of the marketing authorisation

18.2.5. Pandemic influenza vaccine (H5N1) (live attenuated, nasal) - PANDEMIC INFLUENZA VACCINE H5N1 ASTRAZENECA (CAP) - EMEA/H/C/003963/R/0047 (without RMP)

Applicant: AstraZeneca AB

PRAC Rapporteur: Sonja Hrabcik

Scope: Conditional renewal of the marketing authorisation

18.2.6. Rucaparib - RUBRACA (CAP) - EMEA/H/C/004272/R/0030 (without RMP)

Applicant: Clovis Oncology Ireland Limited

PRAC Rapporteur: Annika Folin

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. Brodalumab - KYNTHEUM (CAP) - EMEA/H/C/003959/R/0019 (with RMP)

Applicant: LEO Pharma A/S

PRAC Rapporteur: Eva Segovia

Scope: 5-year renewal of the marketing authorisation

18.3.3. Carglumic acid - UCEDANE (CAP) - EMEA/H/C/004019/R/0011 (without RMP)

Applicant: Eurocept International B.V.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: 5-year renewal of the marketing authorisation

18.3.4. Cariprazine - REAGILA (CAP) - EMEA/H/C/002770/R/0026 (with RMP)

Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: 5-year renewal of the marketing authorisation

18.3.5. Cenegermin - OXERVATE (CAP) - EMEA/H/C/004209/R/0037 (with RMP)

Applicant: Dompe farmaceutici S.p.A.

PRAC Rapporteur: Jan Neuhauser

Scope: 5-year renewal of the marketing authorisation

18.3.6. Cerliponase alfa - BRINEURA (CAP) - EMEA/H/C/004065/R/0034 (without RMP)

Applicant: BioMarin International Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: 5-year renewal of the marketing authorisation

18.3.7. Dupilumab - DUPIXENT (CAP) - EMEA/H/C/004390/R/0053 (without RMP)

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Kimmo Jaakkola

Scope: 5-year renewal of the marketing authorisation

18.3.8. Efavirenz, emtricitabine, tenofovir disoproxil - EFAVIRENZ/EMTRICITABINE/TENOFOVIR DISOPROXIL ZENTIVA (CAP) - EMEA/H/C/004250/R/0025 (without RMP)

Applicant: Zentiva k.s.

PRAC Rapporteur: Martin Huber

Scope: 5-year renewal of the marketing authorisation

18.3.9. Etanercept - ERELZI (CAP) - EMEA/H/C/004192/R/0037 (with RMP)

Applicant: Sandoz GmbH

PRAC Rapporteur: Eva Segovia

Scope: 5-year renewal of the marketing authorisation

18.3.10. Glecaprevir, pibrentasvir - MAVIRET (CAP) - EMEA/H/C/004430/R/0048 (without RMP)

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: 5-year renewal of the marketing authorisation

18.3.11. Insulin lispro - INSULIN LISPRO SANOFI (CAP) - EMEA/H/C/004303/R/0013 (with RMP)

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Annika Folin

Scope: 5-year renewal of the marketing authorisation

18.3.12. Osimertinib - TAGRISSO (CAP) - EMEA/H/C/004124/R/0044 (with RMP)

Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: 5-year renewal of the marketing authorisation

18.3.13. 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

18.3.14. Ribociclib - KISQALI (CAP) - EMEA/H/C/004213/R/0034 (without RMP)

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Anette Kirstine Stark

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 10-13 January 2022 plenary meeting (marked as "a"), for the 20 January 2022 extraordinary PRAC meeting (marked as "b") and the 26 January 2022 extraordinary PRAC meeting/ORGAM TC (marked as "c").

