30 March 2023
EMA/PRAC/56404/2023
Human Medicines Division

Pharmacovigilance Risk Assessment Committee (PRAC)

Minutes of the meeting on 24-27 October 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).

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

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 current coronavirus (COVID-19 outbreak), and the associated EMA Business Continuity Plan (BCP), the meeting was held remotely.

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

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

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

1.2. Agenda of the meeting on 24-27 October 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 26-29 September 2022

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

Post-meeting note: the PRAC minutes of the meeting held on 26-29 September 2022 were published on the EMA website on 17 February 2023 (EMA/PRAC/947562/2022).

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

2.1. Newly triggered procedures

None

2.2. Ongoing procedures

None

2.3. Procedures for finalisation

None

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

3.1. Newly triggered procedures

None

3.2. Ongoing procedures

None

3.3. Procedures for finalisation

3.3.1. Janus kinase (JAK) inhibitors[1]: abrocitinib - CIBINQO (CAP); baricitinib - OLUMIANT (CAP); filgotinib - JYSELECA (CAP); tofacitinib - XELJANZ (CAP); upadacitinib - RINVOQ (CAP) – EMEA/H/A-20/1517

Applicants: AbbVie Deutschland GmbH & Co. KG (Rinvoq), Eli Lilly Nederland B.V. (Olumiant), Galapagos N.V. (Jyseleca), Pfizer Europe MA EEIG (Cibinqo, Xeljanz)

PRAC Rapporteur: Ulla Wändel Liminga; PRAC Co-rapporteur(s): Liana Gross-Martirosyan (Olumiant, Xeljanz), Nikica Mirošević Skvrce (Cibinqo, Jyseleca, Rinvoq)

Scope: Review of the benefit-risk balance following notification by the European Commission (EC) of a referral under Article 20 of Regulation (EC) No 726/2004, based on pharmacovigilance data

Background

A referral procedure under Article 20 of Regulation (EC) No 726/2004 for the review of Janus kinase inhibitors (JAKi), namely Xeljanz (tofacitinib), Cibinqo (abrocitinib), Olumiant (baricitinib), Jyseleca (filgotinib) and Rinvoq (upadacitinib) used in the treatment of inflammatory disorders is to be concluded. The procedure was initiated following the release of the final results from study A3921133[2] (ORAL surveillance) for Xeljanz (tofacitinib) showing an increase incidence of major adverse cardiovascular events (MACE), a higher risk of malignancy with tofacitinib compared to tumour necrosis fibrosis (TNF)-inhibitors in patients with rheumatoid arthritis, as well as a higher incidence of venous thromboembolism (VTE), all-cause of mortality and serious infections in patients treated with tofacitinib compared to TNF-inhibitors. In addition, preliminary results from study I4V-MC-B023[3] for Olumiant (baricitinib) suggested an increased risk of MACE and VTE in patients with rheumatoid arthritis treated with Olumiant (baricitinib) compared to those treated with TNF-inhibitors. For further background, see PRAC minutes February 2022, PRAC minutes June

[1] Indicated for the treatment of inflammatory disorders
[2] A phase 3b/4 randomised safety endpoint study of 2 doses of tofacitinib in comparison to a tumour necrosis fibrosis (TNF) inhibitor in subjects with rheumatoid arthritis
[3] A retrospective observational study to compare baricitinib relative to the standard of care

2022, PRAC minutes September 2022[4] and PRAC minutes October[5] 2022. A final assessment of the data submitted was produced by the Rapporteurs according to the agreed timetable.

Discussion

PRAC discussed the conclusion reached by the Rapporteurs.

PRAC considered the totality of the data submitted during the procedure in relation to the risks of MACE, VTE, malignancy, serious infections and all-cause mortality, including the responses submitted by the MAHs both in writing and during oral explanations, as well as the outcome of an ad-hoc expert group (AHEG) meeting.

PRAC concluded that, based on the currently available data, the increased risk for MACE, VTE, malignancy, serious infections and all-cause mortality observed in study A39211332 (ORAL surveillance) with tofacitinib compared with TNF-inhibitors in subjects with rheumatoid arthritis are considered JAKis class effects. PRAC also concluded that these safety findings observed in patients with rheumatoid arthritis apply to all approved indications for the JAKis used in the treatment of chronic inflammatory disorders. However, the magnitude of the absolute risk depends on the background risk in the respective populations.

To minimise these risks, PRAC recommended implementing warnings for all JAKis included in this review that these medicinal products should only be used in patients 65 years of age and older, who are current or past long-time smoker, with history of atherosclerotic cardiovascular disease or other cardiovascular risk factors, or with other malignancy risk factors (e.g. current, or history of malignancy) if no suitable treatment alternatives are available. Cautious use is recommended in patients with known risk factors for VTE, other than those listed above.

PRAC also recommended to revise the current dosing advice for some of the medicinal products as feasible, in order to lower the dose in certain patient groups with risk factors since the occurrence of MACE, VTE, malignancies, serious infections and all-cause mortality have been observed in a dose dependent manner.

Based on the clinical data presented, PRAC also recommended to include new adverse reactions, namely sepsis with a frequency 'uncommon' for Jyseleca (filgotinib) and Rinvoq (upadacitinib) and non-malignant skin cancer with a frequency 'common' for Rinvoq (upadacitinib).

Moreover, PRAC recommended an update of the key elements of the educational materials and of the RMPs including studies of drug utilisation accordingly.

As a consequence, PRAC concluded that the benefit-risk balance of Cibinqo (abrocitinib), Jyseleca (filgotinib), Olumiant (baricitinib), Rinvoq (upadacitinib) and Xeljanz (tofacitinib) remains favourable subject to the agreed amendments to the product information and other risk minimisation measures.

Summary of recommendation(s)/conclusions

- PRAC adopted, by majority, a recommendation to vary[6] the terms of the marketing authorisation(s) of Xeljanz (tofacitinib), Cibinqo (abrocitinib), Olumiant (baricitinib), Jyseleca (filgotinib) and Rinvoq (upadacitinib) to be considered by CHMP for an opinion – see EMA Press Release entitled 'EMA recommends measures to minimise risk of serious

[4] Held 29 August – 01 September 2022
[5] Held 26 – 29 September 2022
[6] Update of SmPC sections 4.2, 4.4, 4.8 and 5.1. The package leaflet is updated accordingly

side effects with Janus kinase inhibitors for chronic inflammatory disorders' (EMA/861237/2022 Rev.1).

- PRAC agreed on the content of a direct healthcare professional communication (DHPC) along with a communication plan for its distribution.

Twenty-five members voted in favour of the recommendation whilst six members[7] had a divergent view. The Icelandic and Norwegian PRAC members agreed with the recommendation.

Post-meeting note 1: the press release 'EMA confirms measures to minimise risk of serious side effects with Janus kinase inhibitors for chronic inflammatory disorders' representing the opinion provided by CHMP (EMA/27681/2023) was published on the EMA website on 27 January 2023.

Post-meeting note 2: the PRAC recommendation was revised in January 2023. For further details, see PRAC minutes January 2023.

3.4. Re-examination procedures[8]

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

Applicants: Artegodan GmbH, Temmler Pharma GmbH

PRAC Rapporteur: Ulla Wändel Liminga; PRAC Co-rapporteur: Roxana Dondera

Scope: Request for re-examination under Article 32 of Directive 2001/83/EC of the benefit-risk balance following notification by Romania of a referral under Article 31 of Directive 2001/83/EC, based on pharmacovigilance data

Background

Following the PRAC recommendation adopted at the June 2022 meeting to revoke the marketing authorisations of medicinal products containing amfepramone, the MAHs concerned by this referral procedure requested a re-examination of the PRAC recommendation in line with Article 32 of Directive 2001/83/EC. For further background, see PRAC minutes June 2022 and PRAC minutes September 2022[9].

Discussion

PRAC reviewed all available data in relation to the safety concerns of pulmonary, cardiac, cerebrovascular, neuropsychiatric diseases, drug dependence and use in pregnancy, as well as the effectiveness of the risk minimisation measures in place in the context of the efficacy of amfepramone in patients with obesity. This included the responses submitted by the MAHs in writing and during the oral explanations, results from two observational studies performed in German and Danish healthcare databases, the views expressed by a group of independent experts, as well as the grounds for the re-examination submitted by the MAHs.

PRAC noted that the studies supporting the weight reduction effect of amfepramone suffered from serious limitations and considered the clinical relevance of the modest and temporary weight loss observed with amfepramone questionable in the context of the need for long-term weight loss maintenance for patients with obesity.

[7] Amelia Cupelli, Liana Gross-Martirosyan, Eva Jirsová, Nikica Mirošević Skvrce, Sofia Trantza, Tiphaine Vaillant
[8] Re-examination of PRAC recommendation under Article 32 of Directive 2001/83/EC
[9] Held on 29 August – 01 September 2022

PRAC concluded that the currently available data do not change the risks previously established by CPMP, as an outcome of a review under Article 12 of Council Directive 75/319/EEC, to be associated to treatment with amfepramone.

PRAC noted the results of the observational studies and information from spontaneous post-marketing reports showing an unacceptable level of non-adherence to the current measures aimed at minimising the risks of treatment with amfepramone in patients at higher risk of developing adverse drug reactions and the risks known to increase with the treatment duration. PRAC considered that this raised important public health concerns.

Therefore, PRAC concluded that those measures have not been effective in adequately minimising the risks of treatment with amfepramone.

PRAC also discussed the possibility of implementing further risk minimisation measures and concluded that no feasible and proportionate measures could ensure effective minimisation of the risks associated to treatment with amfepramone-containing products, in particular with respect to the risks of pulmonary arterial hypertension, cardio- and cerebro-vascular diseases and of dependence, abuse and tolerance.

PRAC concluded that the risks outweigh the modest temporary benefits of amfepramone as adjunctive therapy to diet, in patients with obesity and a body mass index (BMI) of 30 kg/m^2 or higher, who have not responded to an appropriate weight reducing regimen alone.

Furthermore, PRAC could not identify conditions which, if fulfilled in the future, would demonstrate a positive benefit-risk balance for these medicinal products in a defined patient population.

As a consequence, PRAC maintained its consideration that the benefit-risk balance of amfepramone-containing products is not favourable and recommended the revocation of the marketing authorisations for those medicinal products.

Summary of recommendation(s)/conclusions

- PRAC adopted, by majority, a recommendation to revoke the marketing authorisations for amfepramone-containing products to be considered by CMDh for a position – see EMA Press Release (EMA/844036/2022) entitled 'EMA confirms recommendation to withdraw marketing authorisations for amfepramone medicines' published on 28 October 2022.
- PRAC agreed on the content of a direct healthcare professional communication (DHPC) along with a communication plan for its distribution.

Post-meeting note 1: a revised PRAC recommendation was adopted via written procedure on 07 November 2022 in order to clarify the measures in place in Denmark. Twenty-nine members voted in favour of the recommendation whilst three members[10] had a divergent view. The Icelandic and Norwegian PRAC members agreed with the recommendation.

Post-meeting note 2: the press release entitled 'Withdrawal of marketing authorisations for amfepramone medicines within the EU' (EMA/867253/2022) representing the position adopted by CMDh, also reflecting the date of the European Commission's final legally binding decision applicable in all EU Member States was published on the EMA website on 13 January 2023.

Post-meeting note 3: the PRAC assessment report (EMA/884474/2022) was published on

[10] Eva Jirsová, Anette Kirstine Stark, Ulla Wändel Liminga

the EMA website on 20 January 2023.

3.5. Others

None

4. Signals assessment and prioritisation[11]

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/010

Applicant: AstraZeneca AB

PRAC Rapporteur: David Olsen

Scope: Signal of myelitis transverse

EPITT 19815 – Follow-up to June 2022

Background

For background information, see PRAC minutes June 2022.

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

Discussion

Having considered the available evidence from EudraVigilance and the literature, the MAH's responses and the Rapporteur's assessment, PRAC considered that a causal relationship between myelitis transverse and durvalumab is at least a reasonable possibility. Therefore, PRAC agreed that myelitis transverse should be added to the product information as a warning and as an undesirable effect with a frequency 'not known' and to update the product information guidelines for management of immune-mediated adverse reactions.

Summary of recommendation(s)

- The MAH for Imfinzi (durvalumab) should submit to EMA, within 60 days, a variation to amend[12] the product information.

For the full PRAC recommendation, see EMA/PRAC/845793/2022 published on 21 November 2022 on the EMA website.

[11] 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

[12] Update of SmPC sections 4.2, 4.4 and 4.8. The package leaflet is to be updated accordingly

4.3.2. Elasomeran - SPIKEVAX (CAP) - EMEA/H/C/005791/SDA/059.1

Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Signal of heavy menstrual bleeding

EPITT 19780 – Follow-up to June 2022

Background

For background information, see PRAC minutes June 2022.

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

Discussion

Having considered the available evidence from EudraVigilance, the literature, data from national reviews, observational studies, the MAH's responses together with the Rapporteur's assessment, PRAC considered that a causal relationship between heavy menstrual bleeding and elasomeran is at least a reasonable possibility. Therefore, PRAC agreed that heavy menstrual bleeding should be added to the product information as an undesirable effect with a frequency 'not known'.

Summary of recommendation(s)

- The MAH for Spikevax (elasomeran) should submit to EMA, within 60 days, a variation to amend[13] the product information.

For the full PRAC recommendation, see EMA/PRAC/845793/2022 published on 21 November 2022 on the EMA website.

4.3.3. Ipilimumab - YERVOY (CAP) - EMEA/H/C/002213/SDA/045; nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/SDA/0047

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Signal of pure red cell aplasia and aplastic anaemia

EPITT 19804 – Follow-up to June 2022

Background

For background information, see PRAC minutes June 2022.

The MAH replied to the request for information on the signal of pure red cell aplasia and aplastic anaemia and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence from Eudravigilance, literature and the responses submitted by the MAH, PRAC considered that there is insufficient evidence at present to establish a causal relationship between ipilimumab and/or nivolumab and either pure red cell

[13] Update of SmPC section 4.8. The package leaflet is to be updated accordingly

aplasia or aplastic anaemia. Therefore, PRAC concluded that no regulatory action is warranted at this stage.

Summary of recommendation(s)

- The MAH for Yervoy (ipilimumab) and Opdivo (nivolumab) should continue to monitor cases of pure red cell aplasia and aplastic anaemia in future PSURs.

