22 December 2023
EMA/PRAC/565432/2023
Human Medicines Division

Pharmacovigilance Risk Assessment Committee (PRAC)

Minutes of PRAC meeting on 23-26 October 2023

Chair: Sabine Straus – Vice-Chair: Martin Huber

Disclaimers

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

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

Note on access to documents

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

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1. Introduction

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

The Chairperson opened the 23-26 October 2023 meeting by welcoming all participants. 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[1] 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 23-26 October 2023

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 25-28 September 2023

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

Post-meeting note: the PRAC minutes of the meeting held on 25-28 September 2023 were published on the EMA website on 30 November 2023 (EMA/PRAC/497911/2023).

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

2.1. Newly triggered procedures

None

[1] No alternates for COMP

2.2. Ongoing procedures

None

2.3. Procedures for finalisation

None

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

3.1. Newly triggered procedures

None

3.2. Ongoing procedures

None

3.3. Procedures for finalisation

None

3.4. Re-examination procedures[2]

None

3.5. Others

None

4. Signals assessment and prioritisation[3]

4.1. New signals detected from EU spontaneous reporting systems

See also Annex I 14.1.

4.1.1. Elasomeran - SPIKEVAX (CAP)

Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Signal of postmenopausal haemorrhage

EPITT 20015 – New signal

[2] Re-examination of PRAC recommendation under Article 32 of Directive 2001/83/EC
[3] Each signal refers to a substance or therapeutic class. The route of marketing authorisation is indicated in brackets (CAP for Centrally Authorised Products; NAP for Nationally Authorised Products including products authorised via Mutual Recognition Procedures and Decentralised Procedure). Product names are listed for reference Centrally Authorised Products (CAP) only. PRAC recommendations will specify the products concerned in case of any regulatory action required

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 an increased number of case reports and studies from the literature, the Norwegian Medicines Agency identified a signal of postmenopausal haemorrhage. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by PRAC.

Discussion

Having considered the available evidence from literature and post-marketing data, PRAC agreed that the signal postmenopausal haemorrhage warranted further investigation.

Summary of recommendation(s)

- The MAH for Spikevax (elasomeran) should submit to EMA, within 60 days, a cumulative review of cases of postmenopausal haemorrhage from all sources, including data from clinical trials, scientific literature and post marketing exposure. In addition, the MAH should provide a discussion of the studies by *Suh-Burgmann EJ et al*[4], *Ljung R et al*[5], *Kristine Blix et al*[6], along with a further discussion on possible mechanism(s) of action for the occurrence of postmenopausal haemorrhage following administration of the vaccine, as well as the timing of development of clinical symptoms in relationship to the proposed mechanism of action. Finally, the MAH should provide an observed versus expected (O/E) analysis of all cases with a risk window of 21 days and 42 days including events with unknown time-to-onset (TTO), and/or other justified risk windows if applicable.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.1.2. Esomeprazole - NEXIUM CONTROL (CAP); NAP

Applicant: GlaxoSmithKline Dungarvan Ltd (Nexium Control), various

PRAC Rapporteur: Rugile Pilviniene

Scope: Signal of erectile dysfunction

EPITT 19976 – New signal

Background

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

During routine signal detection activities, a signal of erectile dysfunction was identified by the Italian Medicines Agency (AIFA), based on cases retrieved from EudraVigilance (66 cases), as

[4] Suh-Burgmann EJ, Tierney C, et al. Association between vaccination against COVID -19 and postmenopausal bleeding. Am J Obstet Gynecol. 2022 Dec;227(6):907-908. doi: 10.1016/j. ajog.2022.07.006. Epub 2022 Jul 12. PMID: 35835262; PMCID: PMC9273569

[5] Ljung R, Xu Y, et al. Association between SARS-CoV-2 vaccination and healthcare contacts for menstrual disturbance and bleeding in women before and after menopause: nationwide, register based cohort study. BMJ. 2023 May 3;381:e074778. doi: 10.1136/bmj-2023-074778. PMID: 37137493

[6] Kristine Blix et al. Unexpected vaginal bleeding and COVID-19 vaccination in nonmenstruating women. Sci. Adv.9,eadg1391(2023).DOI:10.1126/sciadv.adg1391

well as on scientific literature and national reviews. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by PRAC.

Discussion

Having considered the available evidence from case reports in EudraVigilance and literature, PRAC agreed that the signal warranted further investigation and to request further information from the MAH(s). Considering the structural similarity between esomeprazole and omeprazole as well as multifactorial causes of sexual dysfunction, PRAC agreed that the signal to be extended to both active substances within a broader MedDRA scope for both female and male individuals.

Summary of recommendation(s)

- In the next PSURs, the MAHs for esomeprazole-containing product(s)[7] and omeprazole-containing product(s)[8] should submit to EMA, a cumulative review of the narrow SMQ 'sexual dysfunction' from all available data including spontaneous case reports, clinical trials and literature, with a discussion on the possible mechanism of action by which proton-pump-inhibitors (PPIs), including both substances, could lead to sexual dysfunction along with the latency of occurring of such disorders. The MAHs should also discuss the need for any possible amendments of the product information (PI) and/or risk management plan (RMP) as warranted.

4.1.3. Tozinameran - COMIRNATY (CAP)

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Signal of postmenopausal haemorrhage

EPITT 19989 – New signal

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 an increased number of case reports and studies from the literature, the Norwegian Medicines Agency identified a signal of postmenopausal haemorrhage. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by PRAC.

Discussion

Having considered the available evidence from literature and post-marketing data, PRAC agreed that the signal warranted further investigation and to request further information from the MAH.

Summary of recommendation(s)

- The MAH for Comirnaty (tozinameran) should submit to EMA, within 60 days, a cumulative review of the signal from all sources including, but not limited to, available

[7] the originator and all MAHs eligible to submit PSURs as per the EURD list requirements with Data Lock Point (DLP) 10 March 2024
[8] the originator and all MAHs eligible to submit PSURs as per the EURD list requirements R with Data Lock Point (DLP) 15 April 2027

data from clinical trials, scientific literature and post marketing exposure. In addition, the MAH should provide a discussion on the studies by *Suh-Burgmann EJ et al*[9], *Ljung R et al*[10], *Kristine Blix et al*[11], along with a further discussion on possible mechanism(s) of action for the occurrence of postmenopausal haemorrhage following administration of the vaccine, as well as the timing of development of clinical symptoms in relationship to the proposed mechanism of action. Finally, the MAH should provide an observed versus expected (O/E) analysis of all cases with a risk window of 21 days and 42 days including events with unknown time-to-onset (TTO), and/or other justified risk windows if applicable.

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

4.2. New signals detected from other sources

None

4.3. Signals follow-up and prioritisation

4.3.1. Amivantamab - RYBREVANT (CAP) - EMEA/H/C/005454/SDA/006

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Gabriele Maurer

Scope: Signal of anaphylactic reaction

EPITT 19928 – Follow up to June 2023

Background

For background information, see PRAC minutes June 2023.

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

Discussion

Having considered the available evidence in EudraVigilance and the responses of the MAH, PRAC considered that the current evidence is insufficient to establish a causal relationship between amivantamab and anaphylactic reactions to further warrant an update to the product information and/or risk management plan at present.

Summary of recommendation(s)

- In the next PSURs, the MAH for Rybrevant (amivantamab) should closely monitor events indicative of anaphylactic reaction using the SMQ anaphylactic reaction (broad) for a baseline search to identify all cases fulfilling the Sampson criteria irrespective of

[9] Suh-Burgmann EJ, Tierney C, et al. Association between vaccination against COVID -19 and postmenopausal bleeding. Am J Obstet Gynecol. 2022 Dec;227(6):907-908. doi: 10.1016/j. ajog.2022.07.006. Epub 2022 Jul 12. PMID: 35835262; PMCID: PMC9273569

[10] Ljung R, Xu Y, et al. Association between SARS-CoV-2 vaccination and healthcare contacts for menstrual disturbance and bleeding in women before and after menopause: nationwide, register based cohort study. BMJ. 2023 May 3;381:e074778. doi: 10.1136/bmj-2023-074778. PMID: 37137493

[11] Kristine Blix et al. Unexpected vaginal bleeding and COVID-19 vaccination in nonmenstruating women. Sci. Adv.9,eadg1391(2023).DOI:10.1126/sciadv.adg1391

whether an immune related reaction (IRR) or an anaphylactic reaction has been reported, including also all cases with elevated serum tryptase levels.

See EMA/PRAC/477436/2023 published on 20 November 2023 on the EMA website.

4.3.2. Dapagliflozin – EDISTRIDE (CAP) - EMEA/H/C/004161/SDA/015, FORXIGA (CAP) - EMEA/H/C/002322/SDA/028, EBYMECT (CAP) - EMEA/H/C/004162/SDA/014, XIGDUO (CAP) - EMEA/H/C/002672/SDA/017, QTERN (CAP) - EMEA/H/C/004057/SDA/009

Applicant: AstraZeneca AB

PRAC Rapporteur: Mari Thorn

Scope: Signal of acquired phimosis and phimosis with dapagliflozin

EPITT 19935 – Follow up to June 2023

Background

For background information, see PRAC minutes June 2023.

The MAH replied to the request for information on the signal of acquired phimosis and phimosis with dapagliflozin and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence in EudraVigilance, literature and the responses from the MAH, PRAC agreed that there is sufficient evidence to establish a causal relationship between dapagliflozin-containing products and acquired phimosis and phimosis with dapagliflozin. Thus, PRAC agreed to update the product information to add that cases of phimosis/acquired phimosis have been reported concurrent with genital infections and in some cases, circumcision was required.

Summary of recommendation(s)

- The MAHs for the dapagliflozin-containing products Edistride, Forxiga, Ebymect, Xigduo and Qtern should submit to EMA, within 60 days, a variation to amend[12] the product information.

For the full PRAC recommendation, see EMA/PRAC/477436/2023 published on 20 November 2023 on the EMA website.

4.3.3. Glucagon-like peptide-1 (GLP-1) receptor agonists: dulaglutide – TRULICITY (CAP) - EMEA/H/C/002825/SDA/014; exenatide – BYDUREON (CAP) - EMEA/H/C/002020/SDA/029, BYETTA (CAP) - EMEA/H/C/000698/SDA/049; insulin degludec, liraglutide – XULTOPHY (CAP) - EMEA/H/C/002647/SDA/005; liraglutide – SAXENDA (CAP) - EMEA/H/C/003780/SDA/019, VICTOZA (CAP) - EMEA/H/C/001026/SDA/039; insulin glargine, lixisenatide – SULIQUA (CAP) - EMEA/H/C/004243/SDA/008; lixisenatide - LYXUMIA (CAP) - EMEA/H/C/002445/SDA/016; semaglutide – OZEMPIC (CAP) - EMEA/H/C/004174/SDA/007, RYBELSUS (CAP) - EMEA/H/C/004953/SDA/012, WEGOVY (CAP) - EMEA/H/C/005422/SDA/006

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

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

Industrie (Lyxumia, Suliqua)

PRAC Rapporteur: Mari Thorn

Scope: Signal of thyroid cancer

EPITT 18292 – Follow up to April 2023

Background

For background information, see PRAC minutes January 2023 and PRAC minutes April 2023.

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

Discussion

Having considered the available evidence in the published literature including the observational studies (*Alves et al 2012*[13], *Bezin et al 2022*[14], *Hu et al 2022*[15], *Bea et al 2023*[16]), non-clinical data, clinical and post-marketing data, as well as the responses from the MAHs, PRAC considered that the current evidence is insufficient to establish a causal relationship between the glucagon-like peptide 1 (GLP-1) receptor agonists (i.e. exenatide, liraglutide, dulaglutide, semaglutide, and lixisenatide) and thyroid cancer to further warrant an update to the product information and/or risk management plan at present.

Summary of recommendation(s)

- In the next PSURs, the MAHs for Ozempic, Rybelsus and Wegovy products containing semaglutide, for Victoza and Saxenda products containing liraglutide, for Xultophy (insulin degludec, liraglutide), for Byetta and Bydureon products containing exenatide, for Lyxumia (lixisenatide), for Suliqua (insulin glargine, lixisenatide) and for Trulicity (dulaglutide) should continue to closely monitor thyroid cancer events including new scientific literature, as part of routine pharmacovigilance and/or in the ongoing category 3 PASS studies in the RMPs as relevant.

See EMA/PRAC/477436/2023 published on 20 November 2023 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.

[13] Alves C. et al. A meta-analysis of serious adverse events reported with exenatide and liraglutide: Acute pancreatitis and cancer. Diabetes Res Clin Pract 2012 Nov;98(2):271-84.
[14] Bezin et al. GLP-1 Receptor Agonists and the Risk of Thyroid Cancer. Bezin et al. 2022 Diabetes Care. 2022 Nov 10; dc221148. doi: 10.2337/dc22-1148. (Online ahead of print)
[15] Hu W, Song R, Cheng R, Liu C, Guo R, Tang W, Zhang J, Zhao Q, Li X, Liu J Use of GLP-1 Receptor Agonists and Occurrence of Thyroid Disorders: a Meta-Analysis of Randomized Controlled Trials. Front Endocrinol (Lausanne). 2022 Jul 11;13:927859.
[16] Bea S, Son H, Bae JH, Cho SW, Shin JY, Cho YM. Risk of thyroid cancer associated with glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in patients with type 2 diabetes: A population-based cohort study. Diabetes Obes Metab. 2023 Sep 21. doi: 10.1111/dom.15292. Online ahead of print

Information on the PRAC advice will be available in the European Public Assessment Reports (EPARs) to be published at the end of the evaluation procedure.