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Sabine Straus [a, b, c]	Chair	Netherlands	No interests declared	Full involvement
Jan Neuhauser [a, c]	Member	Austria	No interests declared	Full involvement
Sonja Hrabcik [a, b, c]	Alternate	Austria	No interests declared	Full involvement
Jean-Michel Dogné [a, c]	Member	Belgium	No interests declared	Full involvement
Laurence de Fays [a, b, c]	Alternate	Belgium	No interests declared	Full involvement
Maria Popova-Kiradjieva [a, b, c]	Member	Bulgaria	No interests declared	Full involvement
Nikica Mirošević Skvrce [a, b, c]	Member	Croatia	No interests declared	Full involvement
Željana Margan Koletić [a, c]	Alternate	Croatia	No interests declared	Full involvement
Elena Kaisis [a, b, c]	Member	Cyprus	No interests declared	Full involvement
Panagiotis Psaras [a, b, c]	Alternate	Cyprus	No interests declared	Full involvement
Eva Jirsová [a, b, c]	Member	Czechia	No interests declared	Full involvement
Jana Lukacisinova [a, b, c]	Alternate	Czechia	No interests declared	Full involvement
Anette Kirstine Stark [a, b, c]	Member	Denmark	No interests declared	Full involvement
Hans Christian Siersted [a, b, c]	Alternate	Denmark	No restrictions applicable to this meeting	Full involvement
Maia Uusküla [c]	Member	Estonia	No interests declared	Full involvement
Krõõt Aab [a, b, c]	Alternate	Estonia	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
Kirsti Villikka [a, b]	Member	Finland	No interests declared	Full involvement
Kimmo Jaakkola [a, b, c]	Alternate	Finland	No interests declared	Full involvement
Tiphaine Vaillant [a, b, c]	Member	France	No interests declared	Full involvement
Nathalie Gault [a, b, c]	Alternate	France	No interests declared	Full involvement
Martin Huber [a, b, c]	Member (Vice-Chair)	Germany	No interests declared	Full involvement
Brigitte Keller-Stanislawski [a, c]	Alternate	Germany	No interests declared	Full involvement
Sofia Trantza [a, b, c]	Member (Mandate as Member for Greece started on 23/12/2021)	Greece	No interest declared	Full involvement
Georgia Gkegka [a, b, c]	Alternate (Mandate as Alternate for Greece started on 23/12/2021)	Greece	No interest declared	Full involvement
Melinda Palfi [a, b, c]	Member	Hungary	No interests declared	Full involvement
Julia Pallos [a, b, c]	Alternate	Hungary	No restrictions applicable to this meeting	Full involvement
Guðrún Stefánsdóttir [a, b, c]	Member	Iceland	No participation in discussions, final deliberations and voting on:	17.4.1. Apremilast - OTEZLA (CAP) - EMEA/H/C/003746/II/0039
Rhea Fitzgerald [a, b, c]	Member	Ireland	No interests declared	Full involvement
Ronan Grimes [a, b, c]	Alternate	Ireland	No interests declared	Full involvement
Amelia Cupelli [a, b, c]	Member	Italy	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
Ilaria Baldelli [a, b, c]	Alternate	Italy	No interests declared	Full involvement
Zane Neikena [a, b, c]	Member	Latvia	No interests declared	Full involvement
