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Human Medicines Division

Pharmacovigilance Risk Assessment Committee (PRAC)

Minutes of the meeting on 07-10 June 2022

Chair: Sabine Straus – Vice-Chair: Martin Huber

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

Note on access to documents

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

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1. Introduction

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

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

In accordance with the Agency's policy on handling of declarations of interests of scientific Committees' members and experts, based on the declarations of interest submitted by the Committee members, alternates and experts and on the topics in the agenda of the meeting, the Committee Secretariat announced 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.

The EMA Secretariat announced the names of the Committee members who delegated their vote via proxy and the Committee members who received such proxy.

1.2. Agenda of the meeting on 07-10 June 2022

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

1.3. Minutes of the previous meeting on 02-05 May 2022

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

Post-meeting note: the PRAC minutes of the meeting held on 02-05 May 2022 were published on the EMA website on 06 February 2023 (EMA/PRAC/955173/2022).

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

2.1. Newly triggered procedures

None

2.2. Ongoing procedures

None

2.3. Procedures for finalisation

None

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

3.1. Newly triggered procedures

None

3.2. Ongoing procedures

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

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

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

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

Background

A referral procedure under Article 20 of Regulation (EC) No 726/2004 is ongoing for Janus kinase inhibitors (JAKi), namely Xeljanz (tofacitinib), Cibinqo (abrocitinib), Olumiant (baricitinib), Jyseleca (filgotinib) and Rinvoq (upadacitinib) indicated in the treatment of several chronic inflammatory disorders such as rheumatoid arthritis, atopic dermatitis, psoriatic arthritis, juvenile idiopathic arthritis, ankylosing spondylitis and ulcerative colitis. The procedure was initiated following the release of the final results from study A3921133[2] (ORAL surveillance) for Xeljanz (tofacitinib) showing an increase incidence of major adverse cardiovascular events (MACE), a higher risk of malignancy with tofacitinib compared to tumour necrosis fibrosis (TNF)-inhibitors in patients with rheumatoid arthritis, as well as a higher incidence of venous thromboembolism (VTE), all-cause of mortality and serious infections in patients treated with tofacitinib compared to TNF-inhibitors. In addition, preliminary results from study I4V-MC-B023[3] for Olumiant (baricitinib) suggested an increased risk of MACE and VTE in patients with rheumatoid arthritis treated with Olumiant

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

(baricitinib) compared to those treated with TNF-inhibitors. For further background, see PRAC minutes February 2022.

Summary of recommendation(s)/conclusions

- PRAC discussed the assessment reports issued by the Rapporteurs.
- PRAC indicated the possible class effect of the safety concerns from long term use of JAKi under review in the current procedure that may impact indications newly approved or currently under assessment by CHMP, namely treatments of ulcerative colitis and non-radiographic axial spondylarthritis for Rinvoq (upadacitinib) as well as treatment of alopecia areata for Olumiant (baricitinib).

The European Commission (EC) extended the scope of the ongoing referral procedure under Article 20 of Regulation (EC) No 726/2004 to review also the impact of the safety concerns of these indications. See addendum to the notification.

- PRAC adopted a list of outstanding issues (LoOI) to be addressed by the MAHs of JAKi-containing products in accordance with a revised timetable (EMA/PRAC/68282/2022 Rev 1).
- PRAC also agreed on the need to convene an ad-hoc expert group (AHEG). PRAC adopted a list of questions (LoQ) to the AHEG.

3.2.2. Terlipressin[4] (NAP) - EMEA/H/A-31/1514

Applicant(s): various

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

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

Background

A referral procedure under Article 31 of Directive 2001/83/EC is ongoing for the review of terlipressin-containing product(s) indicated in the treatment of hepatorenal syndrome (HRS). This procedure was initiated following the assessment of the results from a large clinical trial CONFIRM[5] involving patients with type 1 HRS within the PSUR single assessment (PSUSA) procedure on terlipressin (PSUSA/00002905/202104) concluded in December 2021[6] that raised serious safety concerns due to an increased risk of respiratory failure in patients treated with terlipressin, sometimes with fatal outcome, within 90 days after the first dose compared to those who were given a placebo. For further background, see PRAC minutes January 2022 and PRAC minutes April 2022.

Summary of recommendation(s)/conclusions

- PRAC adopted a revised timetable to reflect the date of the ad-hoc expert group (AHEG) scheduled on 13 June 2022 (EMA/PRAC/2205/2022 rev2).
- PRAC agreed on the list of participants (LoP) for the AHEG.

[4] Indicated in the treatment of hepatorenal syndrome (HRS)
[5] Wong F, et al. Terlipressin plus albumin for the treatment of type 1 hepatorenal syndrome. N Engl J Med. 2021 Mar 4;384(9):818-828. doi: 10.1056/NEJMoa2008290
[6] Held on 29 November – 02 December 2021

3.3. Procedures for finalisation

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

Applicants: Artegodan GmbH, Temmler Pharma GmbH

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

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

Background

A referral procedure under Article 31 of Directive 2001/83/EC for the review of the benefit-risk balance of amfepramone-containing products is to be concluded. This procedure was initiated due to the known serious safety concerns related to the therapeutic class of anorexigens, the cases of cardiac-related adverse drug reactions and cases of pulmonary hypertension reported with amfepramone, and the off-label use despite the risk minimisation measures in place, taking also into account the uncertainties as to clinical relevance of this treatment. For further background, see PRAC minutes February 2021, PRAC minutes July 2021, PRAC minutes October 2021[7] and PRAC minutes November 2021[8].

Discussion

PRAC discussed the conclusion reached by the Rapporteurs.

PRAC reviewed all available data in relation to the safety concerns of pulmonary, cardiac, cerebrovascular, neuropsychiatric diseases, drug dependence and use in pregnancy, as well as the effectiveness of the risk minimisation measures in place in the context of the efficacy of amfepramone in patients with obesity. This included the responses submitted by the MAHs in writing and during a joint oral explanation, results from two observational studies performed in the German and the Danish population, as well as the views expressed by a group of independent experts (ad-hoc expert group (AHEG)) convened in October 2021 in the context of this procedure.

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

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

PRAC also noted the results of the observational studies and information from spontaneous post-marketing reports showing an unacceptable level of non-adherence to the current measures aimed at minimising the risks of treatment with amfepramone in patients at higher risk of developing adverse drug reactions and the risks known to increase with the treatment duration. PRAC considered that this raised important public health concerns. Therefore, PRAC concluded that those measures have not been effective in adequately minimising the risks of treatment with amfepramone.

[7] Held on 27-30 September 2021
[8] Held on 25-28 October 2021

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

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

Furthermore, PRAC could not identify any condition, the fulfilment of which would demonstrate a positive benefit-risk balance for amfepramone-containing products in a defined patient population.

As a consequence, PRAC considered that the benefit-risk balance of amfepramone-containing products is not favourable and recommended the revocation of the marketing authorisations of all amfepramone-containing products.

Summary of recommendation(s)/conclusions

- PRAC adopted a recommendation, by majority, to revoke the marketing authorisations for amfepramone-containing products to be considered by CMDh for a position – see EMA Press Release entitled 'EMA recommends withdrawal of marketing authorisation for amfepramone medicines' (EMA/574597/2022).
- PRAC agreed on the content of a direct healthcare professional communication (DHPC) along with a communication plan for its distribution.

Thirty members voted in favour of the recommendation whilst two members[9] had divergent views[10]. The Icelandic and Norwegian PRAC members agreed with the recommendation.

Post-meeting note: Following the adoption of this recommendation, the MAHs of amfepramone-containing products have requested its re-examination. See PRAC minutes September 2022[11].

3.4. Re-examination procedures[12]

None

3.5. Others

None

[9] Eva Jirsová, Anette Kirstine Stark
[10] The relevant AR containing the divergent views will be published on the EMA website once the procedure is fully concluded
[11] Held 29 August – 01 September 2022
[12] Re-examination of PRAC recommendation under Article 32 of Directive 2001/83/EC

4. Signals assessment and prioritisation[13]

4.1. New signals detected from EU spontaneous reporting systems

See also Annex I 14.1.

4.1.1. Adalimumab - AMGEVITA (CAP), AMSPARITY (CAP), HEFIYA (CAP), HUMIRA (CAP), HULIO (CAP), HUKYNDRA (CAP), HYRIMOZ (CAP), IDACIO (CAP), IMRALDI (CAP), LIBMYRIS (CAP), YUFLYMA (CAP)

Applicants: AbbVie Deutschland GmbH (Humria), Amgen Europe B.V.(Amgevita), Celltrion Healthcare Hungary Kft. (Yuflyma), Fresenius Kabi Deutschland GmbH (Idacio), Pfizer Europe MA EEIG (Amsparity), Sandoz GmbH (Hyrimoz, Hefiya), Samsung Bioepis NL B.V. (Imraldi), Stada Arzneimittel AG (Hukyndra, Libmyris), Viatris Limited (Hulio)

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of menstrual disorder

EPITT 19812 – New signal

Lead Member State(s): SE

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 menstrual disorder was identified by the Netherlands, based on 13 cases retrieved from national spontaneous reporting system. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by PRAC.