4.3.4. Tildrakizumab – ILUMETRI (CAP) - EMEA/H/C/004514/SDA/008

Applicant: Almirall S.A

PRAC Rapporteur: Adam Przybylkowski

Scope: Signal of herpes zoster

EPITT 19801 - Follow-up to June 2022

Background

For background information, see PRAC minutes June 2022.

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

Discussion

Having considered the available evidence from EudraVigilance, literature and the responses submitted by the MAH, PRAC considered that there is insufficient evidence at present to establish a causal relationship between tildrakizumab and herpes zoster. Therefore, PRAC concluded that no regulatory action is warranted at this stage.

Summary of recommendation(s)

- The MAH for Ilumetri (tildrakizumab) should continue to monitor cases of herpes zoster as part of routine safety surveillance.

4.3.5. Tozinameran - COMIRNATY (CAP) - EMEA/H/C/005735/SDA/053.1

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: David Olsen

Scope: Signal of heavy menstrual bleeding

EPITT 19783 – Follow-up to June 2022

Background

For background information, see PRAC minutes June 2022.

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

Discussion

Having considered the available evidence of EudraVigilance, literature, data from national reviews, observational studies and the responses submitted by the MAH, PRAC considered that a causal relationship between heavy menstrual bleeding and tozinameran is at least a

reasonable possibility. Therefore, PRAC agreed that heavy menstrual bleeding should be added to the product information as an undesirable effect with a frequency 'not known'.

Summary of recommendation(s)

- The MAH for Comirnaty (tozinameran) should submit to EMA, within 60 days, a variation to amend[14] the product information.

For the full PRAC recommendation, see EMA/PRAC/845793/2022 published on 21 November 2022 on the EMA website.

4.4. Variation procedure(s) resulting from signal evaluation

None

5. Risk management plans (RMPs)

5.1. Medicines in the pre-authorisation phase

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

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

See also Annex 15.1.

5.1.1. Bardoxolone methyl - EMEA/H/C/005869, Orphan

Applicant: Reata Ireland Limited

Scope: Treatment of chronic kidney disease

5.1.2. Daprodustat - EMEA/H/C/005746

Scope: Treatment of anaemia associated with chronic kidney disease (CKD) in adults

5.1.3. Gadopiclenol - EMEA/H/C/005626

Scope: For diagnostic purposes: contrast-enhanced magnetic resonance imaging (MRI) to improve detection, visualisation and assist in characterisation of lesions in the central nervous system and in other body regions (including breast, liver and prostate)

5.1.4. Gadopiclenol - EMEA/H/C/006172

Scope: For diagnostic purposes: contrast-enhanced magnetic resonance imaging (MRI) to improve detection, visualisation and assist in characterisation of lesions in the central

[14] Update of SmPC section 4.8. The package leaflet is to be updated accordingly

nervous system and in other body regions (including breast, liver and prostate)

5.1.5. Pegunigalsidase alfa - EMEA/H/C/005618, Orphan

Applicant: Chiesi Farmaceutici S.p.A.

Scope: Treatment of Fabry disease

5.1.6. Sodium phenylbutyrate, ursodoxicoltaurine - EMEA/H/C/005901, Orphan

Applicant: Amylyx Pharmaceuticals EMEA B.V.

Scope: Treatment of amyotrophic lateral sclerosis (ALS)

5.1.7. Tremelimumab - EMEA/H/C/006016, Orphan

Applicant: AstraZeneca AB

Scope: Ttreatment of adults with unresectable hepatocellular carcinoma in combination with durvalumab

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

See Annex I 15.2.

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

See also Annex I 15.3.

5.3.1. Lenalidomide - REVLIMID (CAP) - EMEA/H/C/000717/II/0123

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Tiphaine Vaillant

Scope: Update of section 4.4 of the SmPC, Annex IID and Article 127a and the tools/documents included in the Educational Healthcare Professional Kit, in order to harmonise the terminology utilised in the RMP and product information (PI) documents relating to the safety concern of teratogenicity and its risk minimisation measure of the Pregnancy Prevention Plan (PPP) across the 3 immunomodulatory imide drugs (IMiDs). These proposed changes will only have a limited impact on the National Competent Authority (NCA)-approved content/text of the educational materials, and the key messages to the HCP and patients. Furthermore, the regulatory obligations regarding the PPP will not be impacted. The MAH is also taking the opportunity to update the RMP with PASS Protocol milestones. The updated RMP version 38 was provided

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 Revlimid, a centrally authorised product containing lenalidomide, to update the product information in order to harmonise the terminology used in the RMP and product information documents relating to the safety

concern of teratogenicity and its risk minimisation measure of the PPP across the three IMiDs. PRAC is responsible for providing advice to CHMP on the necessary updates to the RMP to support this variation.

Summary of advice

- The RMP for Revlimid (lenalidomide) in the context of the variation procedure under evaluation by PRAC and CHMP could be considered acceptable provided that an update to RMP version 38 and satisfactory responses to the request for supplementary information (RSI) are submitted.
- PRAC agreed with the removal of the pregnancy specific targeted forms included within the educational healthcare professional kit. Additional modifications of the RMP, concerning updates to the information or study milestones for additional pharmacovigilance activities were also agreed. In addition, the MAH should update the details of the proposed additional risk minimisation activities in line with Annex II-D.

5.3.2. Pomalidomide - IMNOVID (CAP) - EMEA/H/C/002682/II/0047, Orphan

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Monica Martínez Redondo

Scope: Update of section 4.4 of the SmPC, Annex IID and Article 127a and the tools/documents included in the Educational Healthcare Professional Kit, in order to harmonise the terminology utilised in the RMP and PI documents relating to the safety concern of teratogenicity and its risk minimisation measure of the Pregnancy Prevention Plan across the 3 immunomodulatory imide drugs (IMiDs). These proposed changes will only have a limited impact on the National Competent Authority (NCA)-approved content/text of the educational materials, and the key messages to the HCP and patients. Furthermore, the regulatory obligations regarding the pregnancy prevention plan (PPP) will not be impacted. The updated RMP version 16 was provided

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 Imnovid, a centrally authorised product containing pomalidomide, to update the product information in order to harmonise the terminology used in the RMP and product information documents relating to the safety concern of teratogenicity and its risk minimisation measure of the PPP across the three IMiDs. PRAC is responsible for providing advice to CHMP on the necessary updates to the RMP to support this variation.

Summary of advice

- The RMP for Imnovid (pomalidomide) in the context of the variation procedure under evaluation by PRAC and CHMP could be considered acceptable provided that an update to RMP version 16 and satisfactory responses to the request for supplementary information (RSI) are submitted.
- PRAC considered that the pregnancy specific targeted forms should not be removed from the educational healthcare professional kit. In addition, the MAH should update the

'Conditions or restrictions with regard to the safe and effective use of the medicinal product' to be implemented by the Member States in line with the details of the proposed additional risk minimisation activities in the RMP and Annex II-D.

5.3.3. Thalidomide - THALIDOMIDE BMS (CAP) - EMEA/H/C/000823/II/0076

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Tiphaine Vaillant

Scope: Update of section 4.4 of the SmPC, Annex IID and Article 127a and the tools/documents included in the Educational Healthcare Professional Kit, in order to harmonise the terminology utilised in the RMP and product information (PI) documents relating to the safety concern of teratogenicity and its risk minimisation measure of the Pregnancy Prevention Plan (PPP) across the 3 immunomodulatory imide drugs (IMiDs). These proposed changes will only have a limited impact on the National Competent Authority (NCA)-approved content/text of the educational materials, and the key messages to the HCP and patients. Furthermore, the regulatory obligations regarding the PPP will not be impacted. The MAH is also taking the opportunity to update the RMP with PASS Protocol milestones, and to make some editorial changes in the labelling. The updated RMP version 20 was provided

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 Thalidomide BMS, a centrally authorised product containing thalidomide, to update the product information in order to harmonise the terminology used in the RMP and product information documents relating to the safety concern of teratogenicity and its risk minimisation measure of the PPP across the three IMiDs. PRAC is responsible for providing advice to CHMP on the necessary updates to the RMP to support this variation.

Summary of advice

- The RMP for Thalidomide BMS (thalidomide) in the context of the variation procedure under evaluation by PRAC and CHMP could be considered acceptable provided that an update to RMP version 20 and satisfactory responses to the request for supplementary information (RSI) are submitted.
- PRAC agreed with the removal of the pregnancy specific targeted forms included within the educational healthcare professional kit. Additional modifications of the RMP, concerning updates to the information or study milestones for additional pharmacovigilance activities were also agreed. In addition, PRAC did not support the removal of the reference to the drug utilisation study to address the risk of off-label use from the RMP. Finally, the MAH should update the details of proposed additional risk minimisation activities in the RMP in line with Annex II-D.

6. Periodic safety update reports (PSURs)

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

See also Annex I 16.1.

6.1.1. Cabotegravir - VOCABRIA (CAP) - PSUSA/00010900/202203

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

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

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Vocabria, a centrally authorised medicine containing cabotegravir 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 Vocabria (cabotegravir) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to change the terminology from 'type I hypersensitivity' to 'hypersensitivity' as an existing undesirable effect, maintaining the same frequency of 'uncommon'. Therefore, the current terms of the marketing authorisation(s) should be varied[15].

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

6.1.2. Dupilumab - DUPIXENT (CAP) - PSUSA/00010645/202203

Applicant: Sanofi-aventis groupe

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.

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

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Dupixent, a centrally authorised medicine containing dupilumab 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 Dupixent (dupilumab) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- The MAH should submit to EMA an updated safety evaluation report addressing the cases of cutaneous T-cell lymphoma (CTCL).
- In the next PSUR, the MAH should provide an updated review of cases of cataract with a special emphasis on paediatric, adolescent and young adult patients. In addition, the MAH should provide detailed reviews of cases of hyperthyroidism and autoimmune thyroiditis, as well as of cases of venous thromboembolic events.

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. Risankizumab - SKYRIZI (CAP) - PSUSA/00010765/202203

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Liana Gross-Martirosyan

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 Skyrizi, a centrally authorised medicine containing risankizumab 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 Skyrizi (risankizumab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add urticaria and rash as undesirable effects with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[16].
- In the next PSUR, the MAH should provide a cumulative review of cases of anaphylactic reactions and propose an update of the product information as warranted. In addition, the MAH should provide a discussion on the observed off-label use patterns as well as

[16] 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.

associated adverse effects. The MAH should propose measures to limit off label use if deemed appropriate.

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. Siponimod - MAYZENT (CAP) - PSUSA/00010818/202203

Applicant: Novartis Europharm Limited

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 Mayzent, a centrally authorised medicine containing siponimod 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 Mayzent (siponimod) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the existing warning on lymphopenia. Therefore, the current terms of the marketing authorisation(s) should be varied[17].
- In the next PSUR, the MAH should provide cumulative reviews of cases of alopecia, medication errors consisting of 'product omission issue' with concomitant symptoms and of cases of seizures (especially the cases with status epilepticus) that reported concomitantly other signs of posterior reversible encephalopathy syndrome (PRES). In addition, the MAH should provide detailed reviews of cases of suicide events and serious cases with depression, of cases of varicella-zoster virus (VZV) infection reactivation, including serious and fatal cases, as well as of cases of bradyarrhythmia that occurred the first week following treatment initiation. The MAH should propose to update the product information as warranted.

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

6.1.5. Sodium zirconium cyclosilicate - LOKELMA (CAP) - PSUSA/00010675/202203

Applicant: AstraZeneca AB

PRAC Rapporteur: Kirsti Villikka

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

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 Lokelma, a centrally authorised medicine containing sodium zirconium cyclosilicate 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 Lokelma (sodium zirconium cyclosilicate) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the warning on gastrointestinal perforation. Therefore, the current terms of the marketing authorisation(s) should be varied[18].

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. Vandetanib - CAPRELSA (CAP) - PSUSA/00009327/202204

Applicant: Genzyme Europe BV

PRAC Rapporteur: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

Background

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

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Caprelsa, a centrally authorised medicine containing vandetanib 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 Caprelsa (vandetanib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the existing warning on skin reactions and to add toxic epidermal necrolysis (TEN) as an undesirable effect

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

with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[19].

- In the next PSUR, the MAH should provide detailed reviews of cases of medication errors, teeth and bone abnormalities in the paediatric population, as well as of cases of fistula. In addition, the MAH should discuss thoroughly any new case of pulmonary hypertension/pulmonary arterial hypertension, tubulointerstitial nephritis and myocarditis.

The frequency of PSUR submission should be revised from 6-monthly to three-yearly and the next PSUR should be submitted to EMA within 90 days of the data lock point. The list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC is updated accordingly.

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

See Annex I 16.2.

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

See also Annex I 16.3.

6.3.1. Amoxicillin (NAP) - PSUSA/00000187/202203

Applicant(s): various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

Background

Amoxicillin is a semi-synthetic broad spectrum penicillin antibiotic indicated for the treatment of bacterial infections caused by amoxicillin-sensitive gram-positive and gram-negative pathogens. Amoxicillin oral formulations are indicated for a series of bacterial infections such as acute bacterial sinusitis, acute otitis media, acute streptococcal tonsillitis and pharyngitis, acute exacerbations of chronic bronchitis, community acquired pneumonia, acute cystitis, asymptomatic bacteriuria in pregnancy, acute pyelonephritis, typhoid and paratyphoid fever, dental abscess with spreading cellulitis, prosthetic joint infections, *Helicobacter pylori* eradication, Lyme disease and prophylaxis of endocarditis. Amoxicillin parenteral formulations are indicated for severe infections of the ear, nose and throat, acute exacerbations of chronic bronchitis, community acquired pneumonia, acute cystitis, acute pyelonephritis, severe dental abscess with spreading cellulitis, prosthetic joint infections, endocarditis, Lyme disease, bacterial meningitis and prophylaxis of endocarditis.

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

[19] Update of SmPC section 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.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of amoxicillin-containing product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add Kounis syndrome and drug-induced enterocolitis syndrome as warnings and as undesirable effects with a frequency 'not known'. In addition, the product information should be updated to add linear IgA disease and aseptic meningitis as undesirable effects with a frequency 'not known'. It should be also updated to include interactions between amoxicillin and methotrexate, and between amoxicillin and probenecid. Finally, it should be updated to amend the existing wording on crystalluria by including acute renal injury. Therefore, the current terms of the marketing authorisation(s) should be varied[20].
- In the next PSUR, the MAH(s) should provide cumulative reviews of cases of deafness/hearing loss, exacerbation of myasthenia gravis, liver injury, acute pancreatitis, resistance/cross-resistance/lack of efficacy, as well as of cases of aseptic meningitis when amoxicillin is used concomitantly with ibuprofen/other non-steroidal anti-inflammatory drugs (NSAID).