Rugile Pilviniene [a, b, c]	Member	Lithuania	No interests declared	Full involvement
Nadine Petitpain [b, c]	Member	Luxembourg	No participation in final deliberations and voting on:	6.3.28. Pholcodine (NAP) - PSUSA/00002396/202105
Anne-Cécile Vuillemin [a, b]	Alternate	Luxembourg	No interests declared	Full involvement
John Joseph Borg [a, b]	Member	Malta	No interests declared	Full involvement
Benjamin Micallef [b, c]	Alternate	Malta	No interests declared	Full involvement
Menno van der Elst [a, c]	Member	Netherlands	No interests declared	Full involvement
Liana Gross-Martirosyan [a, b, c]	Alternate	Netherlands	No interests declared	Full involvement
David Olsen [a, b, c]	Member	Norway	No participation in discussion, final deliberations and voting on:	16.1.34. Larotrectinib - VITRAKVI (CAP) - PSUSA/00010799/202105
Karen Pernille Harg [a, b, c]	Alternate	Norway	No interests declared	Full involvement
Adam Przybylkowski [a, c]	Member	Poland	No interests declared	Full involvement
Katarzyna Ziolkowska [a, b, c]	Alternate	Poland	No interests declared	Full involvement
Ana Diniz Martins [a, b, c]	Member	Portugal	No interests declared	Full involvement
Marcia Sofia Sanches de Castro Lopes Silva [a, c]	Alternate	Portugal	No interests declared	Full involvement
Roxana Dondera [a, b, c]	Member	Romania	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
Alexandra-Maria Spurni [a, b, c]	Alternate	Romania	No interests declared	Full involvement
Marek Juracka [a, b, c]	Member	Slovakia	No interests declared	Full involvement
Anna Mareková [a, b, c]	Alternate	Slovakia	No interests declared	Full involvement
Polona Golmajer [a, b]	Member	Slovenia	No interests declared	Full involvement
Milena Radoha-Bergoc [a, c]	Alternate	Slovenia	No restrictions applicable to this meeting:	Full involvement
Eva Segovia [a, c]	Member	Spain	No interests declared	Full involvement
Maria del Pilar Rayon [a, b, c]	Alternate	Spain	No interests declared	Full involvement
Ulla Wändel Liminga [a, b, c]	Member	Sweden	No interests declared	Full involvement
Annika Folin [a, b, c]	Alternate	Sweden	No interests declared	Full involvement
Annalisa Capuano [a, b, c]	Member	Independent scientific expert	No interests declared	Full involvement
Milou Daniel Drici [a, b, c]	Member	Independent scientific expert	No restrictions applicable to this meeting	Full involvement
Maria Teresa Herdeiro [a, b, c]	Member	Independent scientific expert	No interests declared	Full involvement
Patricia McGettigan [b]	Member	Independent scientific expert	No interests declared	Full involvement
Daniel Morales [a, c]	Member	Independent scientific expert	No restrictions applicable to this meeting	Full involvement
Hedvig Nordeng [a, c]	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, c]	Alternate	Healthcare Professionals' Representative	No participation in final deliberations	14.2.1. Human normal immunoglobulin – FLEBOGAMMA DIF (CAP),