Discussion

Having considered the available evidence from EudraVigilance and the literature, PRAC agreed the signal deserves further analysis and the evaluation should be extended to all tumour necrosis factor alpha (TNFα) inhibitors-containing medicine(s).

Summary of recommendation(s)

- The MAHs for Humira (adalimumab), Remicade (infliximab) and Enbrel (etanercept) should submit to EMA, within 90 days, a cumulative review of menstrual cycle and uterine bleeding disorders in association with adalimumab, infliximab or etanercept, respectively, including a discussion on the biological plausibility for a causal association between the signal and the active substances mentioned above. The MAH should provide data from clinical trials, observational studies and literature, as well as post-marketing data. The MAHs should also discuss the need for risk minimisation measures, including a proposal to update the product information and/or the RMP as warranted.
- A 90-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

[13] 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

4.1.2. Codeine, ibuprofen (NAP)

Applicant(s): various

PRAC Rapporteur: Rhea Fitzgerald

Scope: Signal of renal tubular acidosis and hypokalaemia

EPITT 19820 – New signal

Lead Member State(s): IE

Background

Codeine is an opioid analgesic and ibuprofen a non-steroidal anti-inflammatory drug. In combination, they are indicated in patients older than 12 years of age for the short-term treatment of acute, moderate pain which is not relieved by other analgesics alone, such as rheumatic and muscular pain, backache, neuralgia, migraine, headache, dental pain, dysmenorrhoea, toothache, and symptoms of the common cold and influenza.

During routine signal detection activities, a signal of renal tubular acidosis and hypokalaemia was identified by Ireland, based on 9 cases retrieved from EudraVigilance. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by PRAC.

Discussion

Having considered the available evidence from EudraVigilance and the literature, PRAC agreed that further review is warranted and there is a need to request further data from relevant MAH(s).

PRAC appointed Rhea Fitzgerald as Rapporteur for the signal.

Summary of recommendation(s)

- The originator MAHs for codeine/ibuprofen-containing products (Reckitt Benckiser and Mylan) should submit to EMA, within 60 days, a cumulative review of the signal from all sources, including literature and post-marketing case reports. The MAHs should also discuss the inclusion of a warning on the outer label packaging related to the ibuprofen component as a result of dependence on and chronic abuse of the codeine/ibuprofen products and to provide proposals for updates to the outer label. In addition, the MAHs should include a discussion on the proposed amendments to the product information, as well as a proposal for a direct healthcare professional communication (DHPC) and a communication plan.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.1.3. Ipilimumab - YERVOY (CAP); nivolumab - OPDIVO (CAP)

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Signal of pure red cell aplasia and aplastic anaemia

EPITT 19804 – New signal

Lead Member State(s): DE, NL

Background

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

During routine signal detection activities, a signal of pure red cell aplasia and aplastic anaemia (PRCA) was identified by EMA, based on 52 cases of PRCA retrieved from EudraVigilance, namely 36 cases in association with nivolumab and 16 cases with ipilimumab. The Rapporteurs confirmed that the signal needed initial analysis and prioritisation by PRAC.

Discussion

Having considered the available evidence, including data from EudraVigilance and the literature, PRAC agreed that the signal should be further investigated and requested further data from the MAH.

PRAC appointed Brigitte Keller-Stanislawski as Rapporteur for the signal.

Summary of recommendation(s)

- The MAH for Opdivo (nivolumab) and Yervoy (ipilimumab) should submit to EMA, within 60 days, a cumulative review of cases of PRCA and aplastic anaemia (AA)[14] in association with ipilimumab and nivolumab (stratified by monotherapies and combination therapy), including post-marketing data, clinical trials and relevant literature data. The MAH should also discuss The MAH should also discuss the need for risk minimisation measures, including a proposal to update the product information and/or the RMP as warranted.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.2. New signals detected from other sources

See Annex I 14.2.

4.3. Signals follow-up and prioritisation

4.3.1. Elasomeran - SPIKEVAX (CAP) - EMEA/H/C/005791/SDA/058

Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Signal of amenorrhea

EPITT 19781 – Follow-up to February 2022

Background

For background information, see PRAC minutes February 2022.

[14] According to late-breaking publication which warrants the extension of scope to aplastic anaemia: Younan RG, Raad RA, Sawan BY, Said R. Aplastic anemia secondary to dual cancer immunotherapies a physician nightmare: case report and literature review. Allergy Asthma Clin Immunol. 2021;17(1):112. Published 2021 Oct 26. doi:10.1186/s13223-021-00616-4

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

Discussion

Having considered the data submitted by the MAH for Spikevax (elasomeran) and the Rapporteur's assessment, PRAC concluded that the current evidence is insufficient to warrant an update to the product information at present.

Summary of recommendation(s)

- The MAH for Spikevax (elasomeran) should continue to monitor cases of amenorrhea.
- In the next PSUR, the MAH should submit to EMA, an updated analysis of cases of amenorrhea following vaccination with Spikevax (elasomeran) including a review of literature and case reports.

4.3.2. Elasomeran - SPIKEVAX (CAP) - EMEA/H/C/005791/SDA/059

Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Signal of heavy menstrual bleeding

EPITT 19780 – Follow-up to February 2022

Background

For background information, see PRAC minutes February 2022.

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

Discussion

Having considered the data submitted by the MAH and the Rapporteur's assessment, PRAC agreed that further assessment of the signal is warranted before a conclusion can be drawn.

Summary of recommendation(s)

- The MAH for Spikevax (elasomeran) should submit to EMA, within 60 days, an updated cumulative review of heavy menstrual bleeding post-vaccination and discuss the need to update the product information and/or RMP as warranted.

4.3.3. Gemtuzumab ozogamicin – MYLOTARG (CAP) - EMEA/H/C/004204/SDA/005

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Signal of atypical haemolytic reactions

EPITT 19788 – Follow-up to April 2022

Background

For background information, see PRAC minutes April 2022.

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

Discussion

Having considered the available evidence from EudraVigilance and the literature, including data provided by the MAH together with the Rapporteur's assessment, PRAC agreed that further assessment of the signal is warranted before a conclusion can be drawn.

Summary of recommendation(s)

- The MAH for Mylotarg (gemtuzumab ozogamicin) should submit to EMA, within 60 days, a further review of cases reporting haemolytic reaction of all grades, with more detailed information of clinical and laboratory findings. The MAH should also discuss the importance of following plasma lactate dehydrogenase levels in gemtuzumab ozogamicin-treated patients. Moreover, the possible mechanism of action leading to atypical haemolytic reactions should be discussed. Finally, the MAH should propose to update the product information and/or RMP as warranted.
- A 60 day-timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.3.4. Human normal immunoglobulin[15] – FLEBOGAMMA DIF (CAP) - EMEA/H/C/000781/SDA/025, KIOVIG (CAP) - EMEA/H/C/000628/SDA/042, PRIVIGEN (CAP) - EMEA/H/C/000831/SDA/033; NAP

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

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Signal of thrombocytopenia

EPITT 19764 – Follow-up to January 2022

Background

For background information, see PRAC minutes January 2022.

The MAHs for human normal immunoglobulin (IG)-containing products for intravenous (IV) use replied to the request for information on the signal of thrombocytopenia and the responses were assessed by the Rapporteur.

Discussion

Having considered the available data including the MAHs' reviews and the Rapporteur's assessment, PRAC agreed that at this stage there is insufficient evidence to conclude on a relationship between thrombocytopenia and IV-IG therapy due to the rarity of cases of thrombocytopenia with a temporal association with IV-IG/IG treatment, multiple confounding factors and the lack of a consistent explanation for these cases. Therefore, PRAC concluded that no regulatory action is warranted at this stage.

Summary of recommendation(s)

[15] For intravenous use only

- The MAHs of human normal IG-containing products for IV use should continue to monitor cases of thrombocytopenia as part of routine safety surveillance.

4.3.5. Tozinameran - COMIRNATY (CAP) - EMEA/H/C/005735/SDA/052

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: David Olsen

Scope: Signal of amenorrhea

EPITT 19784 – Follow-up to February 2022

Background

For background information, see PRAC minutes February 2022.

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

Discussion

Having considered the data submitted by the MAH for Comirnaty (tozinameran) and the Rapporteur's assessment, PRAC concluded that the current evidence is insufficient to warrant an update to the product information at present.

Summary of recommendation(s)

- The MAH for Comirnaty (tozinameran) should continue to monitor cases of amenorrhea.
- In the next PSUR, the MAH should submit to EMA an updated analysis of cases of amenorrhea following vaccination with Comirnaty (tozinameran) including a review of literature and case reports.