Please refer to the CHMP pages for upcoming information (https://www.ema.europa.eu/en/committees/committee-medicinal-products-human-use-chmp).

See also Annex I 15.1.

5.1.1. Bevacizumab - EMEA/H/C/005723

Scope: Treatment of neovascular (wet) age-related macular degeneration (nAMD)

5.1.2. Catumaxomab - EMEA/H/C/005697

Scope: Treatment of malignant ascites

5.1.3. Cefepime, enmetazobactam - EMEA/H/C/005431

Scope: Treatment of: 1) complicated urinary tract infections (including pyelonephritis); 2) hospital-acquired pneumonia (HAP) including ventilator associated pneumonia (VAP); 3) patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above and 4) infections due to aerobic Gram-negative organisms in adults with limited treatment options

5.1.4. Danicopan - EMEA/H/C/005517, PRIME, Orphan

Applicant: Alexion Europe

Scope: Treatment of extravascular haemolysis (EVH) in patients with paroxysmal nocturnal haemoglobinuria

5.1.5. Influenza vaccine (H5N1)[17] - EMEA/H/C/006052

Scope: Active immunisation for the prevention of disease caused by the influenza A virus H5N1 subtype contained in the vaccine

5.1.6. Influenza vaccine (H5N1)[18] - EMEA/H/C/006051

Scope: Prophylaxis of influenza

5.1.7. Lecanemab - EMEA/H/C/005966

Scope: Disease modifying treatment in adult patients with Mild Cognitive Impairment due to Alzheimer's disease and Mild Alzheimer's disease (Early Alzheimer's disease)

5.1.8. Polihexanide - EMEA/H/C/005858, Orphan

Applicant: SIFI SPA

[17] Virus A/turkey/Turkey/1/2005 (H5N1) NIBERG-23 strain, HA surface antigen
[18] Virus A/turkey/Turkey/1/2005 (H5N1) NIBERG-23 strain, HA surface antigen

Scope: Treatment of acanthamoeba keratitis

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

See also Annex I 15.2.

5.2.1. Lenvatinib - LENVIMA (CAP) - EMEA/H/C/003727/II/0053

Applicant: Eisai GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of section 5.1 of the SmPC in order to update safety and efficacy information for the hepatocellular carcinoma (HCC) indication, based on interim results from study E7080-M000-508 (STELLAR), listed as a category 3 PASS in the RMP. This is a non-interventional multicentre, observational, phase 4 study to evaluate the safety and tolerability of lenvatinib in patients with advanced or unresectable HCC. RMP version 15.2 has also been submitted

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.

PRAC is evaluating a type II variation procedure for Lenvima, a centrally authorised medicine containing lenvatinib, to update the RMP to reflect the introduction of updated safety and efficacy information in SmPC for the HCC indication, based on interim results from the non-interventional study E7080-M000-508 (STELLAR) listed as a category 3 PASS in the RMP. PRAC is responsible for adopting an outcome based on the assessment report from the PRAC Rapporteur, to be further considered at the level of CHMP, responsible for adopting an opinion on this variation.

Summary of advice

- The RMP for Lenvima (lenvatinib) in the context of the variation procedure under evaluation by PRAC and CHMP could be considered acceptable provided that an update to RMP version 15.2 is submitted.
- PRAC agreed with closing Study 508 and requested the MAH to clarify the submission date of the final study report. In addition, PRAC did not support the MAH's proposal to update section 5.1 of the SmPC to include safety and efficacy information for the current HCC indication based on interim results from Study 508, as the data presented are from an interim analysis with a limited number of enrolled patients. Nevertheless, PRAC considered that based on the available data, the MAH should update the product information to add gastrointestinal perforation as an undesirable effect, where the frequency should be based on data from controlled clinical trials.

5.2.2. Tixagevimab, cilgavimab - EVUSHELD (CAP) - EMEA/H/C/005788/II/0013

Applicant: AstraZeneca AB

PRAC Rapporteur: Kimmo Jaakkola

Scope: Submission of an updated RMP version 5 succession 1 to remove the commitment to

conduct the PASS D8850R00006: a post-authorisation observational study of women exposed to EVUSHELD during pregnancy (O-STEREO)

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.

PRAC is evaluating a type II variation procedure for Evusheld, a centrally authorised medicine containing tixagevimab/cilgavimab, to update the RMP to reflect the removal of the commitment to conduct the PASS D8850R00006. PRAC is responsible for adopting an outcome based on the assessment report from the PRAC Rapporteur, to be further considered at the level of CHMP, responsible for adopting an opinion on this variation. For further background, see PRAC minutes September 2023[19].

S**ummary of advice**

- The RMP version 5.1 for Evusheld (tixagevimab/cilgavimab) in the context of the variation under evaluation by PRAC and CHMP is considered acceptable.
- PRAC agreed with the removal of the PASS D8850R00006 listed as category 3 study in the RMP, however, since 'use in pregnant women' remains as a safety concern in the RMP, the MAH should continue monitoring the use of Evusheld during pregnancy via routine pharmacovigilance surveillance activities and provide a review of the data in the PSURs. No additional pharmacovigilance activities are warranted at this stage, but PRAC agreed that in case the use of Evusheld would significantly change in the future, this issue should be reopened for discussion.

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

See also Annex I 15.3.

5.3.1. Alglucosidase alfa - MYOZYME (CAP) - EMEA/H/C/000636/II/0095

Applicant: Sanofi B.V.

PRAC Rapporteur: Nathalie Gault

Scope: Update of sections 4.4 and 5.2 of the SmPC in order to update warning on immunogenicity. The RMP version 10.0 has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the product information

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 Myozyme, a centrally authorised product containing alglucosidase alfa, to update the warning on immunogenicity in the product information. PRAC is responsible for providing advice to CHMP on the necessary updates to the RMP to support this procedure. For further background, see PRAC minutes April 2023.

[19] Held 28-31 August 2023

Summary of advice

- The RMP version 10.1 for Myozyme (alglucosidase alfa) in the context of the variation under evaluation by CHMP is considered acceptable.
- Regarding the list of safety concerns, PRAC agreed with renaming the important identified risk 'immunogenicity: inhibitory antibodies to rhGAA' as 'immunogenicity leading to loss of response (High sustained IgG antibody titres and or neutralizing antibodies)' and with combining the immunogenicity-related important identified risks under 'infusion associated reactions including hypersensitivity and anaphylactic reactions, with or without development of IgG and IgE antibodies'. PRAC agreed with the removal of the category 3 PASS ALGMYC07390 'Prevalence of immunology testing in patients treated with alglucosidase alfa with significant hypersensitivity/anaphylactic reactions to test the effectiveness of the approved safety information packet (SIP)' (EMEA/H/C/000636/II/0079, opinion issued on 08/07/2021) and AGLU06909/LTS13930 'Pompe Safety Sub-Registry' from the pharmacovigilance plan in the RMP. Regarding the risk minimisation measures (RMMs), PRAC agreed with the amended key elements of the 'safety information packet' for the healthcare professionals regarding immunogenicity. Finally, PRAC considered that the relevance of a supplementary home infusion guide for patients and their caregivers as a requested additional RMMs remains unresolved and should be further assessed as part of the ongoing type II variation EMEA/H/C/000636/II/0094.

5.3.2. Budesonide, formoterol fumarate dihydrate - BUDESONIDE/FORMOTEROL TEVA PHARMA B.V. (CAP) - EMEA/H/C/004882/II/0012/G

Applicant: Teva Pharma B.V.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Grouped variations consisting of: 1) To replace the multidose dry powder inhaler to be used for the delivery of a combination of Budesonide/Formoterol fumarate dihydrate inhalation powder, as well as detect, record, store and transfer inhaler usage information to a mobile application (App); the inhaler is an integrated part of the primary packaging of the medicinal product; 2) To change the name of the medicinal product 3) To update sections 4.2 and 4.4 of the SmPC to reorganise the flow of information within these sections (as approved for DuoResp Spiromax EMEA/H/C/002348), following assessment of the same change for the reference product Symbicort Turbohaler; 4) other quality variations

Background

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

CHMP is evaluating an extension of the therapeutic indication for Budesonide/Formoterol Teva Pharma B.V., a centrally authorised product containing budesonide/formoterol fumarate dihydrate, to replace the multidose dry powder inhaler, change the name of the medicinal product, update the SmPC to reorganise the flow of information and other quality variations. PRAC is responsible for providing advice to CHMP on the necessary updates to the RMP to support this procedure. For further background, see PRAC minutes March 2023.

Summary of advice

- The RMP version 4.1 for Budesonide/Formoterol Teva Pharma B.V. (budesonide/formoterol fumarate dihydrate) in the context of the variation procedure under evaluation by CHMP is considered acceptable.
- PRAC considered that routine pharmacovigilance activities are sufficient to characterise the risks of the product. Therefore, the MAH should closely follow-up the risk 'over/under dose due to misuse of the e-device' as part of the next PSURs, under medication errors subsection. PRAC also considered that routine RMM are sufficient to minimise the risk of the medicinal product in the proposed indication in light of the current knowledge.

5.3.3. Denosumab - PROLIA (CAP) - EMEA/H/C/001120/II/0099

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Mari Thorn

Scope: Update of sections 4.4 and 4.8 of the SmPC in order to update a warning regarding hypocalcaemia and to include reports of life-threatening events and fatal cases occurred in the post marketing setting, particularly in patients with severe renal impairment, receiving dialysis or treatment with other calcium lowering drugs based on the cumulative review of MAH safety database and literature. The package leaflet is updated accordingly. The RMP version 32.0 has also been submitted

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 line extension for Prolia, a centrally authorised product containing denosumab, to update the product information in order to amend the warning regarding hypocalcaemia and to include reports of life-threatening events and fatal cases particularly in patients with severe renal impairment, receiving dialysis or treatment with other calcium lowering drugs. PRAC is responsible for providing advice to CHMP on the necessary updates to the RMP to support this procedure.

Summary of advice

- The RMP for Prolia (denosumab) in the context of the procedure under evaluation by CHMP could be considered acceptable provided that an update to RMP version 32.0 is submitted.
- The MAH should update the RMP to include information regarding the monitoring of calcium in all patients in alignment with the amendments in the product information. In addition, PRAC agreed that the MAH should discuss the need for a DHPC together with a communication plan with regard to the proposed update to monitor calcium levels in all denosumab treated patients considering the level of awareness among healthcare professionals regarding this risk, as well as how calcium levels are currently monitored before and after administration of denosumab in clinical practice.

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. Avelumab - BAVENCIO (CAP) - PSUSA/00010635/202303

Applicant: Merck Europe B.V.

PRAC Rapporteur: Karin Erneholm

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 Bavencio, a centrally authorised medicine containing avelumab 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 Bavencio (avelumab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend a warning/precaution regarding the risk of autoimmune reactions as well as to add sarcoidosis as a warning and as an undesirable effect with a frequency 'uncommon' Therefore, the current terms of the marketing authorisation(s) should be varied[20].
- In the next PSUR, the MAH should present new information on the safety of patients with autoimmune diseases as part of the important identified risk of immune-mediated adverse reactions which is to be added in the list of safety concerns in the RMP and should continue to monitor cases of tumour lysis syndrome and of cholangitis including sclerosing cholangitis. In addition, the MAH should provide cumulative reviews of cases of Sjögren's syndrome and intestinal perforation (as a potential complication of colitis) following avelumab administration, including data from clinical trials, post-marketing case reports and scientific literature, as well as a discussion on a potential biological mechanism for these associations. The MAH should discuss whether an update of the product information is warranted.
- The MAH should submit an updated RMP in order to remove the missing information 'safety in patients with autoimmune disease' and consolidate this safety concern with the important identified risk 'immune-mediated adverse reactions'. The MAH should also discuss whether the safety profile of avelumab in the patient populations referred as 'missing information' in the list of safety concerns differs from the safety profile in the general population and if the existing or future feasible pharmacovigilance activities

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

could further characterise the safety profile of the product with respect to these areas of missing information. Finally, the MAH should discuss the continued need for the patient information brochure and should propose an updated version of the key elements of patient card with the aim to replace the currently available educational materials.

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.

6.1.2. Cenobamate - ONTOZRY (CAP) - PSUSA/00010921/202303

Applicant: Angelini S.p.A.

PRAC Rapporteur: Jo Robays

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 Ontozry, a centrally authorised medicine containing cenobamate 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 Ontozry (cenobamate) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add suicidal ideation as a warning and as an undesirable effect with a frequency 'uncommon'. Therefore, the current terms of the marketing authorisation(s) should be varied[21].
- In the next PSUR, the MAH should continue to monitor cases of psychiatric disorders.
- The MAH should submit an updated RMP to reclassify the important potential risk 'suicidality (class effect)' as an important identified risk entitled 'suicidality' in the list of safety concerns.

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

6.1.3. Eftrenonacog alfa - ALPROLIX (CAP) - PSUSA/00010499/202303

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Gabriele Maurer

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

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 Alprolix, a centrally authorised medicine containing eftrenonacog alfa and issued a recommendation on its marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Alprolix (eftrenonacog alfa) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add anaphylactic shock as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[22].

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. Filgotinib - JYSELECA (CAP) - PSUSA/00010879/202303

Applicant: Galapagos N.V.

PRAC Rapporteur: Nikica Mirošević Skvrce

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 Jyseleca, a centrally authorised medicine containing filgotinib 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 Jyseleca (filgotinib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include vertigo as an undesirable effect with a frequency 'uncommon'. Therefore, the current terms of the marketing authorisation(s) should be varied[23].
- In the next PSUR, the MAH should provide a review of cases of interstitial lung disease, including data from clinical trials and post-marketing exposure with positive dechallenge

[22] Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion.
[23] Update of SmPC sections 4.7 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion.

and/or rechallenge, as well as of cases of peripheral neuropathy, gastrointestinal perforation and venous thromboembolism. The MAH should also discuss the publication by *Ziwei Dong et al*[24] regarding the association between pulmonary embolism and filgotinib.