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 above recommendations for updating the product information are also relevant for amoxicillin-containing products in fixed-dose combinations indicated for eradication of *Helicobacter pylori* infection. In addition, PRAC considered that the drug-drug interactions between amoxicillin and methotrexate, and between amoxicillin and probenecid, are also relevant for methotrexate and probenecid-containing products. Further consideration is to be given at the level of CMDh.

6.3.2. Amoxicillin, clavulanate (NAP) - PSUSA/00000188/202203

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

Amoxicillin is a semi-synthetic broad spectrum penicillin antibiotic and clavulanic acid a beta lactamase inhibitor. In combination, amoxicillin/clavulanate is indicated for the treatment of infections of the upper respiratory tract (e.g. recurrent tonsillitis, sinusitis, otitis media), lower respiratory tract infections (e.g. acute exacerbations of chronic bronchitis, lobar and bronchial pneumonia), genito-urinary tract infections (e.g. pyelonephritis, cystitis, urethritis), skin and soft tissue infections (e.g. abscesses, cellulitis and infected wounds), bone and joint infections (e.g. osteomyelitis) and perioperative antibiotic prophylaxis during surgical procedures.

[20] Update of SmPC section 4.4, 4.5, 4.8 and 4.9. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing amoxicillin/clavulanate 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 amoxicillin/clavulanate-containing product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add Kounis syndrome and drug-induced enterocolitis syndrome as warnings and as undesirable effects with a frequency 'not known', as well as to add linear IgA disease, aseptic meningitis and pancreatitis acute as undesirable effects with a frequency 'not known'. In addition, the product information should be updated to amend the existing wording on crystalluria as a warning and as an undesirable effect by including acute renal injury. Therefore, the current terms of the marketing authorisation(s) should be varied[21].

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

PRAC considered that linear IgA disease, drug-induced enterocolitis syndrome and pancreatitis acute as undesirable effects are also relevant for amoxicillin-containing products in other fixed-dose combinations. Further consideration is to be given at the level of CMDh.

6.3.3. Erythromycin[22] (NAP) - PSUSA/00010808/202203

Applicant(s): various

PRAC Lead: Ronan Grimes

Scope: Evaluation of a PSUSA procedure

Background

Erythromycin is a macrolide antibiotic that is active against gram-positive cocci and gram-positive bacilli as well as some gram-negative cocci and bacilli, that is used in the treatment of infections due to susceptible organisms.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of erythromycin-containing product(s) for systemic use in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the existing information on use during pregnancy, as well as to add a warning regarding the concomitant use of erythromycin and systemic or inhaled corticosteroids, and

[21] Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position.
[22] For systemic use only

hydroxychloroquine or chloroquine. In addition, the product information should be updated to add a contraindication regarding the concomitant use of erythromycin with lomitapide. Therefore, the current terms of the marketing authorisation(s) should be varied[23].

- In the next PSUR, the MAH(s) should provide a discussion on available data from clinical studies on erythromycin levels in breast milk and on available data in relation to potential adverse effects of erythromycin exposure in breastfed infants.

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

6.3.4. Fexofenadine (NAP) - PSUSA/00001388/202203

Applicant(s): various

PRAC Lead: Marie Louise Schougaard Christiansen

Scope: Evaluation of a PSUSA procedure

Background

Fexofenadine is a second-generation, non-sedating antihistamine indicated for the treatment of seasonal allergic rhinitis and chronic idiopathic urticaria, in adults and paediatric population aged above 12 years.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing fexofenadine 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 fexofenadine-containing product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add blurred vision as an undesirable effect with a frequency 'not known', and to include the interaction between fexofenadine and apalutamide. Therefore, the current terms of the marketing authorisation(s) should be varied[24].
- In the next PSUR, the MAH(s) should provide a cumulative review of cases of hypoaesthesia, hypoaesthesia oral and other MedDRA PTs[25] from all available sources, including, clinical, post-marketing and literature data. The MAH(s) should also propose to update the product information as warranted.

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

[23] Update of SmPC sections 4.3, 4.5 and 4.6. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position.
[24] Update of SmPC section 4.5 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position.
[25] Medical dictionary for regulatory activities – Preferred term

6.3.5. Oxycodone (NAP) - PSUSA/00002254/202204

Applicant(s): various

PRAC Lead: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

Background

Oxycodone is an opioid analgesic indicated for the treatment of pain requiring the use of an opioid analgesic and of moderate to severe pain in patients with cancer and post-operative pain.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of oxycodone-containing product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to further minimise the risk of opioid use disorder (OUD) as well as to add toxic leukoencephalopathy as a clinical manifestation of overdose. Therefore, the current terms of the marketing authorisation(s) should be varied[26].

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

6.4. Follow-up to PSUR/PSUSA procedures

See also Annex I 16.4.

6.4.1. Laronidase - ALDURAZYME (CAP) - EMEA/H/C/000477/LEG 056.1

Applicant: Genzyme Europe BV

PRAC Rapporteur: Nathalie Gault

Scope: MAH's response to LEG 056 [Detailed review of cases of hypersensitivity reactions, immunogenicity, infusion-site reaction, overdose, cases suggestive of overdose and use of laronidase by intrathecal route, as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00010581/202107) adopted in December 2021] as per request for supplementary information (RSI) adopted in June 2022.

Background

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

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

Following the evaluation of the most recently submitted PSUR(s) for the above-mentioned medicine(s), PRAC requested the MAH to submit further data on cases of hypersensitivity reactions, immunogenicity, infusion-site reactions, overdose cases and cases suggestive of overdose as well as on use of laronidase by intrathecal route. For background, see PRAC minutes December 2021 and PRAC minutes June 2022. The responses were assessed by the Rapporteur for further PRAC advice.

Summary of advice/conclusion(s)

- Based on the available data and the Rapporteur's assessment, PRAC agreed that the product information should be updated to include a warning on hypersensitivity reactions (including anaphylaxis) and immunogenicity, and to amend the existing information on infusion-site reactions as well as on overdose and overdose symptoms.
- The MAH should submit to EMA, a variation to update[27] the product information accordingly.

6.5. Variation procedure(s) resulting from PSUSA evaluation

6.5.1. Elasomeran - SPIKEVAX (CAP) - EMEA/H/C/005791/II/0077

Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Update of section 4.8 of the SmPC to include acute and delayed urticaria as an adverse reaction, with the frequency 'rare', as requested by the PRAC in the 13th Safety Summary Report (EMEA/H/C/005791/MEA/011.12) concluded in June 2022. 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 thirteen safety summary report (SSR) for the above-mentioned medicine, PRAC requested the MAH to submit a variation to update the product information to add acute and delayed urticaria as an undesirable effect with a frequency 'rare'. For background information, see PRAC minutes June 2022. The type II variation procedure was assessed by the PRAC Rapporteur. 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 that the product information[28] should be updated to include urticaria as an undesirable effect with a frequency 'uncommon'.

[27] Update of SmPC sections 4.4, 4.8, 4.9 and 6.6. The package leaflet is to be updated accordingly
[28] Update of SmPC section 4.8. The package leaflet is to be updated accordingly

6.6. Expedited summary safety reviews[29]

See Annex I 16.6.

7. Post-authorisation safety studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)[30]

See Annex I 17.1.

7.2. Protocols of PASS non-imposed in the marketing authorisation(s)[31]

See Annex I 17.2.

7.3. Results of PASS imposed in the marketing authorisation(s)[32]

7.3.1. Valproate[33] (NAP) - EMEA/H/N/PSR/J/0036

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

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Submission of results for: 'survey among HCP to assess knowledge of HCP and behaviour with regards to pregnancy prevention plan (PPP) as well as receipt/use of DHPC and educational materials' and for 'survey among patients to assess knowledge of the patients with regards to PPP as well as receipt/use of educational materials'

Background

Sodium valproate is indicated for the treatment of epilepsy and for the treatment of manic episodes when lithium is contraindicated or not tolerated. Valproate is also indicated in some EU Member States in prophylaxis of migraine attacks.

Further to the conclusions dated 2018 of the referral procedure under Article 31 of Directive 2001/83/EC (EMEA/H/A-31/1454) conducted by PRAC for valproate-containing medicines, MAHs were required as a condition to the marketing authorisation(s) (Annex IV) to conduct a survey among HCPto assess knowledge of HCP and behaviour with regards to PPP as well as receipt/use of a DHPC and educational materials and survey among patients to assess knowledge of the patients with regards to PPP as well as receipt/use of educational materials.

The MAH Sanofi-Aventis Recherche & Développement on behalf of a consortium submitted to EMA the final results version 1.0 of the 'surveys among HCP and Patients to assess their knowledge and behaviour with respect to the new risk minimisation measures (RMM) for valproate use in Europe'. For further background, see PRAC minutes November 2021[34] and

[29] 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
[30] In accordance with Article 107n of Directive 2001/83/EC
[31] 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
[32] In accordance with Article 107p-q of Directive 2001/83/EC
[33] Valproic acid, sodium valproate, valproate pivoxil, valproate semisodium, valpriomide, valproate bismuth, calcium valproate, valproate magnesium
[34] Held 25-28 October 2021

PRAC minutes June 2022. PRAC discussed the final study results in addition to the MAH's answers to the request for supplementary information (RSI).

Summary of recommendation(s) and conclusions

- Based on the review of the final report of the surveys among HCP and patients and the assessment from the Rapporteur, as well as the MAH's responses to the RSI, PRAC considered that an additional round of assessment was necessary before a final recommendation could be issued.
- Given the PASS results and the available user test of the HCP guide, PRAC agreed that a 'core version of the HCP guide' is warranted in order to facilitate the implementation of the revised version of this document at the National Competent Agencies (NCA) levels. Of note, PRAC usually does not assess and approve the full version of educational materials. However, considering the challenges of the additional RMM for this substance outlined in the past, as well as the results of the surveys indicating a clear need for further improvement of knowledge (and the available user test), PRAC recommended to agree on a 'core version of the HCP guide' which can be translated to national versions and adapted to the national preferences in agreement with NCAs. With regards to the core version of the revised patient's guide, the MAH(s)' proposal is noted as simplified, shortened where needed, slightly restructured, resulting in a document easier to read. However, further updating is required. Therefore, for the next round of assessment, the MAH(s) should also provide a user tested updated core version of the patient guide, addressing PRAC comments. PRAC also agreed that the MAH(s) should seek advice from risk communication experts on how the HCP guide and patient guide might be further improved with regard to visual aid and graphical presentation, as well as on how to communicate the risks of valproate to young girls at menarche who are reaching adulthood. Finally, PRAC agreed that the MAH should submit an updated RMP to include the agreed qualitative study to investigate the barriers of the implementation of valproate PPP measures in Europe and to identify the preferred sources/channels for HCPs to access the information on the PPP as a category 3 study.
- The MAH(s) should submit responses to a further RSI within 60 days to EMA. A 60 day-assessment timetable will be followed.
- PRAC also agreed that the MAH(s) should submit, separately (i.e. via a different procedure) an updated RMP within 90 days after finalisation of the current procedure (EMEA/H/N/PSR/J/0036) in order to include the agreed qualitative study (as a category 3 study) in the pharmacovigilance plan.

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

Also see Annex I 17.4.

7.4.1. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/II/0091

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: Submission of the final safety registry report from study CNTO1275PSO4007:

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

pregnancy research initiative - exposure to ustekinumab during pregnancy: a review and analysis of birth outcomes from the Swedish, Danish, and Finnish medical birth registers (in fulfilment of MEA 024). The RMP (version 22.1) is updated accordingly

Background

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

As stated in the RMP of Stelara (ustekinumab), the MAH conducted a non-imposed non-interventional PASS CNTO1275PSO4007 entitled 'Pregnancy research initiative: exposure to ustekinumab during pregnancy: a review and analysis of birth outcomes from the Swedish, Danish, and Finnish medical birth registers'. The Rapporteur assessed the MAH's final study report and the responses from the MAH to a request for supplementary information (RSI) adopted in June 2022. For further background, see PRAC minutes February 2022 and PRAC minutes June 2022.

Summary of advice

- Based on the available data, the MAH's responses to the RSI and the Rapporteur's review, PRAC considered that the ongoing variation assessing the final study report could be recommended for approval.
- PRAC advised that the product information[36] should be updated to add a warning against use of live vaccines during the first six months following birth in infants exposed to ustekinumab in utero.

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

See Annex I 17.5.

7.6. Others

See Annex I 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.

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.

[36] Update of SmPC sections 4.4, 4.5 and 4.6. The package leaflet is updated accordingly

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

8.1. Annual reassessments of the marketing authorisation

See annex I 18.1.

8.2. Renewals of the marketing authorisation

See Annex I 18.2.

9. Product related pharmacovigilance inspections

9.1. List of planned pharmacovigilance inspections

None

9.2. Ongoing or concluded pharmacovigilance inspections

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

9.3. Others

None

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

10.1. Safety related variations of the marketing authorisation

None

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

None

10.3. Other requests

None

10.4. Scientific Advice

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

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

11.1. Safety related variations of the marketing authorisation

11.1.1. Ifosfamide (NAP) - SE/H/xxxx/WS/585

Applicants: Baxter Medical AB (Holoxan[37])

PRAC Lead: Ulla Wändel Liminga

Scope: PRAC consultation on a work-sharing variation procedure (SE/H/xxxx/WS/585) for ifosfamide-containing medicinal products on the applicability of the conclusions of the referral procedure under Article 31 of Directive 2001/83/EC for ifosfamide-containing solutions (EMEA/H/A-31/1495) and on the product information wording on central nervous system (CNS) toxicity warnings including the associated risk factors, following the recommendation of PSUR single assessment (PSUSA) procedure (PSUSA/00001723/202007) concluded in March 2021, on request of Sweden

Background

Ifosfamide is an alkylating agent indicated in the treatment of various malignancies in oncology and haematology for children and adults.

In the context of the evaluation of a work-sharing variation procedure for ifosfamide-containing medicinal products on the applicability of the conclusions of the referral procedure under Article 31 of Directive 2001/83/EC for ifosfamide-containing solutions (EMEA/H/A-31/1495) and on the product information wording on central nervous system (CNS) toxicity warnings including the associated risk factors, Sweden requested PRAC advice on its assessment.