4.3.6. Tozinameran - COMIRNATY (CAP) - EMEA/H/C/005735/SDA/053

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: David Olsen

Scope: Signal of heavy menstrual bleeding

EPITT 19783 – Follow-up to February 2022

Background

For background information, see PRAC minutes February 2022.

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

Discussion

Having considered the data submitted by the MAH and the Rapporteur's assessment, PRAC agreed that further assessment of the signal is warranted before a conclusion can be drawn.

Summary of recommendation(s)

- The MAH for Comirnaty (tozinameran) should submit to EMA, within 60 days, an updated cumulative review of heavy menstrual bleeding post-vaccination and discuss the need to update the product information and/or RMP as warranted.

4.4. Variation procedure(s) resulting from signal evaluation

None

5. Risk management plans (RMPs)

5.1. Medicines in the pre-authorisation phase

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

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

See also Annex I 15.1.

5.1.1. Coronavirus (COVID-19) vaccine (inactivated, adjuvanted, adsorbed) - EMEA/H/C/006019

Scope: Active immunisation for prevention of coronavirus disease-2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 18 years of age and older

5.1.2. Coronavirus (COVID-19) vaccine (recombinant, adjuvanted) - EMEA/H/C/005754

Scope: Active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2 virus), in individuals 18 years of age and older

5.1.3. Iodine (^{131}I) omburtamab - EMEA/H/C/005499, Orphan

Applicant: Y-Mabs Therapeutics A/S

Scope: Treatment of neuroblastoma

5.1.4. Maralixibat - EMEA/H/C/005857, Orphan

Applicant: Mirum Pharmaceuticals International B.V.

Scope: Treatment of cholestatic liver disease in patients with Alagille syndrome (ALGS) 1 year of age and older

5.1.5. Sutimlimab - EMEA/H/C/005776, Orphan

Applicant: Genzyme Europe BV

Scope: Treatment of haemolysis in adult patients with cold agglutinin disease (CAD)

5.1.6. Tirzepatide - EMEA/H/C/005620

Scope: Treatment of adults with type 2 diabetes mellitus

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

See Annex I 15.2.

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

See also Annex I 15.3.

5.3.1. Crizotinib - XALKORI (CAP) - EMEA/H/C/002489/II/0072

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Tiphaine Vaillant

Scope: Extension of indication to include treatment of paediatric patients aged ≥ 6 to < 18 years with relapsed or refractory systemic anaplastic lymphoma kinase (ALK)-positive anaplastic large cell lymphoma (ALCL) and with unresectable, recurrent, or refractory ALK-positive inflammatory myofibroblastic tumour (IMT) based on the results from: 1) study ADVL0912: a phase 1/2 study of crizotinib, an oral small molecule inhibitor of ALK and C-Met, in children with relapsed/refractory solid tumours and anaplastic large cell lymphoma; 2) study A8081013: a phase 1b open-label study of the safety and clinical activity of crizotinib in tumours with genetic events involving the ALK gene locus. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 8.0) are updated in accordance. In addition, the MAH took the opportunity to update the anatomical therapeutic chemical (ATC) code for crizotinib. Moreover, the MAH took the opportunity to implement a minor change in the list of local representatives in the package leaflet

Background

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

CHMP is evaluating an extension of the therapeutic indication for Xalkori, a centrally authorised product containing crizotinib, to include treatment of paediatric patients aged ≥6 to <18 years with relapsed or refractory systemic anaplastic lymphoma kinase (ALK)-positive anaplastic large cell lymphoma (ALCL) and with unresectable, recurrent, or refractory ALK-positive inflammatory myofibroblastic tumour (IMT). PRAC is responsible for providing advice to CHMP on the necessary updates to the RMP to support this extension of indication. For further background, see PRAC minutes September 2021[16] and PRAC minutes February 2022.

Summary of advice

- The RMP version 8.2 for Xalkori (crizotinib) in the context of the variation under evaluation by CHMP was considered acceptable.

[16] Held on 30 August – 02 September 2021

- PRAC supported the MAH's proposal to add 'bone toxicities and impaired bone growth' in the paediatric population and 'severe vision loss/potential sight threatening event' as important potential risks in the list of safety concerns, as well as the proposed additional pharmacovigilance activities to address these safety concerns.
- PRAC also agreed on the need and on the content of a direct healthcare professional communication (DHPC) along with a communication plan for its distribution.

5.3.2. Dexamethasone - NEOFORDEX (CAP) - EMEA/H/C/004071/II/0017/G

Applicant: Laboratoires CTRS

PRAC Rapporteur: Tiphaine Vaillant

Scope: Grouped variations consisting of: 1) submission of an updated RMP (version 4.3) to remove the score line for sub-division of the 40 mg tablet (as a completion of a category 3 activity) and consequent deletion of the 20 mg posology, including a direct healthcare professional communication (DHPC); 2) other quality variations. In addition, the MAH used the opportunity to update sections from Module 3 of the dossier with 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.

CHMP is evaluating a type II variation for Neofordex, a centrally authorised product containing dexamethasone, to remove the score line for sub-division of the 40 mg tablet (as a completion of a category 3 activity) and consequent deletion of the 20 mg posology, including a direct healthcare professional communication (DHPC). PRAC is responsible for providing advice to CHMP on the necessary updates to the RMP to support this type II variation. For further background, see PRAC minutes May 2022.

Summary of advice

- The RMP version 4.3 for Neofordex (dexamethasone) in the context of the variation under evaluation by CHMP was considered acceptable.
- PRAC agreed with the MAH proposal to add a warning sticker to the outer packaging in order to further highlight the removal of the score-line.
- PRAC also agreed on the need and on the content of a direct healthcare professional communication (DHPC) along with a communication plan for its distribution.

5.3.3. Dupilumab - DUPIXENT (CAP) - EMEA/H/C/004390/II/0060

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Kimmo Jaakkola

Scope: Extension of indication to include treatment of atopic dermatitis in paediatric patients from 6 months to <6 years of age based on final results from study R668-AD-1539: a phase 2/3 study investigating the pharmacokinetics, safety, and efficacy of dupilumab in patients aged ≥6 months to <6 years with moderate-to-severe atopic dermatitis. As a consequence, sections 4.1, 4.2, 4.8, 5.1, 5.2 of the SmPC are updated. The package leaflet and the RMP (version 7.0) are updated in accordance

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 Dupixent, a centrally authorised product containing dupilumab, to include treatment of atopic dermatitis in paediatric patients from 6 months to <6 years of age based on final results from study R668-AD-1539. PRAC is responsible for providing advice to CHMP on the necessary updates to the RMP to support this extension of indication.

Summary of advice

- The RMP for Dupixent (dupilumab) in the context of the variation under evaluation by CHMP was considered acceptable provided that an update to RMP version 7.0 is submitted.
- PRAC considered that 'long-term effects, including paediatric patients' should be added as missing information in the summary of safety concerns. The MAH should discuss the limited data on the youngest age group with still immature immune system, especially in the 6 months to 1-2 years of age and to propose an additional pharmacovigilance activity to address this new safety concern.

5.3.4. Ibrutinib - IMBRUVICA (CAP) - EMEA/H/C/003791/II/0070

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Extension of the existing indication on chronic lymphocytic leukaemia (CLL) to include combination treatment with venetoclax for previously untreated patients based on efficacy and safety data from: 1) study GLOW: a phase 3 trial testing ibrutinib and venetoclax for people with untreated CLL or small lymphocytic lymphoma (SLL); 2) study PCYC-1142-CA (CAPTIVATE): a phase 2 study of the combination of ibrutinib plus venetoclax in subjects with treatment-naïve CLL/SLL. As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated in accordance. The package leaflet and the RMP (version 18.4) are updated accordingly. In addition, the MAH included a justification to support one year-extension of the marketing protection period

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 Imbruvica, a centrally authorised product containing ibrutinib, to amend the existing indication on chronic lymphocytic leukaemia (CLL) to include combination treatment with venetoclax for previously untreated patients based on efficacy and safety data. PRAC is responsible for providing advice to CHMP on the necessary updates to the RMP to support this extension of indication. For further background, see PRAC minutes March 2022.