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. Fingolimod - GILENYA (CAP) - PSUSA/00001393/202302

Applicant: Novartis Europharm Limited

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 Gilenya, a centrally authorised medicine containing fingolimod 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 Gilenya (fingolimod) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAH should provide reviews of cases of serious cases of molluscum contagiosum, of ischemic coronary artery disorders along with a discussion on the update of the product information, if warranted. The MAH should also
- The MAH should submit to EMA, within 4 months, a variation in order to update the wording regarding progressive multifocal leukoencephalopathy (PML) and to update the educational material to improve the general readability of these documents and better address key messages and recommendations for healthcare professionals.

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

6.1.6. Ibritumomab tiuxetan - ZEVALIN (CAP) - PSUSA/00001704/202302

Applicant: Ceft Biopharma s.r.o.

PRAC Rapporteur: Karin Erneholm

Scope: Evaluation of a PSUSA procedure

[24] Ziwei Dong et all Thromboembolic events in Janus kinase inhibitors: A pharmacovigilance study from 2012 to 2021 based on the Food and Drug Administration's Adverse Event Reporting System Br J Clin Pharmacol.. 2022 Sep;88(9):4180-4190

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, as well as the data provided by the MAH in the context of an oral explanation, PRAC reviewed the benefit-risk balance of Zevalin, a centrally authorised medicine containing ibritumomab tiuxetan 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 Zevalin (ibritumomab tiuxetan) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained. This is however, without prejudice to a thorough review of ibritumomab tiuxetan within an appropriate procedure to assess all available data and determine the impact of the safety concerns of second primary malignancies with a special emphasis on myelodysplastic syndrome (MDS)/ acute myeloid leukaemia (AML) on the benefit-risk balance of the product in the approved indications.
- In the next PSUR, the MAH should revise the risk characterisations for 'carcinogenicity (second primary malignancies, other than MDS and AML)' and 'myelodysplastic syndrome (MDS) and acute myeloid leukaemia (AML)' in terms of severity, nature of the risk and background incidence/prevalence.

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

6.1.7. Lorlatinib - LORVIQUA (CAP) - PSUSA/00010760/202303

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Nikica Mirošević Skvrce

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 Lorviqua, a centrally authorised medicine containing lorlatinib 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 Lorviqua (lorlatinib) in the approved indication(s) remains unchanged.

- Nevertheless, the product information should be updated to add proteinuria as an undesirable effect with a frequency 'common'. Therefore, the current terms of the marketing authorisation(s) should be varied[25].
- In the next PSUR, the MAH should submit cumulative reviews of cases under MedDRA PTs: blindness, blindness unilateral, blindness transient, central vision loss and sudden visual loss, as well as of cases of pulmonary arterial hypertension (PAH) or pulmonary hypertension and to discuss in depth the potential causal association between PAH and lorlatinib.

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

6.1.8. Olipudase alfa - XENPOZYME (CAP) - PSUSA/00011003/202303

Applicant: Sanofi 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 Xenpozyme, a centrally authorised medicine containing olipudase alfa and issued a recommendation on its marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Xenpozyme (olipudase alfa) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the wording about the dose escalation scheme and to reflect the cases 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.

6.1.9. Siponimod - MAYZENT (CAP) - PSUSA/00010818/202303

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Maria del Pilar Rayon

[25] Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion.
[26] Update of SmPC sections 4.2, 4.4 and 4.9. 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 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 (PI) should be updated to amend the frequency of the existing undesirable effect progressive multifocal leukoencephalopathy (PML) to 'rare', as well as to amend the warning regarding reduction in heart rate and atrioventricular conduction. Therefore, the current terms of the marketing authorisation(s) should be varied[27].
- In the next PSUR, the MAH should provide cumulative reviews of neutropenia cases, and cases of transaminases elevations, drug-induced liver injury and hepatic failure with a discussion on the need to amend the PI. In addition, the MAH should provide a summary of safety results of the EXCHANGE COVID-19 vaccination sub study, cumulative reviews of cases of bradyarrhythmia occurred during the first week with first dose observation (FDO) including the reason for FDO, and of syncope, including serious cases occurring after the step-up dose period, along with a discussion on risk factors and causality and on the need to amend the PI. The MAH should continue to provide a review of serious cases of Varicella-zoster virus (VZV) infection reactivation. The MAH should also perform a cumulative review of cases of reactivation of chronic viral infections (other than VZV) as Legionella pneumonia and herpes ophthalmic, malignancies (BCC/SCC, melanoma, lymphoma, breast cancer), convulsions that occurred after discontinuation of siponimod, status epilepticus, epilepsy with pre-existing seizures, and depression and suicidality, including data from clinical trials, post-marketing and literature and discuss whether an update of the PI is warranted. Finally, the MAH should provide a cumulative review of cases of lymphopenia in relation to CYP2C9.

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

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

See also Annex I 16.2.

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

6.2.1. Pramipexole - MIRAPEXIN (CAP); SIFROL (CAP); NAP - PSUSA/00002491/202304

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

PRAC Rapporteur: Karin Erneholm

Scope: Evaluation of a PSUSA procedure

Background

Pramipexole is a non-ergot dopamine agonist indicated in adults for the treatment of signs and symptoms of idiopathic Parkinson's disease and for the symptomatic treatment of idiopathic restless legs syndrome (RLS).

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of Mirapexin and Sifrol, centrally authorised medicines containing pramipexole, and nationally authorised medicines containing pramipexole 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 pramipexole-containing product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to highlight that the lowest effective dose should be used in case of restless legs syndrome indication and to add 'restless legs augmentation syndrome' as a warning/precaution and as an undesirable effect with a frequency 'very common'. Therefore, the current terms of the marketing authorisations should be varied[28].
- In the next PSUR, the MAHs for pramipexole-containing products should include 'augmentation' as an important identified risk (for the restless legs syndrome indication) in the list of safety concerns.

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

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

See also Annex I 16.3.

6.3.1. Fluconazole (NAP) - PSUSA/00001404/202303

Applicant(s): various

PRAC Lead: Marie Louise Schougaard Christiansen

Scope: Evaluation of a PSUSA procedure

Background

[28] Update of SmPC sections 4.2, 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

Fluconazole is an antifungal agent indicated for the treatment of cryptococcosis, systemic candidiasis, mucosal candidiasis, genital candidiasis, prevention of fungal infections in patients with malignancy, and deep endemic mycoses in immunocompetent patients.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing fluconazole 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 fluconazole-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the warning on the use during pregnancy and include increased risk of spontaneous abortion in women treated with fluconazole during first and/or second trimester, cardiac malformations and birth defects as adverse pregnancy outcomes. For longer courses of treatment, contraception may be considered. Therefore, the current terms of the marketing authorisation(s) should be varied[29].
- In the next PSUR, the MAHs for fluconazole-containing products should provide a cumulative review of the drug-drug interaction between fluconazole and abrocitinib, including a causality assessment of all cases identified and discuss if an update of the product information is warranted.

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

6.3.2. Furosemide, spironolactone (NAP) - PSUSA/00001493/202303

Applicant(s): various

PRAC Lead: Karin Erneholm

Scope: Evaluation of a PSUSA procedure

Background

Furosemide is a loop diuretic and spironolactone is an aldosterone antagonist. In combination, furosemide/spironolactone is indicated for the treatment of ascites in patients with liver diseases, for the treatment of oedema and congestion of the lungs due to cardiac insufficiency, and oedema in patients with nephrotic syndrome (NS). It is also indicated for the treatment of hypertension under certain conditions.

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

Summary of recommendation(s) and conclusions

[29] Update of SmPC section 4.6. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position

- Based on the review of the data on safety and efficacy, the benefit-risk balance of medicinal products containing furosemide/spironolactone in the approved indication(s) remains unchanged.
- Nevertheless, the product information (PI) should be updated to add a drug-drug interaction between furosemide and aliskiren resulting in reduced plasma concentration of furosemide. Therefore, the current terms of the marketing authorisation(s) should be varied[30].
- In the next PSUR, the MAHs for medicinal products containing furosemide/spironolactone should provide a cumulative review of cases of 'atrial fibrillation' following furosemide or furosemide/spironolactone exposure, including data from spontaneous case reports, clinical trials, literature and include a discussion of the potential mechanism of action. The MAHs should also discuss the need for an update of the PI, if warranted. In addition, all MAHs should include the risk 'pemphigoid' as an important identified risk in the list of safety concerns in the PSURs.

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

6.3.3. Oxycodone (NAP) - PSUSA/00002254/202304

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 medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information (PI) should be updated to add hepatobiliary disorders including sphincter of Oddi dysfunction as a warning, as well as to add sphincter of Oddi dysfunction as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[31].
- In the next PSUR, the originator/brand leader MAH Mundipharma for oxycodone-containing products should provide an analysis of cases under MedDRA SMQ 'drug

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

abuse, dependence and withdrawal', as well as cases reported under the separate preferred terms (PTs): 'drug dependence', 'withdrawal syndrome', 'drug withdrawal syndrome' as well as 'drug abuse' and 'overdose', from 2012 onwards. The MAH Mundipharma should also discuss the publications by *Langford et al.*[32] and *Jones et al.*[33] and present the outcome of its signal evaluation about 'allodynia', briefly addressed as a new signal in the 'late-breaking information' of the current PSUSA. The MAH Hormosan Pharma GmbH should present the outcome of its signal evaluation about 'oromandibular tardive dystonia' in association with oxycodone and escitalopram drug interaction, briefly addressed as a new signal in the 'late-breaking information' of the current PSUSA.

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 Annex I 16.4.

6.5. Variation procedure(s) resulting from PSUSA evaluation

6.5.1. Infliximab - REMICADE (CAP) - EMEA/H/C/000240/II/0243

Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Mari Thorn

Scope: To update section 4.8 of the SmPC to add weight increased to the list of adverse drug reactions (ADRs) with frequency uncommon following PRAC PSUR assessment report (EMA/PRAC/158162/2023-Corr.1) based on the cumulative literature review. The package leaflet is updated accordingly. In addition, the MAH took this opportunity to introduce minor editorial changes

Background

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

Following the evaluation of the most recently submitted PSUR(s) for the above-mentioned medicine(s) concluded in April 2023, PRAC requested the MAH to submit a variation to provide a review of cases of 'weight gain'. 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)

[32] Langford et al. Clinical practice guideline for deprescribing opioid analgesics: summary of recommendations. Med J Aust. 26 June 2023
[33] Jones et al. 2023 Opioid analgesia for acute low back pain and neck pain (the OPAL trial): a randomised placebo-controlled trial. Lancet. 28 June 2023

- Based on the available data and the Rapporteur's assessment, PRAC supported the proposed update of the product information to add 'weight increased' as an undesirable effect with a frequency 'uncommon'[34].

6.5.2. Laronidase - ALDURAZYME (CAP) - EMEA/H/C/000477/II/0085

Applicant: Sanofi B.V.

PRAC Rapporteur: Nathalie Gault

Scope: To update section 4.2 of the SmPC in order to modify the administration instructions following the periodic safety update single assessment (PSUSA) procedure (PSUSA/00001830/202104) adopted in December 2021[35] based on literature review. The package leaflet is updated accordingly. The RMP version 1.0 has also been submitted

Background

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

Following the evaluation of the most recently submitted PSUR(s) for the above-mentioned medicine(s), PRAC requested the MAH to submit a variation to provide data and discuss on whether existing data might support safe administration of the product in home infusion setting, as well as to discuss whether an update of the product information and/or additional risk minimisation measures (aRMMs) is warranted. PRAC is responsible for adopting an outcome based on the assessment report from the PRAC Rapporteur, to be further considered at the level of CHMP, responsible for adopting an opinion on this variation. For further background, see PRAC minutes February 2023 and PRAC minutes June 2023.

Summary of recommendation(s)

- Based on the available data, the Rapporteur's assessment and the responses provided by the MAH, PRAC considered that the MAH should submit updated key elements of the healthcare professional (HCP) and patient/caregiver guides as aRMMs to address the risk of medication errors in the home setting and the risk of infusion associated reactions, as well as an updated product information regarding the administration of the product in the home setting, in line with the request for supplementary information (RSI). .
- The MAH should submit to EMA, within 30 days, responses to the RSI.

6.6. Expedited summary safety reviews[36]

None

[34] Update of SmPC section 4.8. The package leaflet is updated accordingly
[35] Held 29 November – 02 December 2021
[36] Submission of expedited summary safety reports for review in addition to the requirements for submission of PSUR(s) falling within the pandemic period and requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC

7. Post-authorisation safety studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)[37]

See Annex I 17.1.

7.2. Protocols of PASS non-imposed in the marketing authorisation(s)[38]

See Annex I 17.2.

7.3. Results of PASS imposed in the marketing authorisation(s)[39]

7.3.1. Valproate[40] (NAP) - EMEA/H/N/PSR/J/0043

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

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Final study report for a retrospective observational study to investigate the association between paternal exposure to valproate and the risk of congenital anomalies and neurodevelopmental disorders including autism in offspring

Background

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

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, the MAHs were required as a condition to the marketing authorisation(s) (Annex IV) to conduct a retrospective observational study to investigate the association between paternal exposure to valproate and the risk of congenital anomalies and neurodevelopmental disorders including autism in offspring. The MAH Sanofi-Aventis Recherche & Développement, on behalf of a consortium, submitted to EMA the final results of the study. For further background, see PRAC minutes May 2023, PRAC minutes June 2023, PRAC minutes July 2023 and PRAC minutes October 2023[41].