Summary of advice

- Based on the review of the available information, PRAC agreed that the wording on CNS toxicity in the product information should be in line with the one within the referral procedure under Article 31 of Directive 2001/83/EC for ifosfamide-containing solutions (EMEA/H/A-31/1495).

11.1.2. Levonorgestrel[38] (NAP) - SE/H/xxxx/WS/582

Applicant(s): Bayer AB

PRAC Lead: Ulla Wändel Liminga

Scope: PRAC consultation on a worksharing variation procedure (SE/H/xxxx/WS/582) for levonorestrel-containing medicinal products to address the onset of contraceptive efficacy as well as the product information wording to further minimise the risk of insertion after conception, related to the recommendation of PSUR single assessment (PSUSA) procedure (PSUSA/00010828/202105) concluded in January 2022, on request of Sweden

Background

[37] Ifosfamide powder for solution for injection
[38] All indications except emergency contraception

Levonorgestrel is a progestogen indicated as an intrauterine delivery system for contraception for a period up to three years.

In the context of a worksharing variation procedure for levonorgestrel-containing product(s) to address the onset of contraceptive efficacy as well as the product information wording to further minimise the risk of insertion after conception, Sweden requested PRAC advice on its assessment.

Summary of advice

- Based on the review of the available information, PRAC generally agreed with the proposed updates to the product information to improve the existing recommendations regarding insertion of the intrauterine device (IUD), i.e. to avoid insertion after conception in order to prevent the risk of masculinisation of a female foetus if the IUD remains in place during pregnancy. In particular, PRAC concurred to the specific product information updates to further emphasise that subject examinations are needed to be undertaken before IUD insertion to recommend strict adherence to the existing advice to insert the IUD within the first 7 days from onset of the menstrual cycle, and that in case it is not possible to insert the IUD within 7 days from onset of the menstrual cycle, since immediate contraceptive protection is not reliably ensured in that case, women should use a barrier of contraception for the next 7 days after insertion of the IUD to prevent pregnancy.
- Regarding contraceptive efficacy, PRAC considered that these specific aspects are outside the scope of this procedure. The LMS agreed that the Member States' comments received will be carefully considered within the ongoing worksharing variation (SE/H/xxxx/WS/582).

11.2. Other requests

None

12. Organisational, regulatory and methodological matters

12.1. Mandate and organisation of PRAC

12.1.1. PRAC membership

The Chair welcomed Mónica Martínez Redondo as the new alternate for Spain and announced that Maria del Pilar Rayon is the new member for Spain, replacing Eva Segovia whose mandate ended on 02 September 2022.

12.1.2. PRAC Training for Assessors 2022 – course overview

The PRAC Secretariat presented to PRAC the final agenda for the yearly PRAC training for assessors 2022 scheduled on 17 November 2022 with an overview of each session together with organisational elements.

12.1.3. PRAC working group - Best practice guide on using PRAC plenary time efficiently and effectively – update on the implementation of quantitative goals – Q3 2022

In line with the adopted PRAC best practice guidance (BPG) on Committee efficiency (see PRAC minutes May 2016 and PRAC minutes June 2018) and the adopted implementation plan for the BPG including goals to measure compliance with the recommendations (see PRAC minutes June 2016 and PRAC minutes June 2018), the EMA secretariat updated PRAC at the organisational, regulatory and methodological matters (ORGAM) meeting on 10 November 2022, on the quantitative measures collected for Q3 2022 of PRAC meetings. For previous update, see PRAC minutes September 2022.

12.1.4. 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 - summary safety reports (SSRs) timetables

The EMA Secretariat presented to PRAC the proposal for the adapted timetables for the upcoming summary safety reports (SSRs) procedures. PRAC agreed on the proposal.

12.4.2. Coronavirus (COVID-19) pandemic - update

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

12.5. Cooperation with International Regulators

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 2023

PRAC lead: Sabine Straus, Martin Huber

At the organisational, regulatory and methodological matters (ORGAM) meeting on 10 November 2022, the EMA Secretariat provided an overview of planned topics to be included in the PRAC work plan 2023 based on the experience in 2022. Further discussion is planned in January 2023.

12.8. Planning and reporting

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

The EMA Secretariat presented to PRAC an update of 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 January 2022. The presentation included the timelines of the activities for the next months. Further update will be given in due course.

12.8.2. EU Pharmacovigilance system - quarterly workload measures and performance indicators – Q3 2022 and predictions

At the organisational, regulatory and methodological matters (ORGAM) meeting on 10 November 2022, the EMA Secretariat presented to PRAC an overview of the quarterly figures on the EMA pharmacovigilance system-related workload and performance indicators. For previous update, see PRAC minutes September 2022.

12.8.3. PRAC workload statistics – Q3 2022

At the organisational, regulatory and methodological matters (ORGAM) meeting on 10 November 2022, the EMA secretariat presented to PRAC the quarterly and cumulative figures to estimate the evolution of the workload of PRAC for Q3 2022, by reflecting on the number of procedures and agenda items covered at each PRAC plenary meeting. For previous update, see PRAC minutes September 2022.

12.9. Pharmacovigilance audits and inspections

12.9.1. Pharmacovigilance systems and their quality systems

None

12.9.2. Pharmacovigilance inspections

None

12.9.3. Pharmacovigilance audits

None

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

12.10.1. Periodic safety update reports

None

12.10.2. Granularity and Periodicity Advisory Group (GPAG)

PRAC lead: Menno van der Elst, Maia Uusküla

At the organisational, regulatory and methodological matters (ORGAM) meeting on 10 November 2022, PRAC endorsed the GPAG recommendations on the proposal for implementing in the Union reference date list (EURD List) the new PSUR frequencies predicted by the EURD tool in a set of approximately 1,000 active substances which PSURs were deferred to 2025 at the time of the EURD List creation. Additional consultations on the matter will take place at the EMA management level. The EMA Secretariat will inform PRAC on the outcome of these discussions.

12.10.3. PSURs repository

None

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

In line with the criteria for plenary presentation of updates to the EURD List adopted by PRAC in December 2021, PRAC endorsed the draft revised EURD list, version November 2022, reflecting the PRAC's comments impacting on the data lock point (DLP) and PSUR submission frequencies of the substances/combinations PRAC endorsed the newly allocated Rapporteurs for upcoming PSUSAs in accordance with the principles previously endorsed by PRAC see PRAC minutes April 2013.

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

PRAC lead: Menno van der Elst

PRAC was updated on the progress from the signal management review technical (SMART) working group (WG) meeting held remotely on 06 October 2022. The SMART WG discussed the matter of inclusion of unpublished data in the signal assessment report. The group also

discussed about handling of safety signals while other procedures addressing the same issue are ongoing. Further update will be planned in due course.

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

12.13.2. EudraVigilance: change to L2A downloads

The EMA Secretariat presented to PRAC a proposal to amend L2A downloads to completely remove cases from UK, in order to fix the rapid multiplication of duplicates in EudraVigilance, so that it will not affect future signal detection activities. PRAC noted and agreed with the proposal.

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

12.14.3. Good Pharmacovigilance Practice (GVP) module V on '– Risk management systems'- Revision 3 update

The EMA Secretariat presented to PRAC an EMA's proposal to revise GVP module V on 'Risk management systems' together with a plan for the next steps. This revision of GVP module V will be added to the PRAC work plan 2023. PRAC members were invited to send

comments, as well as their intention to contribute to this activity by joining the drafting group together with CHMP and CAT members.

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. Public consultation on a. Good Practice Guide for the use of the EU metadata catalogue and b. Data Quality Framework

The EMA Secretariat provided PRAC with an overview and the activities on the 'Data quality framework' and informed PRAC about the launch of the public consultation on this document starting on 10 October 2022. The EMA Secretariat also presented to PRAC the

objectives of the 'good practice guide for the use of the metadata catalogue of real-world data sources' and informed the Committee on the launch of the public consultation on this document started on 27 September 2022. PRAC members were invited to send comments on both documents.

12.21.2. Good Pharmacovigilance Practice (GVP) – end-of-year update for 2022 and planning for 2023

PRAC lead: Sabine Straus

The EMA Secretariat provided PRAC with an update on GVP development in line with PRAC and EMA work plans for 2022 as planned on a regular basis. PRAC was also updated on the upcoming activities around GVP as a contribution to the PRAC work plan for 2023.

13. Any other business

None

14. Annex I – Signals assessment and prioritisation[39]

14.1. New signals detected from EU spontaneous reporting systems

14.1.1. Olaparib - LYNPARZA (CAP)

Applicant: AstraZeneca AB

PRAC Rapporteur: Amelia Cupelli

Scope: Signal of hepatocellular damage and hepatitis (HLT)

EPITT 19846 – New signal

Lead Member State(s): IT

14.1.2. Ceftriaxone (NAP)

Applicant(s): various

PRAC Rapporteur: Zane Neikena

Scope: Signal of risk of factor V inhibition

EPITT 19853 – New signal

Lead Member State(s): LV

[39] 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

14.2. New signals detected from other sources

14.2.1. Propofol (NAP)

Applicant(s): various

PRAC Rapporteur: Karen Pernille Harg

Scope: Signal of medication errors that could potentially lead to life-threatening/fatal cases

EPITT 19851 – New signal

Lead Member State(s): NO

14.2.2. Voriconazole - VFEND (CAP); VORICONAZOLE ACCORD (CAP); VORICONAZOLE HIKMA (CAP); NAP

Applicant(s): Accord Healthcare S.L.U. (Voriconazole Accord), Hikma Farmaceutica (Portugal), S.A. (Voriconazole Hikma), Pfizer Europe MA EEIG (Vfend), various

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Signal of drug interaction with flucloxacillin leading to subtherapeutic voriconazole levels

EPITT 19849 – New signal

Lead Member State(s): NL

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 medicines mentioned below under evaluation for initial marketing authorisation application. Information on the medicines containing the below listed active substance(s) will be made available following the CHMP opinion on their marketing authorisation(s).

15.1.1. Dapagliflozin - EMEA/H/C/006006

Scope: Treatment of type 2 diabetes mellitus, heart failure and chronic kidney disease

15.1.2. Filgrastim - EMEA/H/C/005888

Scope: Reduction in the duration of neutropenia and the incidence of febrile neutropenia, indicated for the mobilisation of peripheral blood progenitor cells and persistent neutropenia in patients with advanced HIV infection

15.1.3. Sirolimus - EMEA/H/C/005896, Orphan

Applicant: Plusultra pharma GmbH, Hybrid

Scope: Treatment of angiofibroma associated with tuberous sclerosis complex

15.1.4. Sitagliptin, metformin hydrochloride - EMEA/H/C/005778

Scope: Treatment of type 2 diabetes mellitus

15.1.5. Spironolactone - EMEA/H/C/005535

Scope: Indicated for the management of refractory oedema

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

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

15.2.1. Afamelanotide - SCENESSE (CAP) - EMEA/H/C/002548/II/0042, Orphan

Applicant: Clinuvel Europe Limited

PRAC Rapporteur: Martin Huber

Scope: Submission of an updated RMP version 9.1 in order to update the 'allergy and hypersensitivity risk' from potential to identified, following reported cases of positive allergy test results, confirming the causal association between the allergies and afamelanotide

15.2.2. Meningococcal group A, C, W135 and Y conjugate vaccine - MENVEO (CAP) - EMEA/H/C/001095/II/0112

Applicant: GSK Vaccines S.r.l

PRAC Rapporteur: Menno van der Elst

Scope: Submission of an updated RMP version 10 in order to remove several safety concerns

15.2.3. Siltuximab - SYLVANT (CAP) - EMEA/H/C/003708/II/0038, Orphan

Applicant: EUSA Pharma (Netherlands) B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Submission of the report from study ACCELERATE (Advancing Castleman Care with an Electronic Longitudinal Registry, E-Repository, And Treatment/Effectiveness Research): An International Registry for Patients with Castleman Disease - NCT02817997 listed as an obligation in the Annex II of the product information. This is a study Report to cover the data collected for 100 patients over a 5 year period in the ACCELERATE Registry study to collect information or patients with Castleman's Disease who are candidates to receive Sylvant or are currently receiving treatment with Sylvant. The Annex II is updated accordingly

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

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

15.3.1. Albutrepenonacog alfa - IDELVION (CAP) - EMEA/H/C/003955/II/0059, Orphan

Applicant: CSL Behring GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Update of sections 4.2, 4.8 and 5.1 of the SmPC in order to update information and amend the frequencies of adverse drug reactions (ADRs) based on the final results from study CSL654_3003 (listed as a category 3 study in the RMP): an open-label, multicentre, uncontrolled study to evaluate the safety, pharmacokinetics and clinical response of recombinant factor IX albumin fusion protein (rIX-FP) with regard to the prevention and treatment of bleeding in previously untreated patients (PUPs) with haemophilia B. The package leaflet is updated accordingly. The RMP (version 4.0) has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the product information and update the list of local representatives in the package leaflet

15.3.2. Brolucizumab - BEOVU (CAP) - EMEA/H/C/004913/II/0018

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of sections 4.2 and 5.1 of the SmPC in order to introduce an alternative posology regimen for wet AMD and update information based on modelling and simulation studies; the package leaflet is updated accordingly. The RMP version 9.0 has also been submitted

15.3.3. Concentrate of proteolytic enzymes enriched in bromelain - NEXOBRID (CAP) - EMEA/H/C/002246/II/0057, Orphan

Applicant: MediWound Germany GmbH

PRAC Rapporteur: Martin Huber

Scope: Submission of the 24-months' CSR addendum of the MW2010-03-02 (DETECT) category 1 study; a multicentre, multinational, randomised, controlled, assessor blinded study, performed in subjects with thermal burns, to evaluate the efficacy and safety of NexoBrid compared to gel vehicle and compared to standard of care. The provision of the CSR addresses the post-authorisation measure ANX 001.7. An updated RMP version 8.0 was provided as part of the application

15.3.4. Dapagliflozin - EDISTRIDE (CAP) - EMEA/H/C/004161/WS2299/0055; FORXIGA (CAP) - EMEA/H/C/002322/WS2299/0076

Applicant: AstraZeneca AB

PRAC Rapporteur: Mari Thorn

Scope: Extension of indication to include population with heart failure (HF) and low ventricular ejection fraction (LVEF) > 40% for Forxiga and its duplicate Edistride, based on final results from study D169CC00001 (DELIVER); The DELIVER study is a category 3, PASS listed in the dapagliflozin RMP to evaluate the potential risk of lower limb amputation; this was an international, multi-centre, parallel-group, event-driven, randomised, double-blind, placebo-controlled Phase III study in patients with HF and LVEF > 40%, evaluating the

effect of dapagliflozin 10 mg compared with placebo, given once daily in addition to background therapy, including treatments to control co-morbidities, in reducing the composite of cardiovascular (CV) death or an HF event (hospitalisation for HF or urgent HF visit). As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The package leaflets are updated in accordance. Version 27 of the RMP has also been submitted