Summary of advice

- The RMP for Imbruvica (ibrutinib) in the context of the variation procedure under evaluation by CHMP could be considered acceptable provided that an update to RMP version 18.4 and satisfactory responses to the request for supplementary information (RSI) are submitted.
- PRAC supported the MAH's proposal to conduct an observational, retrospective cohort study to better characterize ibrutinib use in patients with severe cardiac disease utilising the approach of real-world data analyses in addition to a comprehensive literature review. Nevertheless, the MAH should submit the protocol for this non-imposed study, to allow for further assessment of the proposed objectives and methods. Additionally, considering the existing concerns regarding sudden cardiac death following the use of ibrutinib, PRAC concluded that the study population should not be limited to those with existing severe cardiac disease and that an appropriate control group should be defined. Moreover, PRAC considered that the occurrence and characterisation of adverse reactions in these patients with severe cardiac failure during ibrutinib treatment should be included as a study objective and that the study should also capture the outcome in these patients. Furthermore, the study should foresee a long follow-up period due to possible occurrence of cardiac adverse reactions several years after starting treatment with ibrutinib. PRAC also considered that the MAH should discuss the need to measure effectiveness of risk minimisation measures (RMM) in a drug utilisation study (DUS).
- PRAC considered that there is a need for a direct healthcare professional communication (DHPC) in order to communicate to healthcare professionals new information on the extent of the cardiac risk, risk factors and actionable advice. The MAH should also propose a DHPC for further assessment.

5.3.5. Mercaptamine - PROCYSBI (CAP) - EMEA/H/C/002465/X/0035, Orphan

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension application to introduce a new pharmaceutical form associated with two new strengths (75 and 300 mg gastro-resistant granules). The RMP (version 7.2) is updated in accordance

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 application for Procysbi, a centrally authorised product containing mercaptamine, to introduce a new pharmaceutical form associated with two new strengths (75 and 300 mg gastro-resistant granules). PRAC is responsible for providing advice to CHMP on the necessary updates to the RMP to support this extension application. For further background, see PRAC minutes November 2021[17] and PRAC minutes April 2022.

Summary of advice

[17] Heldon 25-28 October 2021

- The RMP for Procysbi (mercaptamine) in the context of the variation under evaluation by CHMP could be considered acceptable provided that an update to RMP version 7.3 is submitted.
- PRAC considered that encephalopathy and Ehlers-Danlos-like syndrome should be removed from the list of safety concerns, as they are sufficiently addressed in the product information. Taking into account that the treatment with Procysbi (mercaptamine) is to be initiated under the supervision of a physician experienced in the treatment of cystinosis and that the medicinal product is prescribed and available for patients' treatment for a considerable amount of time, PRAC considered that routine risk minimisation are sufficient to minimise the risks and agreed with the removal of the educational material for physicians from the RMP and Annex II-D on 'Conditions or restrictions with regard to the safe and effective use of the medicinal product' accordingly.

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. Alglucosidase alfa - MYOZYME (CAP) - PSUSA/00000086/202109

Applicant: Genzyme Europe BV

PRAC Rapporteur: Nathalie Gault

Scope: Evaluation of a PSUSA procedure

Background

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

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Myozyme, a centrally authorised medicine containing alglucosidase 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 Myozyme (alglucosidase alfa) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add dyspepsia, dysphagia, transient skin discoloration, blister, palmar erythema, infusion site erythema, infusion site urticaria and hypoxia as undesirable effects with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[18].

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

- At the next regulatory opportunity[19], the MAH should update the RMP to reflect the risks of medication errors and of off-label use in home infusion setting.

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

6.1.2. Aliskiren - RASILEZ (CAP); aliskiren, hydrochlorothiazide - RASILEZ HCT[20] - PSUSA/00000089/202109

Applicant: Noden Pharma DAC

PRAC Rapporteur: Amelia Cupelli

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 Rasilez and Rasilez HCT, a centrally authorised medicine containing aliskiren and a medicine containing aliskiren/hydrochlorothiazide respectively, and issued a recommendation on the marketing authorisation(s) of Rasilez (aliskiren).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Rasilez (aliskiren) and Rasilez HCT (aliskiren/hydrochlorothiazide) 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 abdominal pain, asthenia, fatigue, malaise, aphasia, cerebrovascular accident, dysarthria, anxiety and of confusional state.

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

6.1.3. Alpelisib - PIQRAY (CAP) - PSUSA/00010871/202111

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

Background

[19] And no later than September 2022
[20] European Commission (EC) decision on the withdrawal of the marketing authorisation (MA) for Rasilez HCT dated 20 December 2021

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 Piqray, a centrally authorised medicine containing alpelisib 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 Piqray (alpelisib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add colitis and angioedema as undesirable effects with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[21].

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

6.1.4. Axicabtagene ciloleucel - YESCARTA (CAP) - PSUSA/00010703/202110

Applicant: Kite Pharma EU B.V., ATMP[22]

PRAC Rapporteur: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

Background

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

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Yescarta, a centrally authorised medicine containing axicabtagene ciloleucel 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 Yescarta (axicabtagene ciloleucel) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add status epilepticus as an undesirable effect with a frequency 'common'. Therefore, the current terms of the marketing authorisation(s) should be varied[23].
- In the next PSUR, the MAH should provide detailed reviews of cases of embolism venous, cardiomyopathy, pericardial disease, cardiogenic shock, respiratory failure and pleural disorders. In addition, the MAH should propose to update the product information and/or RMP as warranted. The proposal should include any additional risk

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

minimisation measures for patients with respiratory and/or cardiovascular disease as applicable.

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. Cefiderocol - FETCROJA (CAP) - PSUSA/00010849/202111

Applicant: Shionogi B.V.

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

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

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Fetcroja (cefiderocol) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add blood creatinine increased as an undesirable effect with a frequency 'common', blood urea increased with a frequency 'uncommon' and neutropenia with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[24].
- In the next PSUR, the MAH should review the PSUR summary of safety concerns in line with the PRAC request. In addition, the MAH should implement a targeted follow-up questionnaire to gather all available data from reporting healthcare professionals (HCPs) to further assess 'antibiotic resistance development' classified as an important potential risk.

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. Cobicistat, elvitegravir, emtricitabine, tenofovir alafenamide - GENVOYA (CAP) - PSUSA/00010449/202111

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

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

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 Genvoya, a centrally authorised medicine containing cobicistat/elvitegravir/ emtricitabine/tenofovir alafenamide 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 Genvoya (cobicistat/elvitegravir/emtricitabine/tenofovir alafenamide) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the existing warning on nephrotoxicity. Therefore, the current terms of the marketing authorisation(s) should be varied[25].
- In the next PSUR, the MAH should add 'increased cholesterol and triglycerides with associated cardiovascular events' to the PSUR list of safety concerns as an important potential risk.

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

PRAC considered that a (revised) warning on nephrotoxicity is also relevant for medicinal product(s) of other authorised fixed dose combination(s)-containing tenofofovir alafenamide. Further consideration is to be given at the level of PRAC/CHMP.

6.1.7. Daratumumab - DARZALEX (CAP) - PSUSA/00010498/202111

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Evaluation of a PSUSA procedure

Background

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

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

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

- The current terms of the marketing authorisation(s) should be maintained.
- The MAH should submit to EMA, within 90 days, a variation reviewing all data regarding ocular events, including a detailed causality assessment of all cases with an analysis of the underlying pathophysiological mechanism(s). This should include a proposal to update the product information.
- The MAH should submit to EMA, within 90 days, a variation reviewing all data regarding myocardial infarction, including a detailed an analysis of the possible underlying pathophysiological mechanism(s). The MAH should provide an assessment of any differences between subcutaneous/intravenous routes of administration and include a proposal to update the product information.
- In the next PSUR, the MAH should provide a cumulative review of cases of cytokine release syndrome (CRS) together with an evaluation of the potential causal relationship between daratumumab and CRS. The MAH should include a proposal to update the product information as warranted.

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

6.1.8. Denosumab[26] - PROLIA (CAP) - PSUSA/00000954/202109

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

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 Prolia, a centrally authorised medicine containing denosumab 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 Prolia (denosumab) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAH should provide a discussion on possible options to conduct an observational study to assess the incidence and prevalence of major osteoporotic fractures, including single and multiple vertebral fractures, after treatment discontinuation of Prolia (denosumab).

The frequency of PSUR submission should be revised from two-yearly to three-yearly and the next PSUR should be submitted to EMA within 90 days of the data lock point. The list of

[26] Indicated for osteoporosis and for bone loss associated with hormone ablation in prostate cancer only.

Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC is updated accordingly.

6.1.9. Durvalumab - IMFINZI (CAP) - PSUSA/00010723/202110

Applicant: AstraZeneca AB

PRAC Rapporteur: David Olsen

Scope: Evaluation of a PSUSA procedure

Background

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

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Imfinzi (durvalumab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add psoriasis as an undesirable effect with a frequency 'uncommon'. Therefore, the current terms of the marketing authorisation(s) should be varied[27].

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

6.1.10. Insulin glargine, lixisenatide - SULIQUA (CAP) - PSUSA/00010577/202111

Applicant: sanofi-aventis groupe

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

Background

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

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Suliqua, a centrally authorised medicine containing insulin glargine/lixisenatide and issued a recommendation on its marketing authorisation(s).

Summary of recommendation(s) and conclusions

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

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Suliqua (insulin glargine/lixisenatide) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add delayed gastric emptying as an undesirable effect with a frequency 'rare'. Therefore, the current terms of the marketing authorisation(s) should be varied[28].