Summary of recommendation(s) and conclusions

- PRAC adopted a list of questions (LoQ) and endorsed the list of participants for the stakeholder's meeting (held on 16 November 2023). PRAC also adopted a LoQ for the SAG Neurology (planned for 4 December 2023).

[37] In accordance with Article 107n of Directive 2001/83/EC
[38] 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
[39] In accordance with Article 107p-q of Directive 2001/83/EC
[40] Valproic acid, sodium valproate, valproate pivoxil, valproate semisodium, valpriomide, valproate bismuth, calcium valproate, valproate magnesium
[41] Held 25-28 September 2023

7.3.2. Valproate[42] (NAP) - EMEA/H/N/PSR/J/0045

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

PRAC Rapporteur: Jean-Michel Dogné

Scope: Final study report for a non-interventional retrospective longitudinal study in the United Kingdom and France to investigate the therapeutic strategies after discontinuation of valproate and related substances in clinical practice

Background

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

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, the MAHs were required as a condition to the marketing authorisation(s) (Annex IV) to conduct an observational study to evaluate and identify the best practices for switching of valproate in clinical practice. The MAH Sanofi-Aventis Recherche & Développement, on behalf of a consortium, submitted to EMA the final results of the study.

The final study report version 1.0 dated 30 June 2023 was submitted to EMA and PRAC discussed the final study results.

Summary of recommendation(s) and conclusions

- Based on the review of the final report of the PASS entitled 'non-interventional retrospective longitudinal study in the UK and France to investigate the therapeutic strategies after discontinuation of valproate (VPA) and related substances in clinical practice: VALSE study (VALNAC09344)', PRAC agreed that regulatory implications of the study results are limited and they do not impact the benefit risk balance of valproate-containing products, hence no regulatory actions are deemed necessary at this stage.
- PRAC agreed with the PRAC Rapporteur's conclusion that in about half of the cases where use of valproate was discontinued, the discontinuation was maintained, although major uncertainties remain. The limitations and risk of residual confounding were also discussed. Finally, PRAC noted that planned pregnancy associated with a dose-tapering phase was a strong positive factor for successful valproate discontinuation, but highlighted that this target population is only a limited part of the target group of the valproate-related recommendations and risk minimisation measures.
- PRAC strongly encouraged the consortium of MAHs to publish the results of this study in a scientific journal since sharing these results would be helpful and relevant for future research on this topic.

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

See Annex I 17.4.

[42] Valproic acid, sodium valproate, valproate pivoxil, valproate semisodium, valpriomide, valproate bismuth, calcium valproate, valproate magnesium

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

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

None

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.

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

8.1. Annual reassessments of the marketing authorisation

See Annex I 18.1.

8.2. Conditional renewals of the marketing authorisation

None

8.3. Renewals of the marketing authorisation

See Annex I 18.3.

9. Product related pharmacovigilance inspections

9.1. List of planned pharmacovigilance inspections

None

9.2. Ongoing or concluded pharmacovigilance inspections

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

9.3. Others

None

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

10.1. Safety related variations of the marketing authorisation

None

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

None

10.3. Other requests

None

10.4. Scientific Advice

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

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

11.1. Safety related variations of the marketing authorisation

11.1.1. Hydroxyethyl starch (NAP) - DE/H/xxxx/WS/1360, DE/H/xxxx/WS/1452

Applicant(s): Fresenius Kabi Deutschland GmbH

PRAC Lead: Martin Huber

Scope: Member State (DE) request for PRAC advice on two worksharing variation (WS) procedures (DE/H/xxxx/WS/1360 and DE/H/xxxx/WS/1452) related to the assessment of: (1) the final results from two imposed clinical trials (PHOENICS and TETHYS); and (2) updates of the risk management plan (RMP) and product information (PI) as well as a proposed direct healthcare professional communication (DHPC); submitted by the marketing authorisation holder (MAH) in order to fulfil the conditions for lifting the suspension of marketing authorisations adopted by the Commission on 24 May 2022.

Background

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

In line with the conclusions of the referral procedure under Article 107i of Directive 2001/83/EC (EMEA/H/A-107i/1376) concluded in 2013, MAHs were required as a condition of the marketing authorisations (MAs) to conduct clinical studies on the benefits and risks of

HES solutions in patients with trauma and those undergoing elective surgery. At the time of the referral procedure under Article 107i of Directive 2001/83/EC (EMEA/H/A-107i/1457) concluded in 2018, the PHOENICS clinical trial was ongoing but the TETHYS clinical trial had not started. The MAH Fresenius Kabi submitted two WS variation procedures with: (1) the final results of the two imposed clinical trials and (2) RMP update including revision of the controlled access programme (CAP), a DHPC and a product information (PI) update in order to fulfil the conditions for lifting the suspension of MAs adopted by the Commission on 24 May 2022. Germany, as reference Member State (RMS) of these 2 WS variation procedures, requested a PRAC advice on its assessment.

Summary of advice

- Based on the review of the available information, PRAC did not concur with the RMS assessment and agreed, by majority, that the conditions for lifting the HES MA suspension cannot be considered fulfilled at this stage by the provision of the final results of the PHOENICS and TETHYS clinical trials together with the proposed set of risk minimisation measures (RMMs), i.e., the proposed PI update, revision of the existing CAP and DHPC. Twenty-five members voted in favour of the PRAC advice whilst five members[44] had divergent views. The Icelandic and Norwegian PRAC members agreed with the PRAC advice.
- PRAC considered that the 2 WS variations do not provide any grounds to lift the MA suspension of HES at this stage. This is due to the methodological limitations and lack of patient-relevant downstream effects, which further support limited clinically relevant benefits of HES use, within the approved populations. Furthermore, the proposed RMM amendments did not differ meaningfully to the ones previously assessed by PRAC as part of the 2022 drug utilisation study assessment, and for which PRAC concluded these could not sufficiently ensure safe use of HES and protect patients from harm. As a result, PRAC did not support the RMS overall conclusion that the HES MA suspension can be lifted in the 4 remaining Member States with current MAs (DE, HU, PL and RO).

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 thanked **Željana Margan Koletić** for their contribution as the alternate for Croatia (mandate ended on 20 October 2023).

12.1.2. Vote by proxy

None

[44] Roxana Dondera, Martin Huber, Eva Jirsová, Anna Mareková, Julia Pallos

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

The EMA Secretariat provided PRAC with an update on the characteristics of the post-COVID-19 condition and post-acute sequelae of COVID-19, as well as on possible treatments for adults with this condition, and on the study results regarding the effectiveness of COVID-19 mRNA vaccines' (booster dose and adapted mRNA vaccines) against the new SARS-CoV-2 variants.

12.5. Cooperation with International Regulators

None

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

None

12.7. PRAC work plan

None

12.8. Planning and reporting

12.8.1. EU Pharmacovigilance system - quarterly workload measures and performance indicators – Q3 2023 and predictions

The topic was postponed for the next PRAC plenary meeting.

12.8.2. PRAC workload statistics – Q3 2023

The topic was postponed for the next PRAC plenary meeting.

12.9. Pharmacovigilance audits and inspections

12.9.1. Pharmacovigilance systems and their quality systems

None

12.9.2. Pharmacovigilance inspections

None

12.9.3. Pharmacovigilance audits

None

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

12.10.1. Periodic safety update reports

None

12.10.2. Granularity and Periodicity Advisory Group (GPAG)

None

12.10.3. PSURs repository

None

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

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 2023, 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 2023 (held 23-26 October 2023), the updated EURD list was adopted by CHMP and CMDh at their respective meetings and published on the EMA website, see: Home> Human Regulatory>Post-authorisation>Pharmacovigilance>Periodic safety update reports>> List of Union reference dates and frequency of submission of periodic safety update reports (PSURs)

12.10.5. Periodic safety update reports single assessment (PSUSA) – review of 'other considerations' section in the assessment report – update and proposed way forward

PRAC lead: Sabine Straus

PRAC's Vice-Chairman Martin Huber presented to PRAC a follow-up on the proposal to remove the 'other considerations' section from the PSUSA assessment report (AR) for all PSUSA types (CAP only, mix CAP/NAP and NAPs only) in order to streamline the PSUSA AR and based on the previous discussions at both PRAC and CMDh levels (see PRAC minutes March 2023 and PRAC minutes May 2023). PRAC agreed with the proposal to extend the initial pilot phase until May 2024, with an analysis of the outcome and a discussion on the way forward to be planned for June 2024.

12.11. Signal management

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

None

12.12. Adverse drug reactions reporting and additional monitoring

12.12.1. Management and reporting of adverse reactions to medicinal products

None

12.12.2. Additional monitoring

None

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

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

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

12.13. EudraVigilance database

12.13.1. Activities related to the confirmation of full functionality

None

12.14. Risk management plans and effectiveness of risk minimisations

12.14.1. Risk management systems

None

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

None

12.15. Post-authorisation safety studies (PASS)

12.15.1. Post-authorisation Safety Studies – imposed PASS

None

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

None

12.16. Community procedures

12.16.1. Referral procedures for safety reasons

None

12.17. Renewals, conditional renewals, annual reassessments

None

12.18. Risk communication and transparency

12.18.1. Public participation in pharmacovigilance

None

12.18.2. Safety communication

None

12.19. Continuous pharmacovigilance

12.19.1. Incident management

None

12.20. Impact of pharmacovigilance activities

None

12.21. Others

12.21.1. Good Pharmacovigilance Practice (GVP) – end-of-year update for 2023 and planning for 2024

PRAC lead: Sabine Straus

The EMA Secretariat provided PRAC with an update on GVP development in line with PRAC and EMA work plans for 2023 as planned on a regular basis. PRAC was also updated on the upcoming activities around GVPs as a contribution to the PRAC work plan for 2024.

12.21.2. Presentation of draft reflection paper on 'Use of real-world data to generate real-world evidence in non-interventional studies'

The EMA Secretariat presented to PRAC a brief background on the usefulness of the non-interventional studies in generating real world evidence to support regulatory assessment, as well as an overview of the scope, legal requirements, aim and content of the reflection paper. PRAC members were invited to provide their comments on the draft reflection paper

13. Any other business

None

14. Annex I – Signals assessment and prioritisation[45]

As per the agreed criteria for new signal(s), PRAC adopted without further plenary discussion the recommendation of the Rapporteur to request MAH(s) to submit a cumulative review following standard timetables[46].

14.1. New signals detected from EU spontaneous reporting systems

14.1.1. Osimertinib – TAGRISSO (CAP)

Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: Signal of progressive multifocal leukoencephalopathy

EPITT 19984 – New signal

Lead Member State(s): NL

14.2. New signals detected from other sources

None

15. Annex I – Risk management plans

15.1. Medicines in the pre-authorisation phase

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

15.1.1. Paliperidone - EMEA/H/C/006185

Scope: Treatment of schizophrenia

15.1.2. Pomalidomide - EMEA/H/C/006195

Scope: Treatment of adult patients with relapsed and refractory multiple myeloma (MM) in

[45] 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

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

combination with dexamethasone

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. Dexamethasone - OZURDEX (CAP) - EMEA/H/C/001140/II/0044

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Submission of an updated Annex II and RMP version 11 in order to remove additional risk minimisation measure: Patient guide, audio CD (where required)

15.2.2. Emtricitabine, tenofovir disoproxil - EMTRICITABINE/TENOFOVIR DISOPROXIL ZENTIVA (CAP) - EMEA/H/C/004137/WS2486/0025

Applicant: Zentiva k.s.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Submission of an updated RMP version 5.1 for Emtricitabine/Tenofovir disoproxil in line with the reference medicinal product Truvada (EMEA/H/C/WS2320)

15.2.3. Lacosamide - LACOSAMIDE UCB (CAP) - EMEA/H/C/005243/WS2515/0018; VIMPAT (CAP) - EMEA/H/C/000863/WS2515/0100

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of an updated RMP version 17.0 in order to introduce new updates including the removal of category 3 study EP0158 due to study closure by lack of enrolment, and the removal of category 3 studies (SP848 and EP0034)

15.2.4. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/II/0054

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Submission of an updated RMP version 31.1 in order to modify study A3921427 from an interventional to a non-interventional study. In addition, the MAH has taken the opportunity to update other sections of the RMP

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. Aripiprazole - ABILIFY MAINTENA (CAP) - EMEA/H/C/002755/X/0045

Applicant: Otsuka Pharmaceutical Netherlands B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension application to introduce a new pharmaceutical form associated with two new strengths (720 and 960 mg Prolonged-release suspension for injection). The RMP (version 12.1) is updated in accordance

15.3.2. Avapritinib - AYVAKYT (CAP) - EMEA/H/C/005208/II/0023, Orphan

Applicant: Blueprint Medicines (Netherlands) B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication to include treatment of adult patients with indolent systemic mastocytosis (ISM) for avapritinib based on results from the pivotal part of study BLU-285-2203 (PIONEER), this is a 3-part, randomised, double-blind, placebo-controlled, phase 2 study to evaluate safety and efficacy of avapritinib (BLU-285) in indolent and smoldering systemic mastocytosis with symptoms inadequately controlled with standard therapy. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.6, 4.8, 4.9, 5.1, 5.2 and 5.3 of the SmPC are updated. The package leaflet is updated in accordance. Version 4.0 of the RMP has also been submitted

15.3.3. Azacitidine - AZACITIDINE ACCORD (CAP) - EMEA/H/C/005147/X/0013

Applicant: Accord Healthcare S.L.U.