15.3.5. Diroximel fumarate - VUMERITY (CAP) - EMEA/H/C/005437/II/0005

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Martin Huber

Scope: Submission of the final report from study ALK8700-A301: a phase 3 open label study to evaluate the long-term safety and tolerability of ALKS 8700 in adults with relapsing remitting multiple sclerosis (RRMS) listed as a category 3 study in the RMP. This is a multicentre, open-label study to evaluate the long-term safety, tolerability, and treatment effect over time of diroximel fumarate (DRF) administered for up to 96 weeks in adult participants with RRMS. The RMP version 1.1 has also been submitted

15.3.6. Dupilumab - DUPIXENT (CAP) - EMEA/H/C/004390/II/0062

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Kimmo Jaakkola

Scope: Extension of indication to include treatment of eosinophilic esophagitis (EoE) in adults and adolescents 12 years and older who are inadequately controlled by, are intolerant to, or who are not candidates for conventional medicinal therapy, based on the pivotal Study R668-EE-1774. This is an ongoing phase 3, randomised, double-blind, placebo-controlled, 3-part (A, B, C) safety and efficacy study with an initial 24-week treatment period in adults (≥18 years of age) and adolescents (≥12 to <18 years of age) with EoE, and which includes an extended treatment period to a total of 52 weeks. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, and 5.2 of the SmPC are updated. The package leaflet is updated in accordance. Version 8.0 of the RMP has also been submitted

15.3.7. Dupilumab - DUPIXENT (CAP) - EMEA/H/C/004390/II/0063

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Kimmo Jaakkola

Scope: Extension of indication to include treatment of adults with moderate to severe prurigo nodularis (PN) who are candidates for systemic therapy, based on results from studies EFC16459 and EFC16460 (PRIME and PRIME2); these are two phase 3, 24-week, randomised, double-blind, placebo-controlled, multi-centre, parallel group studies undertaken to evaluate the efficacy and safety of dupilumab in patients 18 years of age and older with moderate to severe PN, who are inadequately controlled on topical prescription therapies or when those therapies are not advisable. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 of the SmPC are updated. The package leaflet is updated in accordance. Version 8.0 of the RMP has also been submitted. As part of this application, the MAH is also requesting a 1-year extension of the market protection

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

Applicant: AstraZeneca AB

PRAC Rapporteur: David Olsen

Scope: Extension of indication to include IMFINZI in combination with tremelimumab for the treatment of adults with unresectable hepatocellular carcinoma (uHCC), based on final results from Study D419CC00002 (HIMALAYA): a randomised, open-label, multi-centre phase III study of durvalumab and tremelimumab as first-line treatment in patients with unresectable hepatocellular carcinoma. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet is updated in accordance. In addition, the MAH took the opportunity to implement minor editorial changes in the SmPC and package leaflet. Version 6.1 of the RMP has also been submitted

15.3.9. Ebola Zaire vaccine (live, attenuated) - ERVEBO (CAP) - EMEA/H/C/004554/II/0025

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication to include the paediatric population from 1 year to less than 18 years of age based on final results from study V920-016 (PREVAC); this is a phase 2, randomised, double-blind, placebo-controlled study of 2 leading Ebola vaccine candidates (Ad26.ZEBOV/MVA-BN-Filo and V920) and 3 vaccine strategies (Ad26.ZEBOV/MVABN-Filo, 1-dose V920, and 2 dose V920) to evaluate immunogenicity and safety in healthy children and adolescents from 1 to 17 years of age and adults 18 years of age and older. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, and 5.3 of the SmPC are updated. The package leaflet is updated in accordance. Version 1.2 of the RMP has also been submitted. In addition, the MAH took the opportunity to update the Annex II and the list of local representatives in the package leaflet

15.3.10. Elasomeran - SPIKEVAX (CAP) - EMEA/H/C/005791/II/0083/G

Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Extension of indication to include a 50-µg booster dose of Spikevax bivalent Original/Omicron BA.1 in children (6 to < 12 years), based on interim results from study P204; this is a Phase 2/3, Three-Part, Open-Label, Dose-Escalation, Age De-escalation and Randomised, Observer-Blind, Placebo-Controlled Expansion Study to Evaluate the Safety, Tolerability, Reactogenicity, and Effectiveness of mRNA-1273 SARS-CoV-2 Vaccine in Healthy Children 6 Months to Less Than 12 Years of Age. As a consequence, sections 2, 4.1, 4.2, 4.4, 4.8, 5.1 and 6.6 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 4.5 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to implement editorial changes. To update sections 4.8, 5.1, and 6.6 of the SmPC to include additional immunogenicity data for the paediatric population (6 to < 18 years) based on Real-World Safety studies

15.3.11. Human normal immunoglobulin - HYQVIA (CAP) - EMEA/H/C/002491/II/0078

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of section 4.8 and 5.1 of the SmPC in order to update safety data in paediatric population based on final results from study 161504 (listed as a category 3 study in the RMP) – post-authorisation safety, tolerability and immunogenicity evaluation of HyQvia in paediatric subjects with primary immunodeficiency diseases. This is a paediatric interventional phase 4 study performed to acquire additional data on safety, tolerability and immunogenicity of HyQvia in paediatric (age two to <18 years) patients with primary immunodeficiency diseases (PIDD). In addition, the MAH is taking this opportunity to update Annex II-D of the PI following procedure EMEA/H/C/002491/II/0070/G. The RMP version 13.1 has also been submitted

15.3.12. Onasemnogene abeparvovec - ZOLGENSMA (CAP) - EMEA/H/C/004750/II/0033/G, Orphan

Applicant: Novartis Europharm Limited, ATMP[40]

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of sections 4.2, 4.4 and 4.8 of the SmPC in order to introduce additional guidance on liver function laboratory tests and monitoring before and after infusion and update information based on new safety information on the topic of acute liver failure (ALF) following two reports of fatal ALF. Update of sections 4.2 and 4.4 of the SmPC in order to provide additional guidance relevant to patient's overall health status prior to dosing and to strengthen the existing description and guidance on systemic immune response. Update of the section 4.4 of the SmPC in order to indicate prompt attention to thrombotic microangiopathy (TMA) and to reflect the risk of life-threatening or fatal outcomes. The package leaflet is updated accordingly. The RMP version 2.0 has also been submitted. In addition, the MAH took the opportunity to update Annex II

15.3.13. Parathyroid hormone - NATPAR (CAP) - EMEA/H/C/003861/II/0042, Orphan

Applicant: Takeda Pharmaceuticals International AG

PRAC Rapporteur: Rhea Fitzgerald

Scope: Submission of the updated protocol from study SHP634-403 listed as a specific obligation in the Annex II of the product information with twice-daily (BID) as the proposed alternative dosing regimen to be evaluated. This is a randomised, 2-Arm, double-blind, phase 4 study to evaluate once daily (QD) versus twice daily (BID) administration of recombinant human parathyroid hormone (rhPTH[1-84]; NATPARA) for the treatment of adults with hypoparathyroidism (HPT). Annex II and the RMP (submitted version 3.4) are updated accordingly

15.3.14. Ponatinib - ICLUSIG (CAP) - EMEA/H/C/002695/II/0064, Orphan

Applicant: Incyte Biosciences Distribution B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension of indication to include treatment of newly diagnosed adult patients with Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL), either with

[40] Advanced therapy medicinal product

Iclusig (ponatinib) in combination with chemotherapy, or with Iclusig (ponatinib) monotherapy after corticosteroid induction in patients not eligible to receive chemotherapy-based regimens, based on final results from studies AP24534-11-001 and INCB 84344-201. As a consequence, sections 4.1, 4.8 and 5.1 of the SmPC are updated. The package leaflet is updated in accordance. Version 22 of the RMP has also been submitted

15.3.15. Remimazolam - BYFAVO (CAP) - EMEA/H/C/005246/X/0002

Applicant: Paion Deutschland GmbH

PRAC Rapporteur: Rhea Fitzgerald

Scope: Extension application to introduce a new pharmaceutical form associated with a new strength (50 mg powder for concentrate for solution for injection/infusion). The new presentation comes with a new indication to include the intravenous induction and maintenance of general anaesthesia (GA) in adults for Byfavo (remimazolam) 50 mg, based on final results from two pivotal trials: 1) study ONO-2745-05: a phase 2b/3, single-blind, randomised, parallel-group study assessing safety and efficacy in induction and maintenance of anaesthesia in American Society of Anesthesiologists (ASA) I/II patients (general surgery); 2) study CNS-7056-022: a phase 3, randomised, propofol controlled, parallel group, confirmatory single-blind efficacy and safety trial during induction and maintenance of anaesthesia in ASA III/IV patients. A new combined version of the SmPC, labelling and package leaflet solely for the 50 mg strength and the GA indication is provided accordingly. The RMP (version 1.1) is updated accordingly. Finally, the MAH requested an extension of the market protection by one additional year

15.3.16. Sacubitril, valsartan - ENTRESTO (CAP) - EMEA/H/C/004062/X/0044/G

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Anette Kirstine Stark

Scope: Extension application to introduce a new pharmaceutical form associated with two new strengths (6 mg/6 mg granules in capsule for opening and 15 mg/16 mg granules in capsule for opening), grouped with a type II variation (C.I.6.a) in order to extend the indication to include treatment of children and adolescents aged one year or older with chronic heart failure with left ventricular systolic dysfunction, based on the results of Study PANORAMA-HF (CLCZ696B2319): a multicentre, open-label, study to evaluate safety, tolerability, pharmacokinetics and pharmacodynamics of sacubitril/valsartan followed by a 52-week randomised, double-blind, parallel group, active-controlled study to evaluate the efficacy and safety of sacubitril/valsartan compared with enalapril in paediatric patients from 1 month to < 18 years of age with heart failure due to systemic left ventricle systolic dysfunction. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.2 of the SmPC are being updated and the package leaflet is updated accordingly. In addition, an updated RMP version 4.0 was provided as part of the application. Further, the MAH requested a one year extension of the market protection

15.3.17. Sacubitril, valsartan - NEPARVIS (CAP) - EMEA/H/C/004343/X/0042/G

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Anette Kirstine Stark

Scope: Extension application to introduce a new pharmaceutical form associated with two new strengths (6 mg/6 mg granules in capsule for opening and 15 mg/16 mg granules in capsule for opening), grouped with a type II variation (C.I.6.a) in order to extend the indication to include treatment of children and adolescents aged one year or older with chronic heart failure with left ventricular systolic dysfunction, based on the results of Study PANORAMA-HF (CLCZ696B2319); a multicentre, open-label, study to evaluate safety, tolerability, pharmacokinetics and pharmacodynamics of sacubitril/valsartan followed by a 52-week randomised, double-blind, parallel group, active-controlled study to evaluate the efficacy and safety of sacubitril/valsartan compared with enalapril in paediatric patients from 1 month to < 18 years of age with heart failure due to systemic left ventricle systolic dysfunction. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.2 of the SmPC are being updated and the package leaflet is updated accordingly. In addition, an updated RMP version 4.0 was provided as part of the application. Further, the MAH requested a one year extension of the market protection

15.3.18. Somapacitan - SOGROYA (CAP) - EMEA/H/C/005030/X/0006/G, Orphan

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Martin Huber

Scope: Extension application to add a new strength of 15 mg/1.5 mL solution for injection in pre-filled pen grouped with a type II variation C.I.6 to add a new indication 'Replacement of endogenous growth hormone (GH) in children and adolescents with growth failure due to growth hormone deficiency (GHD)', based on results from the completed main 52-week period of the confirmatory phase 3 trial (4263), supported with long-term data from the phase 2 trial (4172), up to week 208 completed. As a consequence, sections 4.1, 4.2, 4.3, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated and the package leaflet has been updated accordingly. A revised RMP version 3.0 was provided as part of the application

15.3.19. Tildrakizumab - ILUMETRI (CAP) - EMEA/H/C/004514/II/0036

Applicant: Almirall S.A

PRAC Rapporteur: Adam Przybylkowski

Scope: Addition of 100 mg solution for injection in pre-filled pen which is an integrated part of the primary packaging of the medicinal product. The RMP (version 1.2) is updated accordingly

15.3.20. Tixagevimab, cilgavimab - EVUSHELD (CAP) - EMEA/H/C/005788/II/0003

Applicant: AstraZeneca AB

PRAC Rapporteur: Kimmo Jaakkola

Scope: Update of sections 4.2, 4.8, 4.9, 5.1 and 5.2 of the SmPC in order to change the posology recommendations in the pre-exposure prophylaxis indication based on study TACKLE (D8851C00001). The package leaflet is updated accordingly. The RMP (version 2) has also been submitted

15.3.21. Tozinameran - COMIRNATY (CAP) - EMEA/H/C/005735/X/0147

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Extension application to add a new strength of 5/5 µg (tozinameran, famtozinameran) for children between 5 to 11 years of age. The RMP (version 7.2) is updated in accordance

15.3.22. Treosulfan - TRECONDI (CAP) - EMEA/H/C/004751/II/0012, Orphan

Applicant: medac Gesellschaft fur klinische Spezialpraparate mbH

PRAC Rapporteur: Julia Pallos

Scope: Update of sections 4.5 and 5.2 of the SmPC in order to add drug-drug interaction information with regards to CYP3A4, CYP2C19 and P-gp including physiologically based pharmacokinetic (PBPK) modelling. Version 1.0 of the RMP has also been submitted