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

PRAC considered that the risk of delayed gastric emptying is also relevant to medicinal product(s) containing lixisenatide as a single substance. Further consideration is to be given at the level of PRAC/CHMP.

6.1.11. Irinotecan[29] - ONIVYDE PEGYLATED LIPOSOMAL (CAP) - PSUSA/00010534/202110

Applicant: Les Laboratoires Servier

PRAC Rapporteur: David Olsen

Scope: Evaluation of a PSUSA procedure

Background

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

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Onivyde pegylated liposomal, a centrally authorised medicine containing irinotecan 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 Onivyde pegylated liposomal (irinotecan) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the existing warning on hypersensitivity reactions by adding anaphylactic/anaphylactoid reaction and angioedema as manifestations of hypersensitivity, as well as undesirable effects with a frequency 'not known'. In addition, pruritus, rash/urticaria and erythema should be added as undesirable effects with a frequency 'common', uncommon' and 'not known' respectively. Moreover, the product information should be updated to add a drug-drug interaction between irinotecan and flucytosine (as a prodrug for 5-fluorouracil). Therefore, the current terms of the marketing authorisation(s) should be varied[30].

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

[28] Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion.
[29] Liposomal formulation(s) only
[30] Update of SmPC sections 4.4, 4.5 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion.

6.1.12. Lopinavir, ritonavir - ALUVIA (Art 58[31]) - EMEA/H/W/000764/PSUV/0115

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Nathalie Gault

Scope: Evaluation of a PSUR procedure

Background

For background information on substance(s) and indication(s) of medicinal product(s) identified as 'Art 58', see Human medicine European public assessment report (EPAR) on the EMA website.

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Aluvia, a authorised medicine containing lopinavir/ritonavir and issued a recommendation on its opinion(s) on medicine for use outside the European Union.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Aluvia (lopinavir/ritonavir) in the approved indication(s) remains unchanged.
- The current terms of the opinion(s) should be maintained.
- The Opinion Holder should submit to EMA, within 90 days, a detailed review of cases of torsade de pointes and QT prolongation.
- In the next PSUR, the Opinion Holder should provide a review of cases reporting a fatal outcome.

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.

6.1.13. Lopinavir, ritonavir - KALETRA (CAP) - PSUSA/00001905/202109

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Nathalie Gault

Scope: Evaluation of a PSUSA procedure

Background

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

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

Summary of recommendation(s) and conclusions

[31] Article 58 of Regulation (EC) No 726/2004 allows the Committee for Medicinal Products for Human Use (CHMP) to give opinions, in co-operation with the World Health Organisation (WHO) on medicinal products for human use that are intended exclusively for markets outside of the European Union (EU).

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Kaletra (lopinavir/ritonavir) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- The MAH should submit to EMA, within 90 days, a detailed review of cases of torsade de pointes and QT prolongation.
- In the next PSUR, the MAH should provide a review of cases reporting a fatal outcome.

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.

6.1.14. Onasemnogene abeparvovec - ZOLGENSMA (CAP) - PSUSA/00010848/202111

Applicant: Novartis Gene Therapies EU Limited, ATMP[32]

PRAC Rapporteur: Ulla Wändel Liminga

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 Zolgensma, a centrally authorised medicine containing onasemnogene abeparvovec 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 Zolgensma (onasemnogene abeparvovec) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include information on the severity of thrombocytopenia and further details on the temporal relationship concerning thrombocytopenia and transient thrombocytopenia. Therefore, the current terms of the marketing authorisation(s) should be varied[33].
- In the next PSUR, the MAH should further categorise patients affected by thrombotic microangiopathy (TMA), acute liver failure and severe thrombocytopenia. The MAH should also carefully monitor emerging non-clinical and clinical data related to whether adeno-associated virus serotype 9 (AAV9)-mediated survival motor neuron (SMN) protein expression could result in neurotoxicity.

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.

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

6.1.15. Para-aminosalicylic acid[34] - GRANUPAS (CAP) - PSUSA/00010171/202110 (with RMP)

Applicant: Eurocept International B.V.

PRAC Rapporteur: Ulla Wändel Liminga

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 Granupas, a centrally authorised medicine containing para-aminosalicylic acid 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 Granupas (para-aminosalicylic acid) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add the interaction between para-aminosalicylic acid calcium and tenofovir that can lead to a decrease of tenofovir exposure. Therefore, the current terms of the marketing authorisation(s) should be varied[35].

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

6.1.16. Remdesivir - VEKLURY (CAP) - PSUSA/00010840/202111

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Eva Jirsová

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

[34] Centrally authorised product(s) only
[35] Update of SmPC section 4.5. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion.

- 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[36].
- In the next PSUR, the MAH should update the PSUR list of safety concerns in line with the PRAC recommendation. In addition, the MAH should provide a detailed review of cases reporting possible drug-drug interactions with remdesivir together with a review of the published literature. In addition, the MAH should closely monitor any new cases of pancreatitis. Finally, the MAH should provide a review on treatment failure due to emerging severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants.

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.

6.1.17. Rituximab - BLITZIMA (CAP); MABTHERA (CAP); RIXATHON (CAP); RIXIMYO (CAP); RUXIENCE (CAP); TRUXIMA (CAP) - PSUSA/00002652/202111 (without RMP)

Applicants: Celltrion Healthcare Hungary Kft. (Blitzima, Truxima), Pfizer Europe MA EEIG (Ruxience), Roche Registration GmbH (MabThera), Sandoz GmbH (Rixathon, Riximyo)

PRAC Rapporteur: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

Background

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

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Blitzima, Mabthera, Rixathon, Riximyo, Ruxience and Truxima, centrally authorised medicines containing rituximab 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 Blitzima, Mabthera, Rixathon, Riximyo, Ruxience and Truxima (rituximab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the existing warning on breastfeeding and to add serious viral infections as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[37].
- In the next PSUR, the MAHs should provide cumulative reviews of cases of enteroviral meningoencephalitis, acute polyneuropathy/Guillain-Barré syndrome and of false negative serologic tests of infections. In addition, the MAHs should provide a re-evaluation and a rationale for the current restriction to use effective contraceptive methods during and for 12 months following treatment with rituximab. This should include all available clinical and post-marketing safety data as well as published

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

literature on rituximab exposure during pregnancy, with a particular focus on cases where rituximab was received prior to conception, considering also relevant elimination data. Moreover, the MAHs should consider to prospectively collect safety data in the population of rituximab patients who are breastfeeding and submit plans to increase the knowledge on the safety of rituximab during breastfeeding, discuss any new data on the use of rituximab during breastfeeding and provide an overview of any available study results and/or any interim/final study reports from studies previously included in the RMP. Finally, the MAHs should provide proposal(s) to update the product information as warranted.

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

6.1.18. Tenofovir alafenamide - VEMLIDY (CAP) - PSUSA/00010575/202111

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Amelia Cupelli

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 Vemlidy, a centrally authorised medicine containing tenofovir alafenamide (TAF) 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 Vemlidy (tenofovir alafenamide) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the existing warning on nephrotoxicity. Therefore, the current terms of the marketing authorisation(s) should be varied[38].
- In the next PSUR, the MAH should provide reviews of cases of ocular effects (posterior uveitis), lactic acidosis and drug ineffectiveness. Finally, the MAH should add 'increased cholesterol and triglycerides with associated cardiovascular events' to the PSUR list of safety concerns as an important potential risk.

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.

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

PRAC considered that a (revised) warning on nephrotoxicity is also relevant for medicinal product(s) of authorised fixed dose combination(s)-containing tenofofovir alafenamide. Further consideration is to be given at the level of PRAC/CHMP.

6.1.19. Tofacitinib - XELJANZ (CAP) - PSUSA/00010588/202111 (with RMP)

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

Background

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

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Xeljanz, a centrally authorised medicine containing tofacitinib 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 Xeljanz (tofacitinib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add hypoglycaemia in patients treated for diabetes as a warning. In addition, retinal venous thrombosis should be added as a new warning and added to the existing undesirable effect of venous thromboembolism. Therefore, the current terms of the marketing authorisation(s) should be varied[39].
- This recommendation is without prejudice to the final conclusions of the ongoing procedure for Janus kinase (JAK) inhibitors (EMEA/H/A-20/1517) assessed under Article 20 of Regulation (EC) No 726/2004. See under 3.2.1.
- In the next PSUR, the MAH should review the frequency of venous thromboembolism currently listed as 'uncommon' to also reflect retinal venous thrombosis. The MAH should propose to update the product information as warranted.

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

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

See also Annex I 16.2.