PRAC Rapporteur: Menno van der Elst

Scope: Extension application to introduce a new pharmaceutical form associated with a new strength (10 mg/ml powder for solution for infusion) and a new route of administration (intravenous use). The RMP version 2 is updated in accordance

15.3.4. Bempedoic acid - NILEMDO (CAP) - EMEA/H/C/004958/II/0031

Applicant: Daiichi Sankyo Europe GmbH

PRAC Rapporteur: Kimmo Jaakkola

Scope: Extension of indication to include treatment of adults with established or at high risk for atherosclerotic cardiovascular disease to reduce cardiovascular risk, based on results from study 1002-043 (CLEAR [Cholesterol Lowering via Bempedoic Acid, an ATP citrate lyase (ACL) Inhibiting Regimen]). CLEAR outcomes study is a phase 3 multi-centre randomised, double-blind, placebo-controlled study to evaluate whether long-term treatment with bempedoic acid reduces the risk of major adverse cardiovascular events (MACE) in patients with, or at high risk for, cardiovascular disease who are statin intolerant. As a consequence, sections 4.1, 4.8 and 5.1 of the SmPC are updated. The package leaflet is updated accordingly. Version 4.0 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce minor formatting changes to the product information. As part of the application, the MAH is requesting a 1-year extension of the market protection

15.3.5. Bempedoic acid, ezetimibe - NUSTENDI (CAP) - EMEA/H/C/004959/II/0035

Applicant: Daiichi Sankyo Europe GmbH

PRAC Rapporteur: Kimmo Jaakkola

Scope: Extension of indication to include treatment of adults with established or at high risk for atherosclerotic cardiovascular disease to reduce cardiovascular risk for NUSTENDI, based on results from Study 1002-043, known as the CLEAR [Cholesterol Lowering via Bempedoic Acid, an ATP citrate lyase (ACL) Inhibiting Regimen] outcomes trial, a phase 3, randomised, double-blind, placebo-controlled study to assess the effects of bempedoic acid (ETC-1002) on the occurrence of major cardiovascular events (MACE) in patients with, or at high risk for, cardiovascular disease who are statin intolerant. As a consequence, sections 4.1, 4.8 and 5.1 of the SmPC are updated. The package leaflet is updated in accordance. Version 4.0 of the RMP has also been submitted. As part of the application the MAH is requesting a 1-year extension of the market protection

15.3.6. Cariprazine - REAGILA (CAP) - EMEA/H/C/002770/II/0034

Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Update of sections 4.3 and 4.5 of the SmPC in order to update an existing contraindication and update drug-drug interaction information with CYP3A4 inhibitors, based on final results from study RGH-188-301 (CYPRESS) listed as a category 3 study in the RMP; this is an open-label, single-arm, fixed-sequence study to investigate the effect of erythromycin, a moderate CYP3A4 inhibitor on the pharmacokinetics of cariprazine in male patients with schizophrenia. The package leaflet is updated accordingly. The RMP version 4.0 has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the product information

15.3.7. Cariprazine - REAGILA (CAP) - EMEA/H/C/002770/X/0033

Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Extension application to introduce a new pharmaceutical form (orodispersible tablets). The RMP (version 3.0) is updated in accordance

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

Applicant: MediWound Germany GmbH

PRAC Rapporteur: Martin Huber

Scope: Extension of current indication for removal of eschar in adults with deep partial- and full-thickness thermal burns to the paediatric population for NexoBrid based on interim results from study MW2012-01-01 (CIDS study), listed as Study MW2012-01-01 is a 3-stage, multi-centre, multi-national, randomised, controlled, open label, 2-arm study aiming to demonstrate the superiority of NexoBrid treatment over standard of care (SOC) treatment in paediatric patients (aged 0 to 18 years) with deep partial thickness (DPT) and

full thickness (FT) thermal burns of 1% to 30% of total body surface area (TBSA). As a consequence, sections 4.1, 4.2, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The package leaflet is updated accordingly. Version 9 of the RMP has also been submitted

15.3.9. Dabigatran etexilate - PRADAXA (CAP) - EMEA/H/C/000829/II/0147/G

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: A grouped application consisting of:
C.I.7.a (type IB): 1) to delete the pharmaceutical form "powder and solvent for oral solution, 6.25 mg/ml", as agreed in procedure EMEA/H/C/000829/II/0144.
C.I.4 (type II): 2) Update of section 4.1 of the SmPC in order to modify the indication following the deletion of the powder and solvent for oral solution; the package leaflet is updated accordingly. The RMP version 41.2 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

15.3.10. Faricimab - VABYSMO (CAP) - EMEA/H/C/005642/II/0005

Applicant: Roche Registration GmbH

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Extension of indication to include treatment of adult patients with visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO) for Vabysmo, based on results from the two phase 3 studies: GR41984 (BALATON) in patients with branch retinal vein occlusion (BRVO) and GR41986 (COMINO) in patients with central retinal vein occlusion (CRVO) or hemiretinal vein occlusion (HRVO). These are global, multicentre, randomised, double-masked, active comparator-controlled, parallel-group, 2-part studies evaluating the efficacy, safety, and PK of faricimab. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated. The package leaflet is updated in accordance. Version 3.0 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce minor changes to the product information

15.3.11. Hydroxycarbamide - XROMI (CAP) - EMEA/H/C/004837/II/0019

Applicant: Nova Laboratories Ireland Limited

PRAC Rapporteur: Jo Robays

Scope: Extension of indication to include the prevention of vaso-occlusive complications of sickle cell disease in children from 6 months to 2 years of age for Xromi, based on final results from the paediatric study INV543, listed as a category 3 study in the RMP; this is a single-arm, open-label, multi-centre study in children with sickle cell anaemia over 6 months of age. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet is updated in accordance. Version 4.1 of the RMP has also been submitted

15.3.12. Idecabtagene vicleucel - ABECMA (CAP) - EMEA/H/C/004662/II/0031, Orphan

Applicant: Bristol-Myers Squibb Pharma EEIG, ATMP[47]

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension of indication to include treatment of adult patients with relapsed and refractory multiple myeloma (RRMM) who have received at least two prior therapies, including an immunomodulatory agent, a proteasome inhibitor and an anti-CD-38 antibody and have demonstrated disease progression on the last therapy for Abecma (idecabtagene vicleucel, ide-cel), based on results from study BB2121-MM-003 (MM-003, KarMMa-3). This is a Phase 3, multicentre, randomised, open-label study to compare the efficacy and safety of ide-cel versus standard regimens in subjects with RRMM. As a consequence, sections 2.1, 2.2, 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2, 6.3, 6.4 and 6.6 of the SmPC are updated. The package leaflet and labelling are updated in accordance. Version 3.0 of the RMP has also been submitted. Furthermore, the product information is brought in line with the Guideline on core SmPC, labelling and package leaflet for advanced therapy medicinal products (ATMPs) containing genetically modified cells

15.3.13. Infliximab - REMSIMA (CAP) - EMEA/H/C/002576/II/0133/G

Applicant: Celltrion Healthcare Hungary Kft.

PRAC Rapporteur: Kimmo Jaakkola

Scope: Grouped application comprising three type II variations (C.I.4) as follows:
1) Update of section 4.2, 4.8 and 5.1 of the SmPC in order to add 3-IV induction dosing regimen and dose escalation of subcutaneous maintenance dose from CT-P13 SC 120 mg Q2W to 240 mg Q2W for patients with loss of response and update efficacy and safety information based on Week 54 data from studies CT-P13 3.7 (ulcerative colitis) and CT-P13 3.8 (Crohn's disease), listed as a category 3 study in the RMP; Study CT-P13 3.7 is a randomised, placebo controlled, double-blind, phase 3 study to evaluate the efficacy and safety of the subcutaneous injection of CT-P13 (CT-P13 SC) as maintenance therapy in patients with moderately to severely active ulcerative colitis and study CT-P13 3.8 is a randomised, placebo-controlled, double-blind, phase 3 study to evaluate the efficacy and safety of the subcutaneous injection of CT-P13 (CT-P13 SC) as maintenance therapy in patients with moderately to severely active Crohn's disease.
2) Update of section 4.2 and 5.2 of the SmPC in order to add subcutaneous induction posology and pharmacokinetic information based on Population PK and PK-PD Modelling and Simulation.
3) Update of section 4.2 of the SmPC in order to switch from high-dose IV maintenance (> 5 mg/kg) to subcutaneous maintenance dose of 120 mg every two weeks based on data from REMSWITCH study (Effectiveness of switching from intravenous to subcutaneous infliximab in patients with inflammatory bowel diseases: the REMSWITCH Study).
The RMP version 16.1 has also been submitted. The package leaflet and labelling are updated accordingly. In addition, the MAH took the opportunity to introduce minor updates to the product information

[47] Advanced therapy medicinal product

15.3.14. Influenza vaccine (surface antigen, inactivated, adjuvanted) - FLUAD TETRA (CAP) - EMEA/H/C/004993/II/0043

Applicant: Seqirus Netherlands B.V.

PRAC Rapporteur: Jean-Michel Dogné

Scope: Extension of indication to include adults 50 years of age and older for Fluad Tetra, based on final results from study V118_23; this is a phase 3, randomised, observer-blind, controlled, multicentre, clinical study to evaluate immunogenicity and safety of an MF59-adjuvanted quadrivalent subunit inactivated influenza vaccine in comparison with a licensed quadrivalent influenza vaccine, in adults 50 to 64 years of age. As a consequence, sections 4.1, 4.8 and 5.1 of the SmPC are updated. The labelling and package leaflet are updated in accordance. Version 2.9 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the product information

15.3.15. Mecasermin - INCRELEX (CAP) - EMEA/H/C/000704/II/0080

Applicant: Ipsen Pharma

PRAC Rapporteur: Kirsti Villikka

Scope: Update of sections 4.2, 4.6, and 4.8 of the SmPC in order to modify administration instructions recommendation regarding the monitoring of pre-prandial blood glucose in pre prandial condition and in case of symptoms and to prevent the risk of lipohypertrophy, delete wording in the pregnancy section and update on number of patients with severe primary IGD deficiency (IGFD) based on the cumulative review of safety database, scientific literature and clinical trials data. The package leaflet is updated accordingly. The RMP version 14.0 has also been submitted. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet

15.3.16. Naloxegol - MOVENTIG (CAP) - EMEA/H/C/002810/II/0039

Applicant: Kyowa Kirin Holdings B.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: Update of sections 4.1, 4.2, 4.4, 4.8, 5.1, and 5.2 of the SmPC in order to update information regarding the use of naloxegol in opioid-induced constipation (OIC) patients with cancer-related pain based on real-world data from non-interventional studies (NACASY, KYONAL, and MOVE studies), post-marketing data, and literature. The package leaflet is updated accordingly. The RMP version 8 has also been submitted. In addition, the MAH took the opportunity to implement editorial changes to the SmPC

15.3.17. Natalizumab - TYSABRI (CAP) - EMEA/H/C/000603/II/0136

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Gabriele Maurer

Scope: Update of sections 4.2 and 4.4 of the SmPC to modify administration instructions and update educational guidance to enable the subcutaneous formulation to be administered outside a clinical setting by healthcare professionals based on the cumulative review of post marketing and clinical study data. The package leaflet and Annex IID are

updated accordingly. The RMP version 29.1 has also been submitted. In addition, the MAH took this opportunity to introduce minor editorial changes

15.3.18. Opicapone - ONGENTYS (CAP) - EMEA/H/C/002790/WS2552/0060; ONTILYV (CAP) - EMEA/H/C/005782/WS2552/0015

Applicant: Bial Portela & Companhia S.A.