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			and voting on:	KIOVIG (CAP), PRIVIGEN (CAP); NAP
Cathalijne van Doorne [a, b, c]	Member	Patients' Organisation Representative	No interests declared	Full involvement
Virginie Hivert [a]	Alternate	Patients' Organisation Representative	No restrictions applicable to this meeting	Full involvement
Christelle Bizimungu [a]	Expert *	Belgium	No restrictions applicable to this meeting	Full involvement
Ingrid Bourges [c]	Expert *	Belgium	No restrictions applicable to this meeting	Full involvement
Evelien De Clercq [a]	Expert *	Belgium	No interests declared	Full involvement
Christophe Focke [c]	Expert *	Belgium	No restrictions applicable to this meeting	Full involvement
Jamila Hamdani [a, b, c]	Expert *	Belgium	No interests declared	Full involvement
Jo Robays [b, c]	Expert *	Belgium	No restrictions applicable to this meeting	Full involvement
Martine Sabbe [a]	Expert *	Belgium	No interests declared	Full involvement
Françoise Wuillaume [a, c]	Expert *	Belgium	No interests declared	Full involvement
Petra Kaftanová [a, c]	Expert *	Czechia	No interests declared	Full involvement
Petra Vacková [b]	Expert *	Czechia	No interests declared	Full involvement
Jitka Vokrouhlická [a]	Expert *	Czechia	No interests declared	Full involvement
Ane Blicher Schelde [a]	Expert *	Denmark	No restrictions applicable to this meeting	Full involvement
Annette Cleveland Nielsen [a]	Expert *	Denmark	No restrictions	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			applicable to this meeting	
Kirsten Egebjerg Juul [a]	Expert *	Denmark	No interests declared	Full involvement
Karin Erneholm [a, c]	Expert *	Denmark	No restrictions applicable to this meeting	Full involvement
Helle Gerda Olsen [a]	Expert *	Denmark	No interests declared	Full involvement
Marian Hjortlund Allon [a]	Expert *	Denmark	No interests declared	Full involvement
Moritz Sander [a]	Expert *	Denmark	No interests declared	Full involvement
Per Sindahl [a]	Expert *	Denmark	No restrictions applicable to this meeting	Full involvement
Emma Stadsbjerg [c]	Expert *	Denmark	No interests declared	Full involvement
Kristina Laursen [a]	Expert *	Denmark	No interests declared	Full involvement
Helene Stenbæk Hansen [a]	Expert *	Denmark	No restrictions applicable to this meeting	Full involvement
Josiane Uwera [a, c]	Expert *	Denmark	No restrictions applicable to this meeting	Full involvement
Helve Vestman [c]	Expert *	Estonia	No interests declared	Full involvement
Karima Adamo [a]	Expert *	France	No restrictions applicable to this meeting	Full involvement
Thomas Berbain [c]	Expert *	France	No interests declared	Full involvement
Benjamin Burrus [a]	Expert *	France	No interests declared	Full involvement
Samuel Crommelynck [a]	Expert *	France	No restrictions	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			applicable to this meeting	
Pierre Demolis [a]	Expert *	France	No interests declared	Full involvement
Vincent Gazin [a]	Expert *	France	No interests declared	Full involvement
Mathilde Geynet-Kovacs [a]	Expert *	France	No interests declared	Full involvement
Dina Habib Hanawy [a]	Expert *	France	No restrictions applicable to this meeting	Full involvement
Léo Lambart [a]	Expert *	France	No restrictions applicable to this meeting	Full involvement
Nathalie Morgensztejn [b, c]	Expert *	France	No interests declared	Full involvement
Marie-Caroline Pesquidous [a]	Expert *	France	No restrictions applicable to this meeting	Full involvement
Jean-Michel Race [b, c]	Expert *	France	No restrictions applicable to this meeting	Full involvement
Norontsoa Rasolondramanitra [b, c]	Expert *	France	No interests declared	Full involvement
Youssef Shaim [a]	Expert *	France	No restrictions applicable to this meeting	Full involvement
Laure Tiquet [a]	Expert *	France	No interests declared	Full involvement
Emilie Vittaz [c]	Expert *	France	No interests declared	Full involvement
Nicole Bick [a]	Expert *	Germany	No interests declared	Full involvement
Mark Branschofsky [b, c]	Expert *	Germany	No interests declared	Full involvement
Dennis Lex [a, b, c]	Expert *	Germany	No restrictions	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			applicable to this meeting	
Jörg Engelbergs [c]	Expert *	Germany	No interests declared	Full involvement
Vivien Molitor [a]	Expert *	Germany	No interests declared	Full involvement
Jan Müller-Berghaus [c]	Expert *	Germany	No interests declared	Full involvement
Darío Ortiz de Orué Lucana [b, c]	Expert *	Germany	No interests declared	Full involvement
Susanne Winterscheid [a]	Expert *	Germany	No interests declared	Full involvement
Hilke Zander [c]	Expert *	Germany	No interests declared	Full involvement
Laura Galatti [a]	Expert *	Italy	No interests declared	Full involvement
Kora Doorduyn-van der Stoep [a]	Expert *	Netherlands	No interests declared	Full involvement
Justine van Tongeren [a]	Expert *	Netherlands	No interests declared	Full involvement
Fátima Ventura [b]	Expert *	Portugal	No restrictions applicable to this meeting	Full involvement
Carmen Gallego López Jurado [a]	Expert *	Spain	No interests declared	Full involvement
Alicia Pérez González [c]	Expert *	Spain	No interests declared	Full involvement
Sol Ruiz [c]	Expert *	Spain	No interests declared	Full involvement
Bernice Aronsson [c]	Expert *	Sweden	No restrictions applicable to this meeting	Full involvement
Charlotte Backman [a, b, c]	Expert *	Sweden	No interests declared	Full involvement
Filip Josephson [b]	Expert *	Sweden	No interests declared	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/