[39] 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. Methotrexate - JYLAMVO (CAP); NORDIMET (CAP); NAP - PSUSA/00002014/202110

Applicants: Nordic Group B.V. (Nordimet), Therakind (Europe) Limited (Jylamvo), various

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

Methotrexate is a folic acid analogue. As oncological indications, methotrexate is indicated under certain conditions for the treatment of choriocarcinoma, chorioadenoma destruens, hydatidiform mole, acute lymphoblastic leukaemia (ALL), breast cancer, cervical cancer, ovarian carcinoma, testicular carcinoma, bladder cancer, epidermoid cancers of head and neck, mycosis fungoides, lung cancer, non-Hodgkin's lymphoma, meningeal lymphoma, histiocytic and lymphatic lymphoma, Burkitt's lymphoma, osteosarcoma, meningeal leukaemia. As non-oncological indications, methotrexate is indicated under certain conditions for the treatment of active rheumatoid arthritis in adult patients, polyarthritic forms of severe, active juvenile idiopathic arthritis, when the response to nonsteroidal anti-inflammatory drugs (NSAIDs) has been inadequate, severe psoriasis vulgaris in adult patients which is not adequately responsive to conventional therapy, mild to moderate Crohn's disease either alone or in combination with corticosteroids in adult patients refractory or intolerant to thiopurines. For further background information on substance(s) and indication(s) of centrally authorised product(s) identified as 'CAP', see Human medicine European public assessment report (EPAR) on the EMA website.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of Jylamvo and Nordimet, centrally authorised medicines containing methotrexate, and nationally authorised medicine(s) containing methotrexate and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of methotrexate-containing products in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisations should be maintained.
- In the next PSUR, the MAHs of methotrexate-containing products with indications requiring low-dose methotrexate therapy should provide a review on skin cancer including melanoma.

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

Based on the CHMP 'Safety Working Party (SWP) recommendations on the on the duration of contraception following the end of treatment with a genotoxic drug' (EMA/CHMP/SWP/74077/2020 corr. 3*) and the resulting reviews of available evidence in relation to the mechanism of genotoxicity of methotrexate, PRAC considered that the current advice on the duration of contraceptive use following the end of treatment with methotrexate for men and women should be further reviewed. In addition, PRAC considered that the findings by *Grosen et al* (2021)[40] on methotrexate presence in semen should be further

[40] Grosen A, Bellaguarda E, Nersting J, Hvas C, Liljeqvist-Soltic I, Stein A, et al. Low-dose methotrexate therapy does not affect semen parameters and sperm DNA. Inflammatory Bowel Diseases. 2021: izab205. doi: 10.1093/ibd/izab205

reviewed in the context of methotrexate-containing products with indications requiring low-dose methotrexate therapy. Further consideration is to be given at the level of CHMP/CMDh.

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

See also Annex I 16.3.

6.3.1. Diclofenac[41] (NAP) – PSUSA/00001048/202109

Applicant(s): various

PRAC Lead: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

Background

Diclofenac is a non-steroidal anti-inflammatory drug (NSAID) indicated as systemic formulations for the treatment of rheumatoid arthritis and osteoarthrosis, ankylosing spondylitis. It is also indicated for the treatment of acute pain conditions such as headache, toothache, joint or muscle pain, back pain and primary dysmenorrhoea and for the treatment of acute musculoskeletal disorders and trauma such as periarthritis, tendinitis, tenosynovitis, bursitis, sprains, strains and dislocations. Moreover, it is indicated for the relief of pain in fractures, for the treatment of acute gout and for the control of pain and inflammation in orthopedic, dental and other minor surgeries.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of diclofenac-containing product(s) for systemic use in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add a warning on the use of diclofenac after gestational week 20, due to the risk of renal dysfunction, oligohydramnios and neonatal renal impairment, unless similar or stricter information regarding use in pregnancy is already reflected. In addition, the product information of diclofenac-containing products for intramuscular use should be updated to add injection site reaction/embolia cutis medicamentosa (Nicolau syndrome) as a warning and embolia cutis medicamentosa as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[42].

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

PRAC considered that the risk of foetal renal dysfunction, oligohydramnios and neonatal renal impairment when diclofenac (systemic formulations) is used by the mother after gestational

[41] Systemic formulation(s) only
[42] Update of SmPC sections 4.4, 4.6 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position.

week 20 is also relevant medicinal product(s) containing diclofenac (systemic formulations) in fixed dose combination(s) (FDC). Further consideration is to be given at the level of CMDh.

6.3.2. Methylphenidate (NAP) - PSUSA/00002024/202110

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

Methylphenidate is a central nervous system (CNS) stimulant indicated for the treatment of attention deficit hyperactivity disorder (ADHD) in children between 6 and 18 years of age and adults. In some Member States, it is also indicated for the treatment of narcolepsy in adults.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing methylphenidate 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 methylphenidate-containing product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add epistaxis as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[43].
- In the next PSUR, the MAH(s) should continue to closely monitor the risks included in the PSUR list of safety concerns and present/discuss the results, with a special focus on cases of drug abuse/drug dependence (and diversion) particularly in the context of possible nasal abuse. The MAH(s) should discuss the need for an update of the product information as warranted. In addition, the MAHs should provide a detailed review of cases of pulmonary hypertension and discuss possible mechanisms of actions by which methylphenidate may cause pulmonary hypertension. Also, the MAH(s) should provide a cumulative review of cases reporting cerebral venous sinus thrombosis (CVST), as well as a review of cases of 'sexual maturation delayed', with an emphasis on data on potential interactions of methylphenidate with sex hormones.

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

PRAC considered that the existing educational material[44] comprising three physician educational documents can be discontinued in view of the safety knowledge gained over the past decade and safety information communicated via international and European ADHD

[43] Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position.
[44] Resulting from the referral procedure under Article 31 of Directive 2001/83/EC concluded in 2009 (EMEA/658285/2008)

treatment guidelines. Therefore, routine risk minimisations are considered suitable. Further consideration is to be given at the level of CMDh.

6.3.3. Rabeprazole (NAP) - PSUSA/00002601/202110

Applicant(s): various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

Background

Rabeprazole is a substituted benzimidazole indicated for the treatment of duodenal ulcers, erosive and non-erosive gastroesophageal reflux disease (GERD) as well as for Zollinger-Ellison syndrome (ZES) for the eradication of *Helicobacter pylori* (*H. pylori*) in combination with antibiotic therapy.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing rabeprazole 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 rabeprazole-containing product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add tubulointerstitial nephritis (TIN) as an undesirable effect with a frequency 'rare' and as a new warning on renal impairment. Therefore, the current terms of the marketing authorisation(s) should be varied[45].

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

6.3.4. Soybean phospholipids[46] (NAP) – PSUSA/00010707/202110

Applicant(s): various

PRAC Lead: Željana Margan Koletić

Scope: Evaluation of a PSUSA procedure

Background

Soybean phospholipids[47] are liver therapeutic agent indicated to improve subjective symptoms, such as loss of appetite or a feeling of pressure in the upper right abdomen, in patients with liver damage caused by the toxic effects of certain foods or hepatitis, treatment of gallstones, psoriasis, gestosis including toxaemia of pregnancy, fatty liver, radiation therapy, nutritional supplement, hepatopathy, acute and chronic liver failure as well as hepatic cirrhosis.

[45] 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.
[46] Oral use only
[47] Phosphatidyl choline, phosphatidyl choline/phospholipids, phospholipids

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of soybean phospholipids-containing product(s) for oral use in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add increased blood pressure, palpitations, dizziness, nausea and vomiting as undesirable effects with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[48].
- In the next PSUR, the MAH(s) should provide reviews of cases of drug use during pregnancy and drug exposure in utero, cases of severe allergic reactions, severe cutaneous adverse reactions (SCARs) and of asthenic conditions.

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

6.3.5. Teicoplanin (NAP) - PSUSA/00002878/202111

Applicant(s): various

PRAC Lead: Eva Jirsová

Scope: Evaluation of a PSUSA procedure

Background

Teicoplanin is a glycopeptide antibiotic indicated for the parenteral treatment of complicated skin and soft tissue infections, bone and joint infections, hospital acquired pneumonia, community acquired pneumonia, complicated urinary tract infections, infective endocarditis, peritonitis associated with continuous ambulatory peritoneal dialysis (CAPD) and bacteraemia that occurs in association with any of the indication listed above. It is also indicated as an alternative oral treatment for *Clostridium difficile* infection associated diarrhoea and colitis.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing teicoplanin 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 teicoplanin-containing product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add pancytopenia as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[49].

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

- In the next PSUR, the MAH Sanofi should include a further review of data related to thrombocytopenia and nephrotoxicity in line with the final recommendation based on the results of the imposed PASS[50] finalised in 2020 (EMEA/H/N/PSR/S/0025). The MAHs should provide an analysis on the possibility of a higher risk of teicoplanin induced thrombocytopenia (TIT) and nephrotoxicity in patients with severe hypoalbuminemia (SAH). In addition, the MAHs should provide a cumulative review of cases of interaction between teicoplanin and warfarin together with a proposal to update the product information as warranted. Finally, the MAHs should update their PSUR list of safety concerns in line with the PRAC recommendation.