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Extension of indication to include treatment of signs and symptoms of Parkinson's Disease for Ongentys/Ontilyv, based on final results from study BIA-91067-303; this is a pivotal Phase III, multicentre, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of opicapone in patients with early idiopathic Parkinson's Disease receiving treatment with L-DOPA plus a DDCI, and who are without signs of any motor complication. As a consequence, sections 4.1, 4.2, 4.8, and 5.1 of the SmPC are updated. The package leaflet is updated in accordance. Version 6.0 of the RMP has also been submitted (only applicable to Ongentys) to reflect the changes made upon approval of the informed consent application, to keep consistency between the eCTD lifecycles of the two marketing authorisations (Ongentys and Ontilyv). Furthermore, the product information is brought in line with the latest QRD template version 10.3. In addition, as part of the application the MAH is requesting a 1-year extension of the market protection

15.3.19. Patiromer - VELTASSA (CAP) - EMEA/H/C/004180/X/0031/G

Applicant: Vifor Fresenius Medical Care Renal Pharma France

PRAC Rapporteur: Kirsti Villikka

Scope: Extension application to introduce a new strength (1 g powder for oral suspension), grouped with a type II variation (C.I.6.a) in order to extend the indication to include treatment of population from 6 to 18 years old for Veltassa based on final results from paediatric study RLY5016-206P (EMERALD); this is a phase 2, open-label, multiple dose study to evaluate the pharmacodynamic effects, safety, and tolerability of patiromer for oral suspension in children and adolescents 2 to less than 18 years of age with chronic kidney disease and hyperkalaemia. As a consequence, sections 1, 2, 4.1, 4.2, 4.8, 4.9, 5.1 and 6.5 of the SmPC are updated. The package leaflet and labelling are updated in accordance. Version 2 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce editorial changes

15.3.20. Pegcetacoplan - ASPAVELI (CAP) - EMEA/H/C/005553/II/0011, Orphan

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Kimmo Jaakkola

Scope: Extension of indication to include treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH) not previously treated with a complement inhibitor for ASPAVELI, based on final results from study APL2-308. This is a phase III, randomised, open-label, comparator-controlled study that enrolled adult patients with PNH who had not been treated with a complement inhibitor. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet is updated in accordance. Version 1.1 of the RMP has also been submitted

15.3.21. Pembrolizumab - KEYTRUDA (CAP) - EMEA/H/C/003820/II/0138

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication to include Keytruda in combination with gemcitabine-based chemotherapy for the first-line treatment of locally advanced unresectable or metastatic biliary tract carcinoma in adults, based on final results from study KEYNOTE-966; this is a phase 3 randomised, double-blind study of pembrolizumab plus gemcitabine/cisplatin versus placebo plus gemcitabine/cisplatin as first-line therapy in participants with advanced and/or unresectable biliary tract carcinoma. As a consequence, sections 4.1, 4.4 and 5.1 of the SmPC are updated. The package leaflet is updated in accordance. Version 43.1 of the RMP has also been submitted

15.3.22. Pralsetinib - GAVRETO (CAP) - EMEA/H/C/005413/II/0012

Applicant: Roche Registration GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of sections 4.2, 4.4 and 4.5 of the SmPC in order to amend posology recommendations, warnings and drug-drug interaction (DDI) information regarding the co-administration with CYP3A4 inhibitors, P-gp inhibitors and CYP3A4 inducers based on final results from the DDI study GP43162, listed as a category 3 study in the RMP, as well as results from the physiologically based pharmacokinetic (PBPK) analyses summarised in the PBPK Report 1120689. Study GP43162 is a phase 1, open-label, fixed-sequence study to evaluate the effect of a single dose of cyclosporine on the single dose pharmacokinetics of pralsetinib in healthy subjects. The RMP version 1.6 has also been submitted

15.3.23. Saxagliptin - ONGLYZA (CAP) - EMEA/H/C/001039/II/0057

Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: Update of sections 4.2, 5.1 and 5.2 of the SmPC in order to update safety, efficacy and pharmacokinetic information in paediatric patients with Type 2 diabetes mellitus (T2DM) aged 10 to <18 years of age based on interim results from study D1680C00019 (T2NOW). This is a 26-week, multicentre, randomised, placebo-controlled, double-blind, parallel group, Phase III trial with a 26-week safety extension period evaluating the safety and efficacy of dapagliflozin (5 and 10 mg), and, separately, saxagliptin (2.5 and 5 mg) in paediatric patients with T2DM who were between 10 and below 18 years of age. The package leaflet is updated accordingly. The RMP version 17.1 has also been submitted. In addition, the MAH took the opportunity to bring the product information in line with the latest QRD template and to introduce editorial changes

15.3.24. Selexipag - UPTRAVI (CAP) - EMEA/H/C/003774/X/0038

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Nathalie Gault

Scope: Extension application to add a new strength of 100 µg film-coated tablets in HDPE

bottle. The RMP (version 10.1) is updated in accordance

15.3.25. Selpercatinib - RETSEVMO (CAP) - EMEA/H/C/005375/II/0021

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication to include the treatment of adults and adolescents 12 years and older with advanced rearranged during transfection (RET) fusion-positive thyroid cancer in the first-line setting for RETSEVMO based on interim data from studies LIBRETTO-001 (LOXO-RET-17001) and LIBRETTO-121; LIBRETTO-001 is an open-label, multicentre, global phase 1/2 study of selpercatinib in patients with RET-altered advanced solid tumors. LIBRETTO-121 is a phase 1/2 study of selpercatinib in paediatric patients with advanced RET-altered solid or primary central nervous system tumours. As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The package leaflet is updated in accordance. Version 3.2 of the RMP has also been submitted

15.3.26. Selpercatinib - RETSEVMO (CAP) - EMEA/H/C/005375/II/0022

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication to include the treatment of adults with advanced or metastatic rearranged during transfection (RET) fusion-positive solid tumours with disease progression on or after prior systemic therapies or who have no satisfactory therapeutic options, based on interim data from study LIBRETTO-001 (LOXO-RET-17001); LIBRETTO-001 is an open-label, multicentre, global Phase 1/2 study of selpercatinib in in adult and adolescent patients with advanced RET-altered tumours. As a consequence, sections 4.1, 4.2 and 5.1 of the SmPC are updated. The package leaflet is updated in accordance. Version 3.1 of the RMP has also been submitted. In addition, the MAH took the opportunity to implement editorial changes to the SmPC

15.3.27. Sotorasib - LUMYKRAS (CAP) - EMEA/H/C/005522/II/0007

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Update of sections 4.2 and 5.2 of the SmPC in order to update recommendations for patients with moderate to severe hepatic impairment following final results from study 20200362 listed as a category 3 PASS study in the EU RMP; this is a Phase I clinical study to evaluate the pharmacokinetics (PK) of a single oral dose of sotorasib administered in subjects with moderate or severe hepatic impairment compared with subjects who have normal hepatic function. The EU RMP version 1.0 has also been submitted. In addition, the MAH took the opportunity to bring the product information in line with the latest QRD template version 10.3

15.3.28. Spesolimab - SPEVIGO (CAP) - EMEA/H/C/005874/X/0006/G

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Nathalie Gault

Scope: Extension application to introduce a new pharmaceutical form (solution for injection) associated with a new strength (150 mg) and new route of administration (subcutaneous use), for the prevention of generalised pustular psoriasis (GPP) flares in adults and adolescents from 12 years of age. This line extension is grouped with a type II variation (C.I.6.a) to extend indication for Spevigo 450 mg concentrate for solution for infusion to include treatment of generalised pustular psoriasis (GPP) flares in adolescents (from 12 years of age), based on final results from study 1368-0027 (Effisayil 2) and extrapolation; this is a multi-centre, randomised, parallel group, double blind, placebo controlled, phase IIb dose-finding study to evaluate efficacy and safety of BI 655130 (spesolimab) compared to placebo in preventing GPP flares in patients with history of GPP. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.6, 4.8, 4.9, 5.1 and 5.2 of the SmPC are updated. The Annex II and package leaflet are updated in accordance. Version 2.0 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to introduce editorial changes to the product information and update the list of local representatives in the package leaflet

15.3.29. Tisagenlecleucel - KYMRIAH (CAP) - EMEA/H/C/004090/II/0075, Orphan

Applicant: Novartis Europharm Limited, ATMP[48]

PRAC Rapporteur: Gabriele Maurer

Scope: Update of sections 5.1 and 5.2 of the SmPC in order to update efficacy and pharmacokinetic information based on final results from study CCTL019C2201 PAES in the Annex II (ANX008); this is a Phase II, single arm, multicenter trial to determine the efficacy and safety of CTL019 in adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL). The RMP version 6 has also been submitted. In addition, the MAH took the opportunity to update Annex II.D of the product information

15.3.30. Tozinameran - COMIRNATY (CAP) - EMEA/H/C/005735/II/0188/G

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Grouped application comprising two type II variations as follows:
C.I.4 – 1) Update of section 4.8 of the SmPC in order to update the safety information based on interim (6MPD3 in 12-15yo) and final results from study C4591001, listed as a category 3 study in the RMP. This is a phase 1/2/3, placebo-controlled, randomised, observer-blind, dose-finding study to evaluate the safety, tolerability, immunogenicity, and efficacy of SARS-CoV-2 RNA vaccine candidates against COVID-19 in healthy individuals. An updated RMP version 10.1 has also been submitted.
C.I.11.b – 2) Submission of an updated RMP version 10.1 in order to revise RMP milestones of final study reports of other on-going procedures, including other administrative and editorial changes

[48] Advanced therapy medicinal product

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

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

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

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

16.1.1. Avacopan - TAVNEOS (CAP) - PSUSA/00010967/202303

Applicant: Vifor Fresenius Medical Care Renal Pharma France

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

16.1.2. Betaine anhydrous[49] - CYSTADANE (CAP) - PSUSA/00000390/202302

Applicant: Recordati Rare Diseases

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.3. Bupivacaine, meloxicam - ZYNRELEF[50] - PSUSA/00010880/202303

Applicant: Heron Therapeutics, B.V.

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

16.1.4. Cabotegravir - VOCABRIA (CAP) - PSUSA/00010900/202303

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.5. Certolizumab - CIMZIA (CAP) - PSUSA/00000624/202303

Applicant: UCB Pharma S.A.

[49] Centrally authorised product(s) only
[50] European Commission (EC) decision on the marketing authorisation (MA) withdrawal of Zynrelef dated 05 October 2023

PRAC Rapporteur: Mari Thorn

Scope: Evaluation of a PSUSA procedure

16.1.6. Ciclosporin[51] - IKERVIS (CAP); VERKAZIA (CAP) - PSUSA/00010362/202303

Applicant: Santen Oy

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.1.7. Dabigatran - PRADAXA (CAP) - PSUSA/00000918/202303

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Evaluation of a PSUSA procedure

16.1.8. Dimethyl fumarate[52] - SKILARENCE (CAP) - PSUSA/00010647/202303

Applicant: Almirall S.A

PRAC Rapporteur: Mari Thorn

Scope: Evaluation of a PSUSA procedure

16.1.9. Dupilumab - DUPIXENT (CAP) - PSUSA/00010645/202303

Applicant: Sanofi Winthrop Industrie

PRAC Rapporteur: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

16.1.10. Duvelisib - COPIKTRA (CAP) - PSUSA/00010939/202303

Applicant: Secura Bio Limited

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Evaluation of a PSUSA procedure

16.1.11. Gozetotide - LOCAMETZ (CAP) - PSUSA/00011030/202303

Applicant: Novartis Europharm Limited

PRAC Rapporteur: John Joseph Borg

Scope: Evaluation of a PSUSA procedure

[51] For topical use only
[52] Psoriasis

16.1.12. Idecabtagene vicleucel - ABECMA (CAP) - PSUSA/00010954/202303

Applicant: Bristol-Myers Squibb Pharma EEIG, ATMP[53]

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.13. Lasmiditan - RAYVOW (CAP) - PSUSA/00011011/202304

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Anna Mareková

Scope: Evaluation of a PSUSA procedure

16.1.14. Lutetium (^{177}LU) vipivotide tetraxetan - PLUVICTO (CAP) - PSUSA/00011031/202303

Applicant: Novartis Europharm Limited

PRAC Rapporteur: John Joseph Borg

Scope: Evaluation of a PSUSA procedure

16.1.15. Maralixibat - LIVMARLI (CAP) - PSUSA/00011032/202303

Applicant: Mirum Pharmaceuticals International B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.16. Mepolizumab - NUCALA (CAP) - PSUSA/00010456/202303

Applicant: GlaxoSmithKline Trading Services Limited

PRAC Rapporteur: Gabriele Maurer

Scope: Evaluation of a PSUSA procedure

16.1.17. Mogamulizumab - POTELIGEO (CAP) - PSUSA/00010741/202303

Applicant: Kyowa Kirin Holdings B.V.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Evaluation of a PSUSA procedure

16.1.18. Niraparib - ZEJULA (CAP) - PSUSA/00010655/202303

Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

[53] Advanced therapy medicinal product

16.1.19. Nivolumab, relatlimab - OPDUALAG (CAP) - PSUSA/00011018/202303

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.20. Ofatumumab - KESIMPTA (CAP) - PSUSA/00010927/202303

Applicant: Novartis Ireland Limited

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.1.21. Oritavancin - TENKASI (CAP) - PSUSA/00010368/202303

Applicant: Menarini International Operations Luxembourg S.A.

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.22. Ponesimod - PONVORY (CAP) - PSUSA/00010940/202303

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Karin Erneholm

Scope: Evaluation of a PSUSA procedure

16.1.23. Rilpivirine[54] - REKAMBYS (CAP) - PSUSA/00010901/202303

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

16.1.24. Risankizumab - SKYRIZI (CAP) - PSUSA/00010765/202303

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

16.1.25. Selinexor - NEXPOVIO (CAP) - PSUSA/00010926/202303

Applicant: Stemline Therapeutics B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

[54] For intramuscular use only

16.1.26. Selumetinib - KOSELUGO (CAP) - PSUSA/00010936/202304

Applicant: AstraZeneca AB

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.27. Solriamfetol - SUNOSI (CAP) - PSUSA/00010831/202303

Applicant: Atnahs Pharma Netherlands B.V.

PRAC Rapporteur: Julia Pallos

Scope: Evaluation of a PSUSA procedure

16.1.28. Tebentafusp - KIMMTRAK (CAP) - PSUSA/00010991/202303

Applicant: Immunocore Ireland Limited

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.29. Tepotinib - TEPMETKO (CAP) - PSUSA/00010979/202303

Applicant: Merck Europe B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.30. Tildrakizumab - ILUMETRI (CAP) - PSUSA/00010720/202303

Applicant: Almirall S.A

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.31. Trifluridine, tipiracil - LONSURF (CAP) - PSUSA/00010517/202303

Applicant: Les Laboratoires Servier

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.32. Velmanase alfa - LAMZEDE (CAP) - PSUSA/00010677/202303

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. Timolol, travoprost - DUOTRAV (CAP); NAP - PSUSA/00002962/202302

Applicant: Novartis Europharm Limited (DuoTrav), 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. BCG (bacillus calmette-guérin) for Immunotherapy (NAP) - PSUSA/00000303/202303

Applicant(s): various

PRAC Lead: Gabriele Maurer

Scope: Evaluation of a PSUSA procedure

16.3.2. BCG vaccine (freeze-dried) (NAP) - PSUSA/00000304/202303

Applicant(s): various

PRAC Lead: Roxana Dondera

Scope: Evaluation of a PSUSA procedure

16.3.3. Bicalutamide (NAP) - PSUSA/00000407/202302

Applicant(s): various

PRAC Lead: Karin Erneholm

Scope: Evaluation of a PSUSA procedure

16.3.4. Dienogest, ethinylestradiol (NAP) - PSUSA/00001057/202303

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.3.5. Ethosuximide (NAP) - PSUSA/00001316/202303

Applicant(s): various

PRAC Lead: Karin Erneholm

Scope: Evaluation of a PSUSA procedure

16.3.6. Human plasma[55] (NAP) - PSUSA/00001635/202302

Applicant(s): various

PRAC Lead: Gabriele Maurer

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 017.2

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. Variation procedure(s) resulting from PSUSA evaluation

None

Expedited summary safety reviews[56]

None

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

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

17.1. Protocols of PASS imposed in the marketing authorisation(s)[57]

17.1.1. Alemtuzumab - Lemtrada (CAP) - EMEA/H/C/PSA/S/0107

Applicant: Blueprint Medicines (Netherlands) B.V.