15.3.23. Treosulfan - TRECONDI (CAP) - EMEA/H/C/004751/II/0014, Orphan

Applicant: medac Gesellschaft fur klinische Spezialpraparate mbH

PRAC Rapporteur: Julia Pallos

Scope: Extension of indication to include additional non-malignant transplant indications (non-malignant diseases in the paediatric population) for Trecondi 1 g/5 g powder for solution for infusion based on final 12-months follow-up results of study MC-FludT.16/NM; a randomised phase II interventional study aimed to compare Treosulfan-based conditioning therapy with Busulfan-based conditioning prior to allogeneic haematopoietic stem cell transplantation in paediatric patients with non-malignant diseases.
Further, the MAH proposes to amend an existing warning on skin toxicity based on new literature data. Moreover, the MAH proposes to introduce a slightly modified dosing regimen according to the patient's body surface based on long-term follow-up data of paediatric study MC-FludT.17/M, a Phase II trial to describe the safety and efficacy of Treosulfan based conditioning therapy prior to allogeneic haematopoietic stem cell transplantation in paediatric patients with haematological malignancies, as well as a final analysis of the population pharmacokinetics of treosulfan in paediatric patients. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The package leaflet is updated in accordance. Version 1.0 of the RMP has also been submitted

15.3.24. Upadacitinib - RINVOQ (CAP) - EMEA/H/C/004760/II/0027

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Extension of indication to include treatment of moderately to severely active Crohn's disease in adult patients, based on final results from three Phase III studies, two confirmatory placebo-controlled induction studies (Study M14 431/U-EXCEED/CD-1) and Study M14 433/U-EXCEL/CD-2) and a placebo-controlled maintenance/long-term extension study (Study M14-430/U-ENDURE/CD-3). M14-431 study is a Phase III, multicentre, Randomised, Double-Blind, Placebo-Controlled Induction Study of the Efficacy and Safety of

Upadacitinib (ABT-494) in Subjects with Moderately to Severely Active Crohn's Disease Who Have Inadequately Responded to or are Intolerant to Biologic Therapy. M14-433 study is a Phase III, multicentre, Randomised, Double-Blind, Placebo Controlled Induction Study of the Efficacy and Safety of Upadacitinib (ABT-494) in Subjects with Moderately to Severely Active Crohn's Disease Who Have Inadequately Responded to or are Intolerant to Conventional and/or Biologic Therapies. M14-430 study is an ongoing Phase III, multicentre, Randomised, Double-Blind, Placebo-Controlled Maintenance and Long-Term Extension Study of the Efficacy and Safety of Upadacitinib (ABT-494) in Subjects with Crohn's Disease Who Completed the Studies M14-431 or M14-433. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The package leaflet is updated in accordance. Version 11 of the RMP has also been submitted

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

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

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

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

16.1.1. Apremilast - OTEZLA (CAP) - PSUSA/00010338/202203

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Monica Martínez Redondo

Scope: Evaluation of a PSUSA procedure

16.1.2. Avacopan - TAVNEOS (CAP) - PSUSA/00010967/202203

Applicant: Vifor Fresenius Medical Care Renal Pharma France

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

16.1.3. Avelumab - BAVENCIO (CAP) - PSUSA/00010635/202203

Applicant: Merck Europe B.V.

PRAC Rapporteur: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

16.1.4. Brolucizumab - BEOVU (CAP) - PSUSA/00010829/202204

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.5. Bupivacaine, meloxicam - ZYNRELEF (CAP) - PSUSA/00010880/202203

Applicant: Heron Therapeutics, B.V.

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

16.1.6. Cangrelor - KENGREXAL (CAP) - PSUSA/00010360/202203

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.1.7. Cenobamate - ONTOZRY (CAP) - PSUSA/00010921/202203

Applicant: Angelini S.p.A.

PRAC Rapporteur: Jo Robays

Scope: Evaluation of a PSUSA procedure

16.1.8. Ciclosporin[41] - IKERVIS (CAP); VERKAZIA (CAP) - PSUSA/00010362/202203

Applicants: Santen Oy

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.1.9. Cinacalcet - MIMPARA (CAP) - PSUSA/00000756/202202

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Mari Thorn

Scope: Evaluation of a PSUSA procedure

16.1.10. Dabigatran - PRADAXA (CAP) - PSUSA/00000918/202203

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

[41] Topical use only

16.1.11. Duvelisib - COPIKTRA (CAP) - PSUSA/00010939/202203

Applicant: Secura Bio Limited

PRAC Rapporteur: Željana Margan Koletić

Scope: Evaluation of a PSUSA procedure

16.1.12. Ebola vaccine (rDNA[42], replication-incompetent) - MVABEA (CAP); ZABDENO (CAP) - PSUSA/00010857/202203

Applicants: Janssen-Cilag International N.V.

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

16.1.13. Filgotinib - JYSELECA (CAP) - PSUSA/00010879/202203

Applicant: Galapagos N.V.

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Evaluation of a PSUSA procedure

16.1.14. Ganirelix - ORGALUTRAN (CAP) - PSUSA/00001517/202202

Applicant: Organon N.V.

PRAC Rapporteur: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

16.1.15. Idecabtagene vicleucel - ABECMA (CAP) - PSUSA/00010954/202203

Applicant: Bristol-Myers Squibb Pharma EEIG, ATMP[43]

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.16. Lapatinib - TYVERB (CAP) - PSUSA/00001829/202203 (with RMP)

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.17. Lorlatinib - LORVIQUA (CAP) - PSUSA/00010760/202203

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Evaluation of a PSUSA procedure

[42] Recombinant deoxyribonucleic acid
[43] Advanced therapy medicinal product

16.1.18. Mepolizumab - NUCALA (CAP) - PSUSA/00010456/202203

Applicant: GlaxoSmithKline Trading Services Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.19. Mifamurtide - MEPACT (CAP) - PSUSA/00002059/202203

Applicant: Takeda France SAS

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.20. Mogamulizumab - POTELIGEO (CAP) - PSUSA/00010741/202203

Applicant: Kyowa Kirin Holdings B.V.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Evaluation of a PSUSA procedure

16.1.21. Naldemedine - RIZMOIC (CAP) - PSUSA/00010753/202203

Applicant: Shionogi B.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

16.1.22. Niraparib - ZEJULA (CAP) - PSUSA/00010655/202203

Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.1.23. Obiltoxaximab - OBILTOXAXIMAB SFL (CAP) - PSUSA/00010885/202203

Applicant: SFL Pharmaceuticals Deutschland GmbH

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

16.1.24. Ofatumumab - KESIMPTA (CAP) - PSUSA/00010927/202203

Applicant: Novartis Ireland Limited

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.1.25. Ponesimod - PONVORY (CAP) - PSUSA/00010940/202203

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

16.1.26. Rilpivirine[44] - REKAMBYS (CAP) - PSUSA/00010901/202203

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

16.1.27. Selinexor - NEXPOVIO (CAP) - PSUSA/00010926/202203

Applicant: Stemline Therapeutics B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.28. Selumetinib - KOSELUGO (CAP) - PSUSA/00010936/202204

Applicant: AstraZeneca AB

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.29. Solriamfetol - SUNOSI (CAP) - PSUSA/00010831/202203

Applicant: TMC Pharma (EU) Limited

PRAC Rapporteur: Julia Pallos

Scope: Evaluation of a PSUSA procedure

16.1.30. Tepotinib - TEPMETKO (CAP) - PSUSA/00010979/202203

Applicant: Merck Europe B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.31. Tildrakizumab - ILUMETRI (CAP) - PSUSA/00010720/202203

Applicant: Almirall S.A

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

[44] Intramuscular use only

16.1.32. Velaglucerase alfa - VPRIV (CAP) - PSUSA/00003103/202202

Applicant: Takeda Pharmaceuticals International AG

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.33. Velmanase alfa - LAMZEDE (CAP) - PSUSA/00010677/202203

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Jan Neuhauser

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. Travoprost - IZBA (CAP); TRAVATAN (CAP); NAP - PSUSA/00003011/202202

Applicant(s): Novartis Europharm Limited (Izba, Travatan), various

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

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

16.3.1. Alprazolam (NAP) - PSUSA/00000109/202203

Applicant(s): various

PRAC Lead: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

16.3.2. Amlodipine (NAP) - PSUSA/00000174/202203

Applicant(s): various

PRAC Lead: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

16.3.3. Aprotinin (NAP) - PSUSA/00000230/202202

Applicant(s): various

PRAC Lead: Marie Louise Schougaard Christiansen

Scope: Evaluation of a PSUSA procedure

16.3.4. Aviptadil, phentolamine mesilate (NAP) - PSUSA/00010814/202202

Applicant(s): various

PRAC Lead: Marie Louise Schougaard Christiansen

Scope: Evaluation of a PSUSA procedure

16.3.5. Cabergoline (NAP) - PSUSA/00000477/202203

Applicant(s): various

PRAC Lead: Valentina Di Giovanni

Scope: Evaluation of a PSUSA procedure

16.3.6. Chloroprocaine hydrochloride (NAP) - PSUSA/00010078/202203

Applicant(s): various

PRAC Lead: Željana Margan Koletić

Scope: Evaluation of a PSUSA procedure

16.3.7. Clodronic acid (NAP); clodronic acid, lidocaine (NAP) - PSUSA/00010650/202202

Applicant(s): various

PRAC Lead: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

16.3.8. Diphtheria, tetanus, pertussis (acellular, component) vaccine (adsorbed) (NAP); diphtheria, tetanus, pertussis (acellular, component) vaccine (adsorbed) reduced antigens contents (NAP) - PSUSA/00001125/202203

Applicant(s): various

PRAC Lead: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.3.9. Eplerenone (NAP) - PSUSA/00001236/202203

Applicant(s): various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.3.10. Fluticasone propionate (NAP) - PSUSA/00001454/202202

Applicant(s): various

PRAC Lead: Polona Golmajer

Scope: Evaluation of a PSUSA procedure

16.3.11. Frovatriptan (NAP) - PSUSA/00001484/202203

Applicant(s): various

PRAC Lead: Eva Jirsová

Scope: Evaluation of a PSUSA procedure

16.3.12. Germanium (^{68}Ge) chloride, gallium (^{68}Ga) chloride (NAP) - PSUSA/00010364/202203

Applicant(s): various

PRAC Lead: Eva Jirsová

Scope: Evaluation of a PSUSA procedure

16.3.13. Naratriptan (NAP) - PSUSA/00002126/202202

Applicant(s): various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.3.14. Nicorandil (NAP) - PSUSA/00002152/202202

Applicant(s): various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.3.15. Phleum pratense[45] [46] [47] (NAP) - PSUSA/00010475/202203

Applicant(s): various

PRAC Lead: Mari Thorn

Scope: Evaluation of a PSUSA procedure

16.3.16. Rocuronium (NAP) - PSUSA/00002656/202202

Applicant(s): various

PRAC Lead: Eva Jirsová

Scope: Evaluation of a PSUSA procedure

16.3.17. Sodium iodide (^{131}I) (NAP) - PSUSA/00002753/202203

Applicant(s): various

PRAC Lead: Marcia Sofia Sanches de Castro Lopes Silva

[45] Allergen for therapy
[46] For oromucosal use only
[47] Medicinal product(s) authorised via mutually recognition procedure only

Scope: Evaluation of a PSUSA procedure

16.3.18. Varicella vaccine (live) (NAP) - PSUSA/00010473/202203

Applicant(s): various

PRAC Lead: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

16.3.19. Zolmitriptan (NAP) - PSUSA/00003150/202203

Applicant(s): various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.4. Follow-up to PSUR/PSUSA procedures

16.4.1. Venetoclax - VENCLYXTO (CAP) - EMEA/H/C/004106/LEG 017

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Eva Jirsová

Scope: From II-0031: Commitment to provide targeted tumour lysis syndrome (TLS) assessment reports on a biannual basis (submitted annually within the PSUR, and 6 months after the PSUR submission in a separate report) through 2023, and annually thereafter, as per the RMP v8.0. These biannual assessment reports ensure close monitoring of the important identified risk of TLS, and the evaluation of the impact of newly implemented risk minimisation measures for TLS, on adherence to both already existing and updated recommendation added to the SmPC, the impact of the DHPC distributed to haematologists, and the patient card

16.5. Follow-up to PSUR/PSUSA procedures

None

16.6. Variation procedure(s) resulting from PSUSA evaluation

16.6.1. Coronavirus (COVID-19) vaccine (inactivated, adjuvanted, adsorbed) - COVID-19 VACCINE (INACTIVATED, ADJUVANTED) VALNEVA (CAP) - EMEA/H/C/006019/MEA 009.2

Applicant: Valneva Austria GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

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

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)[48]

17.1.1. Avapritinib – AYVAKYT (CAP) - EMEA/H/C/PSA/S/0092

Applicant: Blueprint Medicines

PRAC Rapporteur: Menno van der Elst

Scope: Substantial amendment to an agreed protocol for study BLU-285-1406: an observational study evaluating safety and efficacy of avapritinib in the first line treatment of patients with Platelet derived Growth Factor Alpha D842V mutated gastrointestinal stromal tumour

17.1.2. Chlormadinone acetate, ethinylestradiol (NAP) - EMEA/H/N/PSA/J/0072.2

Applicant: Gedeon Richter Plc

PRAC Rapporteur: Martin Huber

Scope: Protocol for a case control study comparing levonorgestrel and chlormadinone acetate (CMA) to compare the venous thromboembolism (VTE) risk of combined oral contraceptives (COCs) containing CMA 2mg / ethinylestradiol (EE) 30 µg, compared to COCs containing levonorgestrel (LNG) 0.15mg, both combined with 30 µg ethinylestradiol (EE), as required in the outcome of the referral procedure under Article 31 of Directive 2001/83/EC on Combined hormonal contraceptives completed in January 2014 (EMEA/H/A-31/1356)]

17.1.3. Lenalidomide - REVLIMID - EMEA/H/C/PSA/S/0093

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Tiphaine Vaillant

Scope: Substantial amendment to a previously agreed protocol for a PASS (listed as a specific obligation in the Annex II of the product information): post-authorisation, non-interventional, retrospective, drug-utilisation study to describe the pattern of use of lenalidomide in patients with myelodysplastic syndromes (MDS)

17.1.4. Valproate[49] (NAP) - EMEA/H/N/PSP/J/0094.3

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

PRAC Rapporteur: Liana Gross-Martirosyan

[48] In accordance with Article 107n of Directive 2001/83/EC
[49] Valproic acid, sodium valproate, valproate pivoxil, valproate semisodium, valpriomide, valproate bismuth, calcium valproate, valproate magnesium

Scope: MAH's response to PSP/J/0094.2 [protocol for a joint retrospective study of multiple European data sources characterising neurodevelopmental disorders in children exposed in utero to valproate and/or other antiepileptic drugs with long-term follow-up] as per the request for supplementary information (RSI) adopted in April 2022