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

See Annex I 16.5.

6.6. Expedited summary safety reviews[51]

See also Annex I 16.6.

6.6.1. Elasomeran - SPIKEVAX (CAP) - EMEA/H/C/005791/MEA 011.12

Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Thirteenth expedited summary safety report (SSR) for Spikevax (elasomeran) during the coronavirus disease (COVID-19) pandemic

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 assessed the thirteenth expedited summary safety report (SSR) for the safety monitoring of Spikevax (elasomeran) as part of the safety monitoring of the vaccine. At the plenary meeting, PRAC adopted its conclusions.

Summary of advice/conclusion(s)

[50] A prospective, observational cohort, evaluating the incidence of nephrotoxicity and other adverse events of interest in patients treated with the higher recommended teicoplanin loading dose (12mg/kg twice a day), and comparison with external historical comparator data

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

- The MAH should submit to EMA, within 60 days, a variation to update the product information by adding urticaria as an undesirable effect. The MAH is requested to propose a frequency based on all the available data.
- In addition, the MAH should submit to EMA, within 45 days, a variation to update the occurrence of myocarditis, based on the available data in young adult males and to update the product information on the risk of myocarditis after a third dose of Spikevax (elasomeran).
- PRAC agreed that no further SSR are required, taking into account the post-marketing experience since authorisation, the characterisation of the safety profile, and since no specific topics that would require prompt review have been identified in the current SSR. The safety profile of Spikevax (elasomeran) will continue to be monitored in future PSURs, with the routine signal detection activities in place, as well as within the additional pharmacovigilance activities as outlined in the RMP of Spikevax (elasomeran).

6.6.2. Tozinameran - COMIRNATY (CAP) - EMEA/H/C/005735/MEA 002.13

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Fourteenth expedited summary safety report (SSR) for Comirnaty (tozinameran) during the coronavirus disease (COVID-19) pandemic

Background

Tozinameran is a COVID-19 mRNA Vaccine (nucleoside modified) indicated, as Comirnaty, for active immunisation to prevent COVID-19 caused by SARS-CoV-2 virus, in individuals 12 years of age and older.

PRAC assessed the fourteenth expedited summary safety report (SSR) for the safety monitoring of Comirnaty (tozinameran), as part of the safety monitoring of the vaccine. At the plenary meeting, PRAC adopted its conclusions.

Summary of advice/conclusion(s)

- The MAH should submit to EMA, within 45 days, a variation to update the occurrence of myocarditis, based on the available data in the age group 5-11 years and to update the product information on the risk of myocarditis after a third dose of Comirnaty (tozinameran).
- In the next PSUR, the MAH should provide a cumulative review of cases of sudden sensorineural hearing loss following vaccination with Comirnaty (tozinameran) and propose an update of the product information and/or RMP as warranted.
- PRAC agreed that no further SSR are required, taking into account the post-marketing experience since authorisation, the characterisation of the safety profile, and since no specific topics that would require prompt review have been identified in the current SSR. The safety profile of Comirnaty (tozinameran) will continue to be monitored in future PSURs, with the routine signal detection activities in place, as well as within the additional pharmacovigilance activities as outlined in the RMP of Comirnaty (tozinameran).

7. Post-authorisation safety studies (PASS)

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

See Annex I 17.1.

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

See also Annex I 17.2.

7.2.1. Rivaroxaban - XARELTO (CAP) - EMEA/H/C/000944/MEA 049.1

Applicant: Bayer AG

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Protocol for study 22194 (listed as a category 3 study in the RMP): a multi-national, observational, cross-sectional study to evaluate the effectiveness of risk minimisation measures (RMM) provided to physicians and parents/caregivers (P/C) of children for the use of Xarelto (rivaroxaban) oral suspension for the treatment of venous thromboembolism (VTE) and to provide insight on the risk of medication errors (MEs) in routine clinical practice (feasibility report assessed by PRAC in July 2021 (MEA 049))

Background

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

As part of the RMP for Xarelto (rivaroxaban), the MAH was required to conduct a study to evaluate the effectiveness of risk minimisation measures (RMM) provided to physicians and parents/caregivers (P/C) of children for the use of Xarelto (rivaroxaban) oral suspension for the treatment of venous thromboembolism (VTE) and to provide insight on the risk of medication errors in routine clinical practice. The MAH submitted the study protocol which was assessed by the Rapporteur. PRAC was requested to provide advice to CHMP on the protocol submitted by the MAH. For further background, see PRAC minutes July 2021.

Summary of advice

- Based on the review of the protocol and the assessment from the Rapporteur, PRAC considered the protocol for Xarelto (rivaroxaban) is not acceptable at this stage.
- PRAC considered that the data proposed to be collected in the surveys are not sufficiently focused on the main safety concerns, hence a more focused collection of issues regarding reconstitution and dosing would be more appropriate. PRAC advised that the implementation of a specific adverse reaction follow-up questionnaire (FUQ) would be a more suitable alternative to complement spontaneous reporting of medication errors. In addition, PRAC considered that concern regarding medication errors in children below 2 years of age should be given particular attention in the PSURs. Consequently, PRAC advised that the study should be removed from the RMP.

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

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

See Annex I 17.3.

7.4. Results of PASS non-imposed in the marketing authorisation(s)[55]

See Annex I 17.4.

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

See Annex I 17.5.

7.6. Others

See Annex I 17.6.

7.7. New Scientific Advice

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

7.8. Ongoing Scientific Advice

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

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

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

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

See Annex I 18.2.

8.3. Renewals of the marketing authorisation

See Annex I 18.3.

[54] In accordance with Article 107p-q of Directive 2001/83/EC
[55] 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

9. Product related pharmacovigilance inspections

9.1. List of planned pharmacovigilance inspections

9.1.1. Risk-based programme for routine pharmacovigilance inspections of marketing authorisation holders connected with human centrally authorised products

Scope: Pharmacovigilance inspection programme 2022-2026 (first revision for 2022)

PRAC agreed the list of planned pharmacovigilance inspections for 2022-2026, proposed by the Pharmacovigilance Inspectors Working Group (PhV IWG) according to a risk-based approach. This list is subsequently due for adoption at CHMP.

In addition, the EMA Secretariat announced that EMA will organise a pharmacovigilance inspectors training course on 29 and 30 September 2022 and presented PRAC with the draft Agenda of the event. All EU assessors were invited to attend this course.

9.2. Ongoing or concluded pharmacovigilance inspections

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

9.3. Others

None

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

10.1. Safety related variations of the marketing authorisation

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

Applicant: Stemline Therapeutics B.V.

PRAC Rapporteur: Menno van der Elst

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

See also 15.3.28.

Background

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

A type II variation for Elzonris (tagraxofusp) is under evaluation at CHMP to assess the final report from study 20255431, a non-interventional post-authorisation study on blood brain barrier (BBB) models in order to determine a potential toxicity biomarker to further investigate the risk of choroid plexus lesions based on samples from primates. PRAC was requested to provide advice on this variation. For further background, see PRAC minutes January 2022 and PRAC minutes April 2022.

Summary of advice

- Based on the review of the available information and assessment, PRAC considered that the existing warning in the product information on choroid plexus lesions is sufficient to guide on appropriate risk minimisation measures to undertake in case of central nervous system (CNS) damage during use of Elzonris (tagraxofusp). Nevertheless, PRAC agreed that it does not exclude any further description on specific examination(s) to be introduced in the product information as warranted.

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. N(2)-L-alanyl-L-glutamine (NAP) - DE/H/xxxx/WS/1108

Applicant: MAH Fresenius Kabi Deutschland GmbH (Dipeptamin)

PRAC Lead: Martin Huber

Scope: PRAC consultation on a worksharing variation procedure evaluating the data from spontaneous reports, literature, clinical trials and updated guidelines on the use of N(2)-L-alanyl-L-glutamine, as discussed at PRAC and agreed by CMDh following the conclusion of the PSUSA procedure (PSUSA/00003158/202103) concluded in December 2021, on request of Germany

Background

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

In the context of the evaluation of a worksharing variation procedure evaluating data from spontaneous reports, literature, clinical trials and updated guidelines on the use of N(2)-L-alanyl-L-glutamine, as discussed at PRAC during the PSUSA procedure (PSUSA/00003158/202103) concluded in December 2021, Germany as the reference Member State (RMS) requested a PRAC advice on its assessment. For further background, see PRAC minutes December 2021[56].

Summary of advice

- Based on the review of the available information and the RMS assessment, PRAC agreed that the new data reviewed in the procedure does impact the benefit-risk balance of N(2)-L-alanyl-L-glutamine-containing product(s). PRAC noted the comments raised on the product information and advised that further consideration should be given by the RMS in the context of the variation procedure, by CMDh and the relevant National Competent Authority (NCA) as applicable.