PRAC Rapporteur: Karin Erneholm

Scope: Substantial amendment to the protocol of a non-interventional PASS to investigate

[55] Pooled and treated for virus inactivation
[56] 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
[57] In accordance with Article 107n of Directive 2001/83/EC

drug utilisation and safety monitoring patterns for Lemtrada (alemtuzumab)

17.1.2. Valproate[58] (NAP) - EMEA/H/N/PSP/J/0075.13

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

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Responses to the 2nd RSI of the 4th interim report and statistical analysis plan for drug utilisation study (DUS) extension (DUS ext.) to assess the effectiveness of the new risk minimisation measures and to further characterise the prescribing patterns for valproate and related substances [MAH's response to PSP/J/0075.12]

17.2. Protocols of PASS non-imposed in the marketing authorisation(s)[59]

17.2.1. Avatrombopag - DOPTELET (CAP) - EMEA/H/C/004722/MEA 003.4

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Monica Martinez Redondo

Scope: MAH's response to MEA 003.3 and revised protocol for a study to further characterise the long-term safety profile of avatrombopag in patients with primary chronic immune thrombocytopenia in European patient registers and electronic healthcare databases as requested in the conclusions of variation II/0004/G finalised in December 2020 as per the request for supplementary information (RSI) adopted June 2023

17.2.2. Cannabidiol - EPIDYOLEX (CAP) - EMEA/H/C/004675/MEA 007.3

Applicant: Jazz Pharmaceuticals Ireland Limited

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: MAH's response to MEA 007.2 [protocol amendment for study GWEP19022 (listed as a category 3 study in the RMP): a prospective, observational cohort long-term safety study to assess the potential for chronic liver injury in patients treated with Epidyolex (cannabidiol oral solution) when used under conditions of routine clinical care] as per the request for supplementary information (RSI) adopted in July 2021.

17.2.3. Coronavirus (COVID-19) vaccine (recombinant protein receptor binding domain fusion heterodimer) - BIMERVAX (CAP) - EMEA/H/C/006058/MEA 008

Applicant: Hipra Human Health S.L.

PRAC Rapporteur: Zane Neikena

Scope: Protocol submission for the non-imposed, non-interventional, category 3 post authorisation observational study to assess the safety of Bimervax using electronic health record (HER) databases in Europe (PASS VAC4EU)

[58] Valproic acid, sodium valproate, valproate pivoxil, valproate semisodium, valpriomide, valproate bismuth, calcium valproate, valproate magnesium
[59] 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

17.2.4. Coronavirus (COVID-19) vaccine (recombinant protein receptor binding domain fusion heterodimer) - BIMERVAX (CAP) - EMEA/H/C/006058/MEA 009

Applicant: Hipra Human Health S.L.

PRAC Rapporteur: Zane Neikena

Scope: Protocol submission for the non-imposed, non-interventional, category 3 PASS of the COVID-19 Vaccines International Pregnancy Exposure Registry (C-VIPER) to assess the occurrence of obstetric, neonatal, and infant outcomes among women administered with Bimervax during pregnancy

17.2.5. Ivosidenib - TIBSOVO (CAP) - EMEA/H/C/005936/MEA 003

Applicant: Les Laboratoires Servier

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Protocol submission for a non-imposed/non-interventional, category 3 study in the RMP to evaluate the effectiveness of the Ivosidenib Patient Alert Card included in the additional risk minimisation measures, for awareness of differentiation syndrome in acute myeloid leukaemia (AML) patients, using process indicators for awareness, receipt of the material, utility and knowledge

17.2.6. Linaclotide - CONSTELLA (CAP) - EMEA/H/C/002490/MEA 009.7

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Martin Huber

Scope: 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 13)

17.2.7. Mavacamten - CAMZYOS (CAP) - EMEA/H/C/005457/MEA 001

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Kimmo Jaakkola

Scope: Submission of protocol for a non-imposed, non-interventional post-authorisation long-term observational study in Europe (MAVEL-HCM) in a real-world setting in patients with obstructive hypertrophic cardiomyopathy (oHCM) to characterise the following safety concerns: 'heart failure due to systolic dysfunction', 'patients with Class IV NYHA', 'patients being treated with disopyramide', 'patients being treated with a combination of β-blockers and non-dihydropyridine calcium-channel blockers (verapamil/diltiazem)', and 'long-term safety, including detrimental CV effects'

17.2.8. Mavacamten - CAMZYOS (CAP) - EMEA/H/C/005457/MEA 002

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Kimmo Jaakkola

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

17.2.9. Romosozumab - EVENITY (CAP) - EMEA/H/C/004465/MEA 001.7

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Tiphaine Vaillant

Scope: MAH's response to MEA 001.6 [protocol amendment for study OP0005: a European non-interventional PASS to study the adherence to the risk minimisation measures (RMMs) in the product information by estimating the compliance with contraindications and target indication(s) amongst incident romosozumab users, and analysing the utilisation pattern using the EU-adverse drug reactions (EU-ADR) Alliance] as per the request for supplementary information adopted in July 2023

17.2.10. Romosozumab - EVENITY (CAP) - EMEA/H/C/004465/MEA 002.7

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Tiphaine Vaillant

Scope: MAH's response to MEA 002.6 [protocol amendment for study OP0004: European non-interventional PASS to evaluate potential differences in terms of serious cardiovascular adverse events between romosozumab and currently available therapies used in comparable patients in real-world conditions using the EU-adverse drug reactions (EU-ADR) Alliance] as per the request for supplementary information adopted in July 2023

17.2.11. Romosozumab - EVENITY (CAP) - EMEA/H/C/004465/MEA 003.5

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Tiphaine Vaillant

Scope: MAH's response to MEA 003.4 [protocol amendment for study OP0006: evaluate potential differences in terms of serious infection between romosozumab and currently available therapies used in comparable patients in real-world conditions using the EU-adverse drug reactions (EU-ADR) Alliance] as per the request for supplementary information adopted in July 2023

17.2.12. Tirzepatide - MOUNJARO (CAP) - EMEA/H/C/005620/MEA 002.1

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to MEA 002 [protocol for study I8F-MC-B011: Tirzepatide Pancreatic Malignancy Study to evaluate the incidence of pancreatic malignancy among patients with

type 2 diabetes mellitus (T2DM) treated with tirzepatide and to compare the incidence of pancreatic malignancy among patients treated with tirzepatide to patients treated with alternative treatments for clinical indications approved for GLP-1 Ras in Europe] as per the request for supplementary information adopted in April 2023

17.2.13. Tirzepatide - MOUNJARO (CAP) - EMEA/H/C/005620/MEA 005.1

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to MEA 005 [protocol for study I8F-MC-B013: a database linkage study to evaluate the important potential risk of medullary thyroid cancer] as per the request for supplementary information adopted in April 2023

17.2.14. Tozinameran - COMIRNATY (CAP) - EMEA/H/C/005735/MEA 037.5

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to MEA 037.4 [A non-interventional PASS in US to assess the occurrence of safety events of interest, including myocarditis and pericarditis, among individuals in the general US population and in subcohorts of interest within selected data sources participating in the US Sentinel System] as per request for supplementary information (RSI) adopted in February 2023

17.2.15. Upadacitinib - RINVOQ (CAP) - EMEA/H/C/004760/MEA 017.1

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Revised protocol for study P23-480: a comparative cohort study of long-term safety of upadacitinib for the treatment of ulcerative colitis and Chron's disease in a real-world setting in Europe

17.2.16. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/MEA 044.17

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: MAH's response to MEA 044.16 [PASS CNTO1275PSO4056] as per request for supplementary information (RSI) adopted in June 2023:
Progress report / Request for supplementary information required by 7 August 2023:
The MAH is asked to provide further information on the following events, considered by the investigator related to ustekinumab: Tinea versicolour, Balanitis candida

17.2.17. Valoctocogene roxaparvovec - ROCTAVIAN (CAP) - EMEA/H/C/005830/MEA 005.1

Applicant: BioMarin International Limited, ATMP[60]

[60] Advanced therapy medicinal product

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to MEA 005 [Protocol of a survey of Haematologists to Assess the Effectiveness of the Additional Risk Minimisation Measures for ROCTAVIAN addressing the outstanding points in the MEA005 assessment report] as per request for supplementary information (RSI) adopted in June 2023

17.2.18. Voclosporin - LUPKYNIS (CAP) - EMEA/H/C/005256/MEA 002.1

Applicant: Otsuka Pharmaceutical Netherlands B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: MAH's response to MEA 002 [protocol No 348-201-00021: non-imposed/non-interventional, listed as category 3 study in the RMP, observational PASS in Europe to further characterise and quantify long-term safety profile with respect to neurotoxicity, chronic nephrotoxicity, and malignancy with use of voclosporin] as per the request for supplementary information (RSI) adopted in June 2023

17.3. Results of PASS imposed in the marketing authorisation(s)[61]

None

17.4. Results of PASS non-imposed in the marketing authorisation(s)[62]

17.4.1. Alglucosidase alfa - MYOZYME (CAP) - EMEA/H/C/000636/II/0093

Applicant: Sanofi B.V.

PRAC Rapporteur: Nathalie Gault

Scope: Submission of the final non-interventional Pompe Registry Report 2022 (MEA024 and MEA025)

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

Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Mari Thorn

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

[61] In accordance with Article 107p-q of Directive 2001/83/EC
[62] 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

17.4.3. Dimethyl fumarate - TECFIDERA (CAP) - EMEA/H/C/002601/II/0082

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Martin Huber

Scope: Update of section 4.6 of the SmPC in order to update information on pregnancy based on results from study 109MS402 - Tecfidera (dimethyl fumarate) Pregnancy Exposure Registry, listed as a category 3 study in the RMP; this is an observational study and aims to address the safety concern of effects on pregnancy outcome and prospectively evaluates pregnancy outcomes in women with multiple sclerosis (MS) who were exposed to a Registry-specified Biogen MS product during the eligibility window for that product. The package leaflet is updated accordingly. The RMP version 15.1 has also been submitted. In addition, the MAH has taken the opportunity to introduce editorial changes to the product information

17.4.4. Elasomeran - SPIKEVAX (CAP) - EMEA/H/C/005791/II/0110

Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Submission of the final report from study P903 - US PASS (NCT04958954), listed as a category 3 study in the RMP: post-marketing safety of SARS-CoV-2 Spikevax vaccine in the US for the active surveillance, signal refinement and self-controlled risk interval (SCRI) signal evaluation in HealthVerity. This submission addresses the post-authorisation measure MEA/003

17.4.5. Tacrolimus - ADVAGRAF (CAP) - EMEA/H/C/000712/WS2519/0071/G; MODIGRAF (CAP) - EMEA/H/C/000954/WS2519/0046/G

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Eamon O Murchu

Scope: A grouped application consisting of: 1) submission of the final report from study F506-PV-0001 listed as a category 3 study in the RMP for Advagraf and Modigraf: NI-PASS of outcomes associated with the use of tacrolimus around conception, or during pregnancy or lactation using data from Transplant Pregnancy Registry International (TPRI). The RMP version 5.0 has also been submitted; and 2) to include the feasibility assessment of using alternative secondary-use data sources to replicate the TPRI study as a category 3 additional pharmacovigilance activity in the RMP, including the milestones for the progress report and the final report of the feasibility assessment, related to EMEA/H/C/000712/MEA/032 and EMEA/H/C/000954/MEA/024

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

17.5.1. Avapritinib - AYVAKYT (CAP) - EMEA/H/C/005208/SOB 009.1

Applicant: Blueprint Medicines (Netherlands) B.V.