17.2. Protocols of PASS non-imposed in the marketing authorisation(s)[50]

17.2.1. Anifrolumab - SAPHNELO (CAP) - EMEA/H/C/004975/MEA 001

Applicant: AstraZeneca AB

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Protocol for study D3461R00028: a multiple database study of the use (and safety) of anifrolumab in women with SLE during pregnancy

17.2.2. Bimekizumab - BIMZELX (CAP) - EMEA/H/C/005316/MEA 002.1

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Submission of a revised protocol for study PS0038: a non-interventional cohort study on the safety of bimekizumab in patients with plaque psoriasis comparing the risk of safety outcomes of interest in bimekizumab exposed patients compared to patients exposed to other biologics

17.2.3. Bimekizumab - BIMZELX (CAP) - EMEA/H/C/005316/MEA 003.1

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Liana Gross-Martirosyan

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

17.2.4. Bimekizumab - BIMZELX (CAP) - EMEA/H/C/005316/MEA 004.1

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Submission of a revised protocol for study PS0037: an observational cohort study to evaluate bimekizumab exposure during pregnancy and monitor the safety of bimekizumab use in pregnancy

17.2.5. Coronavirus (COVID-19) vaccine (Ad26.COV2-S, recombinant) - JCOVDEN (CAP) - EMEA/H/C/005737/MEA 010.2

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Ulla Wändel Liminga

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

Scope: Submission of a revised protocol for study VAC31518COV4001 (listed as category 3 study in the RMP): a post-authorisation, observational study to assess the safety of Ad26.COV2.S using health insurance claims and/or electronic health record (EHR) database(s) in the United States, including FDA feedback

17.2.6. Coronavirus (COVID-19) vaccine (recombinant, adjuvanted) - NUVAXOVID (CAP) - EMEA/H/C/005808/MEA 004.1

Applicant: Novavax CZ, a.s.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: MAH's response to MEA 004 [protocol for study 2019nCoV-402: UK Post-Authorisation Safety Study Using the Clinical Practice Research Datalink (CPRD): A surveillance study to characterize the safety profile of Nuvaxovid in adults aged 18 years and older in the real-world setting using the UK CPRD] as per request for supplementary information (RSI) adopted in July 2022

17.2.7. Drospirenone, estetrol - DROVELIS (CAP) - EMEA/H/C/005336/MEA 001.3

Applicant: Chemical Works of Gedeon Richter Plc. (Gedeon Richter Plc.)

PRAC Rapporteur: Martin Huber

Scope: MAH's response to MEA 001.2 [protocol for an international active surveillance study (INAS-NEES): a prospective non-interventional comparative cohort observational study to characterize and compare the risks of estetrol/drospirenone with combined oral contraceptive-containing levonorgestrel (COC-LNG) in a study population that is representative of the actual users of these preparations. The main clinical outcome of interest is venous thromboembolism (VTE), specifically deep venous thrombosis (DVT) and pulmonary embolism (PE)] as per the request for supplementary information (RSI) adopted in July 2022

17.2.8. Drospirenone, estetrol - LYDISILKA (CAP) - EMEA/H/C/005382/MEA 001.3

Applicant: Estetra SRL

PRAC Rapporteur: Martin Huber

Scope: MAH's response to MEA 001.2 [protocol for an international active surveillance study (INAS-NEES): a prospective non-interventional comparative cohort observational study to characterize and compare the risks of estetrol/drospirenone with combined oral contraceptive-containing levonorgestrel (COC-LNG) in a study population that is representative of the actual users of these preparations. The main clinical outcome of interest is venous thromboembolism (VTE), specifically deep venous thrombosis (DVT) and pulmonary embolism (PE) [final study report expected in December 2029] (from initial opinion/marketing authorisation (MA))] as per the request for supplementary information (RSI) adopted in July 2022

17.2.9. Elasomeran - SPIKEVAX (CAP) - EMEA/H/C/005791/MEA 066.1

Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: MAH's response to MEA 066 [protocol for study mRNA-1273-P911: long-term outcomes of myocarditis following administration of Spikevax (COVID-19 vaccine mRNA)] as per request for supplementary information (RSI) adopted in July 2022

17.2.10. Inebilizumab - UPLIZNA (CAP) - EMEA/H/C/005818/MEA 001

Applicant: Horizon Therapeutics Ireland DAC

PRAC Rapporteur: Amelia Cupelli

Scope: Protocol for an observational pregnancy safety study in women with neuromyelitis optica spectrum disorder (*NMOSD*) exposed to Uplizna (ineblizumab)

17.2.11. Inebilizumab - UPLIZNA (CAP) - EMEA/H/C/005818/MEA 003

Applicant: Horizon Therapeutics Ireland DAC

PRAC Rapporteur: Amelia Cupelli

Scope: Protocol for a real-world observational study of outcomes for patients with neuromyelitis optica spectrum disorder (NMOSD) treated with inebilizumab in Europe

17.2.12. Inebilizumab - UPLIZNA (CAP) - EMEA/H/C/005818/MEA 004

Applicant: Horizon Therapeutics Ireland DAC

PRAC Rapporteur: Amelia Cupelli

Scope: Protocol for a safety study of patients with neuromyelitis optica spectrum disorder (NMOSD) patients receiving inebilizumab following closure of the open-label period (N-MOmentum LT)

17.2.13. Linaclotide - CONSTELLA (CAP) - EMEA/H/C/002490/MEA 009.6

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Martin Huber

Scope: MAH's response MEA 009.5 [substantial amendment to a protocol previously agreed for PASS EVM-18888: linaclotide safety study assessing the complications of diarrhoea and associated risk factors in selected European populations with irritable bowel syndrome with constipation (IBS-C) for Constella (linaclotilde) 290µg capsule (protocol version 10.0)] as per request for supplementary information (RSI) adopted in June 2022

17.2.14. Lonapegsomatropin - SKYTROFA (CAP) - EMEA/H/C/005367/MEA 001.1

Applicant: Ascendis Pharma Endocrinology Division A/S

PRAC Rapporteur: Martin Huber

Scope: MAH's response to MEA 001 [protocol for study VV-SUB-056752: a prospective, non-interventional, long-term, safety study of patients treated with lonapegsomatropin to further characterize the potential long-term safety risks of lonapegsomatropin in patients treated with under real-world conditions in the post-marketing setting] as per request for supplementary information (RSI) adopted in June 2022

17.2.15. Ponesimod - PONVORY (CAP) - EMEA/H/C/005163/MEA 001.2

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Anette Kirstine Stark

Scope: MAH's response to MEA 001 [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 together with a statistical analysis plan (SAP)] as per the request for supplementary information (RSI) adopted in June 2022

17.2.16. Ponesimod - PONVORY (CAP) - EMEA/H/C/005163/MEA 004.2

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Anette Kirstine Stark

Scope: MAH's response to MEA 004.1 [protocol for study PCSNSP003693 (listed as a category 3 study in the RMP): a survey among healthcare professionals (neurologists treating patients with multiple sclerosis (MS) along with MS specialist nurses) in selected European countries to evaluate knowledge and behaviours required for the safe use of ponesimod] as per the request for supplementary information (RSI) adopted in June 2022

17.2.17. Rivaroxaban - XARELTO (CAP) - EMEA/H/C/000944/MEA 049.3

Applicant: Bayer AG

PRAC Rapporteur: Mari Thorn

Scope: MAH's response to MEA 049.2 and updated protocol of Xarelto Paediatric VTE PASS drug utilisation study: an observational, longitudinal, multi-source drug utilisation safety study to evaluate the drug use patterns and safety of rivaroxaban oral suspension in children under two years with venous thromboembolism (study number 22195) as per supplementary information (RSI) adopted in June 2022

17.3. Results of PASS imposed in the marketing authorisation(s)[51]

None

17.4. Results of PASS non-imposed in the marketing authorisation(s)[52]

17.4.1. Flutemetamol (^{18}F) - VIZAMYL (CAP) - EMEA/H/C/002557/II/0029

Applicant: GE Healthcare AS

PRAC Rapporteur: Martin Huber

Scope: Submission of the final report from study (GE067-027) listed as a category 3 study in the RMP in addition to a comprehensive root-cause analysis on the contributing factors having an impact on reader performance as requested by PRAC. This is a non-interventional

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

PASS to evaluate the effectiveness of VIZAMYL reader training in Europe. The RMP version 3.4 has also been submitted and updated to reflect the completion of study GE067-028, previously assessed in MEA 003.3

17.4.2. Lopinavir, ritonavir - KALETRA (CAP) - EMEA/H/C/000368/II/0193

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Nathalie Gault

Scope: Submission of the final report from study P19-106 listed as a category 3 study in the RMP. This is a European Pregnancy and Paediatric Infections Cohort Collaboration (EPPICC) observational study assessing the safety and effectiveness of Kaletra oral solution in children aged 14 days to 2 years with human immunodeficiency virus 1 (HIV-1) infection in Europe. The RMP version 10.0 has also been submitted

17.4.3. Tafamidis - VYNDAQEL (CAP) - EMEA/H/C/002294/II/0081, Orphan

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Tiphaine Vaillant

Scope: Update of section 5.1 of the SmPC in order to update information based on final results from study B3461029 listed as a Specific Obligation in the Annex II of the product information. This is a non-interventional PASS sub-study evaluating effects of tafamidis on disease progression in patients with non-Val30Met mutations and symptomatic neuropathy. Consequently, the MAH proposes a switch from marketing authorisation under exceptional circumstances to full marketing authorisation given the fulfilment of the SOB. The Annex II and package leaflet are updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet

17.4.4. Vortioxetine - BRINTELLIX (CAP) - EMEA/H/C/002717/II/0037

Applicant: H. Lundbeck A/S

PRAC Rapporteur: Jo Robays

Scope: Submission of the final report from study PASS 16034N listed as a category 3 study in the RMP. This is a non-interventional PASS of vortioxetine in Europe - An analysis of European automated healthcare databases. The RMP version 4.0 has also been submitted

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

17.5.1. Abatacept - ORENCIA (CAP) - EMEA/H/C/000701/MEA 069

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Kimmo Jaakkola

Scope: Interim report for study IM101816: a nationwide post-marketing study (PMS) on the safety of abatacept treatment in Sweden using the ARTIS register

17.5.2. Abatacept - ORENCIA (CAP) - EMEA/H/C/000701/MEA 070

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Kimmo Jaakkola

Scope: Interim report for study IM101803: a nationwide post-marketing study (PMS) on the safety of abatacept treatment in Denmark using the ARTIS Register

17.5.3. Avapritinib - AYVAKYT (CAP) - EMEA/H/C/005208/SOB 009

Applicant: Blueprint Medicines (Netherlands) B.V.

PRAC Rapporteur: Menno van der Elst

Scope: First progress report for study BLU-285-1406 is an imposed non-interventional PASS aiming to confirm the safety and efficacy of avapritinib in the treatment of adult patients with unresectable or metastatic gastrointestinal stromal tumours (GIST) harbouring the PDGFRA D842V mutation, given as Specific Obligation 3 (SOB3) of the conditional marketing authorisation. The submission of the first progress report is in line with agreed milestones in the final PASS protocol assessment report from PRAC (procedure number EMEA/H/C/PSP/S/0089.1 issued on 10 June 2021)

17.5.4. Axicabtagene ciloleucel - YESCARTA (CAP) - EMEA/H/C/004480/ANX 002.4

Applicant: Kite Pharma EU B.V., ATMP[53]

PRAC Rapporteur: Anette Kirstine Stark

Scope: Second interim report for study KT-EU-471-0117: a long-term, non-interventional study of recipients of Yescarta for treatment of relapsed or refractory diffuse large B-cell lymphoma and primary mediastinal B-cell lymphoma (EU PAS Register no.: EUPAS32539)

17.5.5. Coronavirus (COVID-19) vaccine (ChAdOx1-S [recombinant]) - VAXZEVRIA (CAP) - EMEA/H/C/005675/MEA 006.7

Applicant: AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

Scope: First annual report for study D8110C00003 (C-VIPER): COVID-19 Vaccines International Pregnancy Registry of Women Exposed to AZD1222 Immediately Before or During Pregnancy (Period covered 01/06/2021-31/05/2022) and MAH's response for MEA 006.5

17.5.6. Elasomeran - SPIKEVAX (CAP) - EMEA/H/C/005791/MEA 003.7

Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Sixth interim report for a study (listed as a category 3 study in the RMP): a post authorisation safety of Spikevax (elasomeran) in the US - an enhanced pharmacovigilance study to provide additional evaluation of adverse events of special interest (AESI) and

[53] Advanced therapy medicinal product

emerging validated safety signals [P903]

17.5.7. Filgrastim - FILGRASTIM HEXAL (CAP) - EMEA/H/C/000918/MEA 007.13

Applicant: Hexal AG

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to MEA 007.12 [eleventh annual report for study EP06-501 (SMART): a non-interventional, prospective, long-term safety data collection of Zarzio/Filgrastim Hexal (filgrastim) in healthy unrelated stem cell donors undergoing peripheral blood progenitor cell (PBPC) mobilisation] as per request for supplementary information (RSI) adopted in June 2022

17.5.8. Filgrastim - ZARZIO (CAP) - EMEA/H/C/000917/MEA 007.13

Applicant: Sandoz GmbH

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to MEA 007.12 Response to MEA-007.12 [eleventh annual report for study EP06-501 (SMART): a non-interventional, prospective, long-term safety data collection of Zarzio/Filgrastim Hexal (filgrastim) in healthy unrelated stem cell donors undergoing peripheral blood progenitor cell (PBPC) mobilisation] as per request for supplementary information (RSI) adopted in June 2022

17.5.9. Givosiran - GIVLAARI (CAP) - EMEA/H/C/004775/MEA 006.3

Applicant: Alnylam Netherlands B.V.