PRAC Rapporteur: Menno van der Elst

Scope: 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 GIST harbouring the PDGFRA D842V mutation, given as Specific Obligation 3 (SOB3) of the Conditional Marketing Authorisation for AYVAKYT. The submission of the first progress report is in line with agreed milestones in the Final PASS Protocol Assessment Report from the Pharmacovigilance Risk Assessment Committee (procedure number EMEA/H/C/PSP/S/0089.1 issued on 10 June 2021)

17.5.2. Axicabtagene ciloleucel - YESCARTA (CAP) - EMEA/H/C/004480/ANX 002.6

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

PRAC Rapporteur: Karin Erneholm

Scope: Title: Long-term, non-interventional study of recipients of Yescarta for treatment of relapsed or refractory Diffuse Large B-cell Lymphoma and Primary Mediastinal B-cell Lymphoma

17.5.3. Bimekizumab - BIMZELX (CAP) - EMEA/H/C/005316/MEA 005

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: From Initial MAA: Study PS0014: A multicenter, open-label study to assess the long-term safety, tolerability, and efficacy of bimekizumab in adult study participants with moderate-to-severe chronic plaque PSO. Assess the safety and efficacy of long-term use of bimekizumab

17.5.4. Coronavirus (COVID-19) vaccine (ChAdOx1-S [recombinant]) - VAXZEVRIA (CAP) - EMEA/H/C/005675/MEA 006.9

Applicant: AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

Scope: From Initial MAA: C-VIPER Study (D8110C00003); COVID-19 Vaccines International Pregnancy Registry of Women Exposed to AZD1222 Immediately Before or During Pregnancy

17.5.5. Difelikefalin - KAPRUVIA (CAP) - EMEA/H/C/005612/MEA 002

Applicant: Vifor Fresenius Medical Care Renal Pharma France

PRAC Rapporteur: Mari Thorn

Scope: A Multicenter, Randomised, Double-blind, Placebo-controlled 12-Week Study to Evaluate the Safety and Efficacy of Oral Difelikefalin in Advanced Chronic Kidney Disease Subjects With Moderate-to-Severe Pruritus and Not on Dialysis With an up to 52-Week Long-term Extension

[63] Advanced therapy medicinal product

17.5.6. Difelikefalin - KAPRUVIA (CAP) - EMEA/H/C/005612/MEA 003

Applicant: Vifor Fresenius Medical Care Renal Pharma France

PRAC Rapporteur: Mari Thorn

Scope: A Multicenter, Randomised, Double-blind, Placebo-controlled 12-Week Study to Evaluate the Safety and Efficacy of Oral Difelikefalin in Advanced Chronic Kidney Disease Subjects With Moderate-to-Severe Pruritus and Not on Dialysis With an up to 52-Week Long-term Extension

17.5.7. Difelikefalin - KAPRUVIA (CAP) - EMEA/H/C/005612/MEA 004

Applicant: Vifor Fresenius Medical Care Renal Pharma France

PRAC Rapporteur: Mari Thorn

Scope: A Two-part, Multicenter, Randomised, Double-blind Study to Evaluate the Efficacy and Safety of Oral Difelikefalin as Adjunct Therapy to a Topical Corticosteroid for Moderate-to-Severe Pruritus in Adult Subjects With Atopic Dermatitis

17.5.8. Givosiran - GIVLAARI (CAP) - EMEA/H/C/004775/MEA 006.6

Applicant: Alnylam Netherlands B.V.

PRAC Rapporteur: Martin Huber

Scope: From Initial MAA: Company Sponsored AHP Registry; A global observational longitudinal prospective registry of patients with acute hepatic porphyria (AHP)

17.5.9. Naltrexone hydrochloride, bupropion hydrochloride - MYSIMBA (CAP) - EMEA/H/C/003687/MEA 003.15

Applicant: Orexigen Therapeutics Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: PASS Study NB-451: An observational retrospective drug utilisation study (DUS) of Mysimba (naltrexone hydrochloride/bupropion hydrochloride) in Europe and the United States to describe the demographic and baseline characteristics of users of Mysimba, evaluate patterns of Mysimba initiation and use

17.6. Others

None

17.7. New Scientific Advice

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

17.8. Ongoing Scientific Advice

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

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

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

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

Based on the review of the available pharmacovigilance data for the medicine(s) listed below and the CHMP Rapporteur's assessment report, PRAC considered that either the renewal of the marketing authorisation procedure could be concluded - and supported the renewal of their marketing authorisations for an unlimited or additional period, as applicable - or no amendments to the specific obligations of the marketing authorisation under exceptional circumstances for the medicines listed below were recommended. As per the agreed criteria, the procedures were finalised at the PRAC level without further plenary discussion.

18.1. Annual reassessments of the marketing authorisation

18.1.1. Nelarabine - ATRIANCE (CAP) - EMEA/H/C/000752/S/0062 (without RMP)

Applicant: Sandoz Pharmaceuticals d.d.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Annual reassessment of the marketing authorisation

18.1.2. Vestronidase alfa - MEPSEVII (CAP) - EMEA/H/C/004438/S/0036 (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

None

18.3. Renewals of the marketing authorisation

18.3.1. Lusutrombopag - MULPLEO (CAP) - EMEA/H/C/004720/R/0018 (without RMP)

Applicant: Shionogi B.V.

PRAC Rapporteur: Mari Thorn

Scope: 5-year renewal of the marketing authorisation

18.3.2. Paclitaxel - PAZENIR (CAP) - EMEA/H/C/004441/R/0015 (with RMP)

Applicant: ratiopharm GmbH

PRAC Rapporteur: Menno van der Elst

Scope: 5-year renewal of the marketing authorisation

18.3.3. Pegvaliase - PALYNZIQ (CAP) - EMEA/H/C/004744/R/0038 (without RMP)

Applicant: BioMarin International Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: 5-year renewal of the marketing authorisation

18.3.4. Risankizumab - SKYRIZI (CAP) - EMEA/H/C/004759/R/0039 (without RMP)

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: 5-year renewal of the marketing authorisation

18.3.5. Treosulfan - TRECONDI (CAP) - EMEA/H/C/004751/R/0019 (without RMP)

Applicant: medac Gesellschaft fur klinische Spezialpraparate mbH

PRAC Rapporteur: Julia Pallos

Scope: 5-year renewal of the marketing authorisation

18.3.6. Zanamivir - DECTOVA (CAP) - EMEA/H/C/004102/R/0017 (without RMP)

Applicant: GlaxoSmithKline Trading Services Limited

PRAC Rapporteur: Ulla Wändel Liminga

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 23-26 October 2023 meeting.

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	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Jo Robays	Alternate	Belgium	No interests declared	
Maria Popova-Kiradjieva	Member	Bulgaria	No interests declared	
Nikica Mirošević Skvrce	Member	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	
Marie Louise Schougaard Christiansen	Member	Denmark	No interests declared	
Karin Erneholm	Alternate	Denmark	No interests declared	
Maia Uusküla	Member	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	
Martin Huber	Member (Vice-Chair)	Germany	No interests declared	
Gabriele Maurer	Alternate	Germany	No participation in final deliberations and voting on:	16.1.19. Nivolumab, relatlimab - OPDUALAG (CAP) - PSUSA/00011018 /202303
Sofia Trantza	Member	Greece	No interests declared	
Georgia Gkegka	Alternate	Greece	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Julia Pallos	Member	Hungary	No participation in final deliberations and voting on:	15.3.12. Idecabtagene vicleucel - ABECMA (CAP) - EMEA/H/C/004662/II/0031 , Orphan 16.1.12. Idecabtagene vicleucel - ABECMA (CAP) - PSUSA/00010954/202303 16.1.19. Nivolumab, relatlimab - OPDUALAG (CAP) - PSUSA/00011018/202303 17.2.7. Mavacamten - CAMZYOS (CAP) - EMEA/H/C/005457/MEA 001 17.2.8. Mavacamten - CAMZYOS (CAP) - EMEA/H/C/005457/MEA 002
Melinda Palfi	Alternate	Hungary	No interests declared	
Guðrún Stefánsdóttir	Member	Iceland	No restrictions applicable to this meeting	
Rhea Fitzgerald	Member	Ireland	No interests declared	
Eamon O Murchu	Alternate	Ireland	No interests declared	
Amelia Cupelli	Member	Italy	No interests declared	
Valentina Di Giovanni	Alternate	Italy	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Zane Neikena	Member	Latvia	No interests declared	
Rugile Pilviniene	Member	Lithuania	No interests declared	
Lina Seibokiene	Alternate	Lithuania	No restrictions applicable to this meeting	
Nadine Petitpain	Member	Luxembourg	No restrictions applicable to this meeting	
John Joseph Borg	Member	Malta	No interests declared	
Benjamin Micallef	Alternate	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:	16.3.4. Dienogest, ethinylestradiol (NAP) - PSUSA/00001057/202303
Pernille Harg	Alternate	Norway	No interests declared	
Adam Przybylkowski	Member	Poland	No interests declared	
Katarzyna Ziolkowska	Alternate	Poland	No interests declared	
Ana Sofia Diniz Martins	Member	Portugal	No interests declared	
Roxana Dondera	Member	Romania	No interests declared	
Irina Sandu	Alternate	Romania	No interests declared	
Anna Mareková	Member	Slovakia	No interests declared	
Miroslava Gocova	Alternate	Slovakia	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Milena Radoha-Bergoc	Alternate	Slovenia	No participation in final deliberations and voting on:	4.1.2. Esomeprazole - NEXIUM CONTROL (CAP); NAP
Maria del Pilar Rayon	Member	Spain	No interests declared	
Monica Martinez Redondo	Alternate	Spain	No interests declared	
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	
Patricia McGettigan	Member	Independent scientific expert	No interests declared	
Tania Schink	Member	Independent scientific expert	No participation in final deliberations and voting on:	4.3.3. Glucagon-like peptide-1 (GLP-1) receptor agonists: dulaglutide – TRULICITY (CAP) - EMEA/H/C/002825/SDA/014; exenatide – BYDUREON (CAP) - EMEA/H/C/002020/SDA/029, BYETTA (CAP) - EMEA/H/C/000698/SDA/049; insulin degludec, liraglutide – XULTOPHY (CAP) - EMEA/H/C/002647/SDA/005; liraglutide –

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				SAXENDA (CAP) - EMEA/H/C/003780/SDA/019, VICTOZA (CAP) - EMEA/H/C/001026/SDA/039; insulin glargine, lixisenatide – SULIQUA (CAP) - EMEA/H/C/004243/SDA/008; lixisenatide - LYXUMIA (CAP) - EMEA/H/C/002445/SDA/016; semaglutide – OZEMPIC (CAP) - EMEA/H/C/004174/SDA/007, RYBELSUS (CAP) - EMEA/H/C/004953/SDA/012, WEGOVY (CAP) - EMEA/H/C/005422/SDA/006 16.1.27. Solriamfetol - SUNOSI (CAP) - PSUSA/00010831/202303 17.2.9. Romosozumab - EVENITY (CAP) - EMEA/H/C/004465/MEA 001.7 17.2.10. Romosozumab - EVENITY (CAP) - EMEA/H/C/004465/MEA 002.7 17.2.11. Romosozumab - EVENITY (CAP) - EMEA/H/C/004465/MEA 003.5
Hedvig Nordeng	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
Roberto Frontini	Member	Healthcare Professionals' Representative	No participation in final deliberations and voting on:	16.3.6. Human plasma (NAP) - PSUSA/00001635 /202302
Salvatore Messana	Alternate	Healthcare Professionals' Representative	No interests declared	
Marko Korenjak	Alternate	Patients' Organisation Representative	No interests declared	
Laurence de Fays	Expert	Belgium	No interests declared	
Fabrice Moore	Expert	Belgium	No interests declared	
Melita Dumančić	Expert	Croatia	No restrictions applicable to this meeting	
Barbara Kovačić	Expert	Croatia	No interests declared	
Petar Mas	Expert	Croatia	No interests declared	
Marian Hjortlund Allon	Expert	Denmark	No interests declared	
Hanna Belcik Christensen	Expert	Denmark	No restrictions applicable to this meeting	
Barbara Blicher Thomsen	Expert	Denmark	No interests declared	
Alexander Braathen	Expert	Denmark	No interests declared	
Pernille Lynge Gammelgaard	Expert	Denmark	No interests declared	
Nicklas Hasselblad Lundstrøm	Expert	Denmark	No interests declared	
Kirsten Egebjerg Juul	Expert	Denmark	No interests declared	
Irene Mandrup Krüger	Expert	Denmark	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Kristina Laursen	Expert	Denmark	No interests declared	
Torsten Holm Nielsen	Expert	Denmark	No restrictions applicable to this meeting	
Helle Gerda Olsen	Expert	Denmark	No interests declared	
Moritz Sander	Expert	Denmark	No interests declared	
Aynur Sert	Expert	Denmark	No interests declared	
Per Sindahl	Expert	Denmark	No interests declared	
Helene Stenbæk Hansen	Expert	Denmark	No restrictions applicable to this meeting	
Camille de-Kervasdoue	Expert	France	No interests declared	
Stéphanie Hueber	Expert	France	No interests declared	
Mariem Loukil	Expert	France	No interests declared	
Juliette Maupu	Expert	France	No interests declared	
Thomas Grueger	Expert	Germany	No interests declared	
Dennis Lex	Expert	Germany	No interests declared	
Diāna Inga Paegle	Expert	Latvia	No interests declared	
Talip Eroglu	Expert	Netherlands	No interests declared	
Lisa Heltzel	Expert	Netherlands	No interests declared	
Anita Volkers	Expert	Netherlands	No interests declared	
Inge Zomerdijk	Expert	Netherlands	No interests declared	
Carla Torre	Expert	Portugal	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Natividad Galiana	Expert	Spain	No restrictions applicable to this meeting	
Consuelo Mejías	Expert	Spain	No interests declared	
Miguel del Rey	Expert	Spain	No interests declared	
Charlotte Backman	Expert	Sweden	No interests declared	
Kristina Magnusson-Lundqvist	Expert	Sweden	No interests declared	
Karin Mathold	Expert	Sweden	No interests declared	
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: Abbreviations in CXMP and CMD documents and in relation to EMA regulatory activities (europa.eu)

21. Explanatory notes

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

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

(Items 2 and 3 of the PRAC minutes)

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

Signals assessment and prioritisation

(Item 4 of the PRAC minutes)

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

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

Risk Management Plans (RMPs)
(Item 5 of the PRAC minutes)

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

Assessment of Periodic Safety Update Reports (PSURs)
(Item 6 of the PRAC minutes)

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

Post-authorisation Safety Studies (PASS)
(Item 7 of the PRAC minutes)

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

Product related pharmacovigilance inspections
(Item 9 of the PRAC minutes)

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

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