PRAC Rapporteur: Martin Huber

Scope: Interim report for study ALN-AS1-006: a global observational longitudinal prospective registry of patients with acute hepatic porphyria (AHP) [ELEVATE]

17.5.10. Ofatumumab - KESIMPTA (CAP) - EMEA/H/C/005410/MEA 003.1

Applicant: Novartis Ireland Limited

PRAC Rapporteur: Amelia Cupelli

Scope: MAH's response to MEA 003 [First annual interim report for COMB157G2399 (ALITHIOS) study (listed as a category 3 study in the RMP): an open-label, single arm, multicentre extension study evaluating long-term safety, tolerability and effectiveness of ofatumumab in subjects with relapsing multiple sclerosis] as per request for supplementary information (RSI) as adopted in June 2022

17.5.11. Selexipag - UPTRAVI (CAP) - EMEA/H/C/003774/MEA 001.8

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Nathalie Gault

Scope: MAH's response to MEA 001.7 [fifth annual interim report for PASS AC-065A401 (EXPOSURE): an observational cohort study of pulmonary arterial hypertension (PAH)

patients newly treated with either Uptravi (selexipag) or any other PAH-specific therapy in routine clinical practice] as per request for supplementary information (RSI) adopted in June 2022

17.6. Others

17.6.1. Ulipristal acetate - ESMYA (CAP) - EMEA/H/C/002041/MEA 028.3

Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: MAH's request for cancelling the study PGL18-001: a retrospective drug utilisation study (DUS) through a chart review across four major EU countries [final study report expected by Q2 2020], as requested in the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 completed in May 2018 (EMEA/H/A-20/1460)]

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

Applicant: Amryt Pharmaceuticals DAC

PRAC Rapporteur: Menno van der Elst

Scope: Annual reassessment of the marketing authorisation

18.1.2. Nelarabine - ATRIANCE (CAP) - EMEA/H/C/000752/S/0058 (without RMP)

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Annual reassessment of the marketing authorisation

18.1.3. Smallpox vaccine (live modified vaccinia virus Ankara) - IMVANEX (CAP) - EMEA/H/C/002596/S/0077 (without RMP)

Applicant: Bavarian Nordic A/S

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Annual reassessment of the marketing authorisation

18.1.4. Vestronidase alfa - MEPSEVII (CAP) - EMEA/H/C/004438/S/0032 (without RMP)

Applicant: Ultragenyx Germany GmbH

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Annual reassessment of the marketing authorisation

18.2. Conditional renewals of the marketing authorisation

18.2.1. (1r,2s,5s)-n-((1s)-1-cyano-2-((3s)-2-oxopyrrolidin-3-yl)ethyl)-3-((2s)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido) butanoyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide, ritonavir - PAXLOVID (CAP) - EMEA/H/C/005973/R/0023 (without RMP)

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Martin Huber

Scope: Conditional renewal of the marketing authorisation

18.2.2. Bedaquiline - SIRTURO (CAP) - EMEA/H/C/002614/R/0050 (without RMP)

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Conditional renewal of the marketing authorisation

18.3. Renewals of the marketing authorisation

18.3.1. Bictegravir, emtricitabine, enofovir alafenamide - BIKTARVY (CAP) - EMEA/H/C/004449/R/0052 (without RMP)

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: 5-year renewal of the marketing authorisation

18.3.2. Darvadstrocel - ALOFISEL (CAP) - EMEA/H/C/004258/R/0036 (with RMP)

Applicant: Takeda Pharma A/S, ATMP[54]

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: 5-year renewal of the marketing authorisation

18.3.3. Dolutegravir, rilpivirine - JULUCA (CAP) - EMEA/H/C/004427/R/0049 (without RMP)

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Nathalie Gault

Scope: 5-year renewal of the marketing authorisation

[54] Advanced therapy medicinal product

18.3.4. Ex vivo expanded autologous human corneal epithelial cells containing stem cells - HOLOCLAR (CAP) - EMEA/H/C/002450/R/0048 (without RMP)

Applicant: Holostem Terapie Avanzate s.r.l., ATMP[55]

PRAC Rapporteur: Rhea Fitzgerald

Scope: 5-year renewal of the marketing authorisation

18.3.5. Fulvestrant - FULVESTRANT MYLAN (CAP) - EMEA/H/C/004649/R/0016 (without RMP)

Applicant: Mylan Pharmaceuticals Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: 5-year renewal of the marketing authorisation

18.3.6. Glibenclamide - AMGLIDIA (CAP) - EMEA/H/C/004379/R/0014 (without RMP)

Applicant: Ammtek

PRAC Rapporteur: Maria del Pilar Rayon

Scope: 5-year renewal of the marketing authorisation

18.3.7. Prasugrel - PRASUGREL MYLAN (CAP) - EMEA/H/C/004644/R/0014 (without RMP)

Applicant: Mylan Pharmaceuticals Limited

PRAC Rapporteur: Anette Kirstine Stark

Scope: 5-year renewal of the marketing authorisation

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

Applicant: Amgen Europe B.V., BREDA

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: 5-year renewal of the marketing authorisation

18.3.9. Velmanase alfa - LAMZEDE (CAP) - EMEA/H/C/003922/R/0029 (without RMP)

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Jan Neuhauser

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 24-27 October 2022 meeting.

[55] Advanced therapy medicinal product

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

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Martin Huber	Member (Vice-Chair)	Germany	No interests declared	
Brigitte Keller-Stanislawski	Alternate	Germany	No interests declared	
Sophia Trantza	Member	Greece	No interests declared	
Georgia Gkegka	Alternate	Greece	No interests declared	
Julia Pallos	Member	Hungary	No participation in final deliberations and voting on:	4.3.3. Ipilimumab - YERVOY (CAP) - EMEA/H/C/002213/SDA/045; nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/SDA/0047 5.3.1. Lenalidomide - REVLIMID (CAP) - EMEA/H/C/000717/II/0123 5.3.2. Pomalidomide - IMNOVID (CAP) - EMEA/H/C/002682/II/0047, Orphan 5.3.3. Thalidomide - THALIDOMIDE BMS (CAP) - EMEA/H/C/000823/II/0076 16.1.15. Idecabtagene vicleucel - ABECMA (CAP) - PSUSA/00010954/202203 17.1.3. Lenalidomide - REVLIMID - EMEA/H/C/PSA/S/0093 17.5.1. Abatacept - ORENCIA (CAP) - EMEA/H/C/000701/MEA 069 17.5.2. Abatacept - ORENCIA (CAP) - EMEA/H/C/000701/MEA 070
Melinda Palfi	Alternate	Hungary	No interests declared	
Guðrún Stefánsdóttir	Member	Iceland	No participation in final	16.1.1. Apremilast - OTEZLA (CAP) -

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			deliberations and voting on:	PSUSA/00010338/202203 16.1.9. Cinacalcet - MIMPARA (CAP) - PSUSA/00000756/202202 18.3.8. Trastuzumab - KANJINTI (CAP) - EMEA/H/C/004361/R/0022 (without RMP)
Rhea Fitzgerald	Member	Ireland	No interests declared	
Ronan Grimes	Alternate	Ireland	No interests declared	
Amelia Cupelli	Member	Italy	No interests declared	
Valentina Di Giovanni	Alternate	Italy	No interests declared	
Rugile Pilviniene	Member	Lithuania	No interests declared	
Lina Seibokiene	Alternate	Lithuania	No participation in discussion, final deliberations and voting on:	17.2.17. Rivaroxaban - XARELTO (CAP) - EMEA/H/C/000944/MEA 049.3
Nadine Petitpain	Member	Luxembourg	No restrictions applicable to this meeting	
John Joseph Borg	Member (CHMP member)	Malta	No interests declared	
Menno van der Elst	Member	Netherlands	No interests declared	
Liana Gross-Martirosyan	Alternate	Netherlands	No interests declared	
David Olsen	Member	Norway	No participation in final deliberations and voting on:	11.1.2. Levonorgestrel (NAP) - SE/H/xxxx/WS/582 16.3.7. Clodronic acid (NAP); clodronic acid, lidocaine (NAP) - PSUSA/00010650/202202 17.2.17. Rivaroxaban - XARELTO (CAP) -

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				EMEA/H/C/000944/ MEA 049.3
Karen Pernille Harg	Alternate	Norway	No interests declared	
Adam Przybylkowski	Member	Poland	No interests declared	
Katarzyna Ziolkowska	Alternate	Poland	No interests declared	
Ana Diniz Martins	Member	Portugal	No interests declared	
Marcia Silva	Alternate	Portugal	No interests declared	
Roxana Dondera	Member	Romania	No interests declared	
Alexandra - Maria Spurni	Alternate	Romania	No interests declared	
Anna Mareková	Member	Slovakia	No interests declared	
Lucia Kuráková	Alternate	Slovakia	No interests declared	
Polona Golmajer	Member	Slovenia	No interests declared	
Maria del Pilar Rayon	Member	Spain	No interests declared	
Monica Martinez Redondo	Alternate	Spain	No participation in discussion, final deliberations and voting on:	14.1.2. Ceftriaxone (NAP) 15.3.5. Diroximel fumarate - VUMERITY (CAP) - EMEA/H/C/005437/II/0005
Ulla Wändel Liminga	Member	Sweden	No interests declared	
Mari Thorn	Alternate	Sweden	No restrictions applicable to this meeting	
Annalisa Capuano	Member	Independent scientific expert	No interests declared	
Milou Daniel Drici	Member	Independent scientific expert	No interests declared	
Maria Teresa Herdeiro	Member	Independent scientific expert	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Patricia McGettigan	Member	Independent scientific expert	No interests declared	
Hedvig Nordeng	Member	Independent scientific expert	No interests declared	
Roberto Frontini	Member	Healthcare Professionals' Representative	No restrictions applicable to this meeting	
Salvatore Messana	Alternate	Healthcare Professionals' Representative	No interests declared	
Declan Noone	Member	Patients' Organisation Representative	No interests declared	
Marko Korenjak	Alternate	Patients' Organisation Representative	No restrictions applicable to this meeting	
Laurence de Fays	Expert	Belgium	No interests declared	
Christophe Focke	Expert	Belgium	No interests declared	
Jamila Hamdani	Expert	Belgium	No interests declared	
Françoise Wuillaume	Expert	Belgium	No interests declared	
Anna Kroupová	Expert	Czechia	No interests declared	
Barbara Blicher Thomsen	Expert	Denmark	No interests declared	
Karin Erneholm	Expert	Denmark	No restrictions applicable to this meeting	
Marianne Hald Clemmensen	Expert	Denmark	No restrictions applicable to this meeting	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Astrid Hestbæk	Expert	Denmark	No restrictions applicable to this meeting	
Katrine Jønsson	Expert	Denmark	No interests declared	
Irene Mandrup Krüger	Expert	Denmark	No interests declared	
Julia Maslovskaja	Expert	Estonia	No interests declared	
Outi Mäki-Ikola	Expert	Finland	No restrictions applicable to this meeting	
Samuel Crommelynck	Expert	France	No interests declared	
Vincent Gazin	Expert	France	No interests declared	
Jean-Michel Race	Expert	France	No interests declared	
Wilma Fischer-Barth	Expert	Germany	No interests declared	
Jelena Katic	Expert	Germany	No interests declared	
Dennis Lex	Expert	Germany	No interests declared	
Tania Meier	Expert	Germany	No interests declared	
Karin Seifert	Expert	Germany	No interests declared	
Grainne Kirwan	Expert	Ireland	No interests declared	
Cinzia Ciceroni	Expert	Italy	No interests declared	
Valentina Conti	Expert	Italy	No interests declared	
Sara Galluzzo	Expert	Italy	No interests declared	
Armando Genazzani	Expert	Italy	No interests declared	
Elita Poplavska	Expert	Latvia	No interests declared	
Marianne Klanker	Expert	Netherlands	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Marcel Kwa	Expert	Netherlands	No interests declared	
Anita Volkers	Expert	Netherlands	No interests declared	
Inge Zomerdijk	Expert	Netherlands	No interests declared	
Lars Peter Engeset Austdal	Expert	Norway	No interests declared	
Fernanda Inês Carvalho Pereira Ribeiro Vaz (Inês Vaz)	Expert	Portugal	No interests declared	
Bruno Sepodes	Expert	Portugal	No interests declared	
Carla Torre	Expert	Portugal	No interests declared	
Sandu Irina	Expert	Romania	No interests declared	
Miguel del Rey	Expert	Spain	No interests declared	
Consuelo Mejías	Expert	Spain	No interests declared	
Charlotte Backman	Expert	Sweden	No interests declared	
Kristina Dunder	Expert	Sweden	No interests declared	
Karin Hellgren	Expert	Sweden	No interests declared	
Filip Josephson	Expert	Sweden	No interests declared	
Sofia Persson	Expert	Sweden	No interests declared	
Gunilla Sjölin Forsberg	Expert	Sweden	No restrictions applicable to this meeting	
Anna Vikerfors	Expert	Sweden	No interests declared	
A representative from the European Commission attended the meeting				
Meeting run with support from relevant EMA staff				

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

20. Annex III - List of acronyms and abbreviations

For a list of acronyms and abbreviations used in the PRAC minutes, see:
Home>Committees>PRAC>Agendas, minutes and highlights

21. Explanatory notes

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

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

(Items 2 and 3 of the PRAC minutes)

A referral is a procedure used to resolve issues such as concerns over the safety or benefit-risk balance of a medicine or a class of medicines. In a referral, EMA is requested to conduct a scientific assessment of a particular medicine or class of medicines on behalf of the European Union (EU). For further detailed information on safety related referrals please see:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000150.jsp&mid=WC0b01ac05800240d0

Signals assessment and prioritisation

(Item 4 of the PRAC minutes)

A safety signal is information on a new or incompletely documented adverse event that is potentially caused by a medicine and that warrants further investigation. Signals are generated from several sources such as spontaneous reports, clinical studies and the scientific literature. The evaluation of safety signals is a routine part of pharmacovigilance and is essential to ensuring that regulatory authorities have a comprehensive knowledge of a medicine's benefits and risks.
The presence of a safety signal does not mean that a medicine has caused the reported adverse event. The adverse event could be a symptom of another illness or caused by another medicine taken by the patient. The evaluation of safety signals is required to establish whether or not there is a causal relationship between the medicine and the reported adverse event.
The evaluation of safety signals may not necessarily conclude that the medicine caused the adverse event in question. In cases where a causal relationship is confirmed or considered likely, regulatory action may be necessary and this usually takes the form of an update of the summary of product characteristics and the package leaflet.

Risk Management Plans (RMPs)

(Item 5 of the PRAC minutes)

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

Assessment of Periodic Safety Update Reports (PSURs)

(Item 6 of the PRAC minutes)

A PSUR is a report providing an evaluation of the benefit-risk balance of a medicine, which is submitted by marketing authorisation holders at defined time points following a medicine's authorisation.

PSURs summarises data on the benefits and risks of a medicine and includes the results of all studies carried out with this medicine (in the authorised and unauthorised indications).

Post-authorisation Safety Studies (PASS)

(Item 7 of the PRAC minutes)

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

Product related pharmacovigilance inspections

(Item 9 of the PRAC minutes)

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

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