11.2. Other requests

None

12. Organisational, regulatory and methodological matters

12.1. Mandate and organisation of PRAC

12.1.1. PRAC membership

The Chair welcomed Roberto Frontini and Salvatore Antonio Giuseppe Messana as a member and alternate, respectively, representing healthcare professionals nominated by the European Commission (EC). The Chair also welcomed Declan Noone and Marko Korenjak as a member and alternate, respectively, representing patients' organisations nominated by the EC. For further information on the Commission decision appointing members and alternates of PRAC representing healthcare professionals and patients' organisations, see PRAC minutes May 2022.

The Chair also informed the Committee that Marek Juračka was to step down from PRAC after the current meeting as the member for Slovakia. The Chair thanked him for hjs contribution to the work of the Committee.

12.1.2. Vote by proxy

Luxembourg gave a proxy to France to vote on behalf of Luxembourg during the entire meeting.

12.2. Coordination with EMA Scientific Committees or CMDh-v

None

[56] Held 29 November – 02 December 2021

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

12.3.1. Healthcare Professionals Working Party (HCPWP) and Patients and Consumers Working Party (PCWP) - Nomination of PRAC representative(s)

The EMA Secretariat launched call for nomination of PRAC representatives for the Patients' and Consumers' Working Party (PCWP) and the Healthcare Professionals' Working Party (HCPWP) for a new three-year mandate.

Post-meeting note: Roberto Frontini was appointed as HCP PRAC representative (as member) within the HCPWP. Declan Noone was appointed as Patient PRAC Representative (as member) and Marko Korenjak as Patient PRAC Representative (as alternate) within the PCWP.

12.3.2. Healthcare Professionals Working Party (HCPWP) and Patients and Consumers Working Party (PCWP) - work plan 2022-2025

The EMA Secretariat informed PRAC about the 2022-2025 work plan for Patients' and Consumers' Working Party (PCWP) and the Healthcare Professionals' Working Party (HCPWP), including the shared work areas and objectives.

12.4. Cooperation within the EU regulatory network

12.4.1. Coronavirus (COVID-19) pandemic - update

The EMA Secretariat updated PRAC on the activities of the COVID-19 EMA pandemic Task Force (ETF), including an overview of ongoing clinical trials and epidemiological studies and initiatives, as well as a summary of medicines in development as potential treatments for COVID-19, as well as authorised medicines and their effectiveness against new coronavirus SARS-CoV-2 variants and their safety surveillance. In addition, the EMA Secretariat provided an update on the vaccines and medicinal products to be used for the prevention and treatment of monkey pox disease.

12.4.2. PRAC strategic review and learning meeting (SRLM) under the French presidency of the European Union (EU) Council – Paris, France, 22 - 24 June 2022 - agenda

PRAC lead: Tiphaine Vaillant, Nathalie Gault

PRAC was presented with a draft agenda for the 'PRAC strategic review and learning meeting (SRLM)' under the French presidency of the Council of the European Union (EU). The meeting will be held in person in Paris, France.

12.5. Cooperation with International Regulators

None

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

12.6.1. Coronavirus (COVID-19)-medicines monitoring: CONSIGN[57] consortium project – COVID-19 infection and medicines in pregnancy – update

PRAC lead: Sabine Straus, Ulla Wändel Liminga

At the organisational, regulatory and methodological matters (ORGAM) meeting on 21 June 2022, the EMA Secretariat updated PRAC on the progress of the CONSIGN project, including the interim results and conclusions of the EMA funded study. PRAC will be kept informed about further developments and final results. For background, see PRAC minutes February 2021.

12.7. PRAC work plan

None

12.8. Planning and reporting

None

12.9. Pharmacovigilance audits and inspections

12.9.1. Pharmacovigilance systems and their quality systems

None

12.9.2. Pharmacovigilance audits

None

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

12.10.1. Periodic safety update reports

None

12.10.2. Granularity and Periodicity Advisory Group (GPAG)

None

12.10.3. PSURs repository

None

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

PRAC endorsed the draft revised EURD list, version June 2022, reflecting PRAC's comments

[57] Covid-19 infectiOn aNd medicineS In pregnancy

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 June 2022, the updated EURD list was adopted by CHMP and CMDh at their June 2022 meetings and published on the EMA website, see: Home> Human Regulatory>Post-authorisation>Pharmacovigilance>Periodic safety update reports>EURD list> List of Union reference dates and frequency of submission of periodic safety update reports (PSURs)

12.11. Signal management

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

PRAC lead: Menno van der Elst

PRAC was updated on the ongoing activities and the progress from the 'SMART working group meeting on Processes' held on 10 May 2022, including a proposal for a revision of the frequency of the CAPs eRMR, as well as some clarifications needed regarding the signal confirmation process in the European pharmacovigilance issues tracking tool (EPITT).

12.11.2. Signal and safety analytics project

The EMA Secretariat presented to PRAC the signal and safety analytics (SSA) project which is part of the data analytics programme. The SSA project aims at replacing the technology behind EudraVigilance data analysis system (EVDAS), electronic Reaction Monitoring Report (eRMR), and adrreports.eu website, along with improving the system performance, enhancing the user interface, and implementing a more user-oriented approach to retrieving data from EudraVigilance. In order to further engage with the EU regulatory network, the project will be also presented to the Pharmacovigilance Business team with the proposal to have volunteers from NCAs to form a key users' group to represent the NCAs EVDAS users in the project. A call for expression of interest for PRAC Sponsor for this project was launched amongst PRAC. PRAC members should contact the EMA Secretariat by 24 June 2022.

Post-meeting note: Martin Huber was nominated as PRAC Sponsor for the signal and safety analytics project.

12.12. Adverse drug reactions reporting and additional reporting

12.12.1. Management and reporting of adverse reactions to medicinal products

None

12.12.2. Additional monitoring

None

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

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

Post-meeting note: The updated additional monitoring list was published on the EMA website, 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. Coronavirus (COVID-19) vaccines - benefit-risk contextualisation of COVID-19 vaccines in the EU

The EMA Secretariat presented PRAC with the Benefit-Risk contextualisation tool used to quantify both vaccine-specific benefits and risks related to COVID-19 vaccines, including the methodology behind the implementation of this tool as well as the data sources used. PRAC noted the tool.

12.21.2. Data analysis and real-world interrogation network (DARWIN EU) – selection of studies supportive for PRAC decision-making to be performed in DARWIN EU year 1

At the organisational, regulatory and methodological matters (ORGAM) meeting on 21 June 2022, the EMA Secretariat presented to PRAC an update on DARWIN EU, the implementation roadmap, as well the selected data partners to be onboarded in the project during the first year. PRAC was presented also with a selection of proposed studies to be included in DARWIN EU, together with an update on the use of real-world evidence in PRAC decision-making. For further background, see PRAC minutes March 2022.

EMA Secretariat presented a call for expression of interest for PRAC volunteers to liaise between PRAC and DARWIN EU team and facilitate study selection, as well as to provide input on protocols and study results. Interest members should contact the EMA Secretariat by 24 June 2022. An update will be presented to PRAC in Q3 2022.

12.21.3. EMA-funded studies - coronavirus (COVID-19) lessons learnt and future perspectives for PRAC decision-making

At the organisational, regulatory and methodological matters (ORGAM) meeting on 21 June 2022, the EMA secretariat presented to PRAC an overview of the EMA funded COVID-19 vaccine studies (2020-2022) and pointed out lessons learnt, together with several points to consider for further improvement of the decision-making process, such as communication, timelines, data collection, level of urgency, international collaboration etc. The EMA Secretariat will provide regular updates to PRAC on the next steps and on the implementation of the lessons learnt.

12.21.4. Good Pharmacovigilance Practice (GVP) – mid-year update

PRAC Lead: Sabine Straus

PRAC was provided with an overview of the GVP module status, including an update on the ongoing or planned work on new or revised GVP modules together with their scope, proposed timelines for PRAC discussion and adoption. This also included an outline of the planned GVP updates included in the workplan for 2022. A call for PRAC volunteers to join the 'Multistakeholder working group on digital support tools to risk minimisation measures and their effectiveness evaluation' (WG) was launched. Interested PRAC members are invited to send an e-mail to EMA Secretariat by 15 July 2022.

13. Any other business

None

14. Annex I – Signals assessment and prioritisation[58]

14.1. New signals detected from EU spontaneous reporting systems

As per the agreed criteria for new signal(s), PRAC adopted without further plenary discussion the recommendation of the Rapporteur to request MAH(s) to submit a cumulative review following standard timetables[59].

14.1.1. Durvalumab - IMFINZI (CAP)

Applicant: AstraZeneca AB

PRAC Rapporteur: David Olsen

Scope: Signal of myelitis transverse

EPITT 19815 – New signal

Lead Member State(s): NO

14.1.2. Temozolomide – TEMODAL (CAP), TEMOMEDAC (CAP), TEMOZOLOMIDE ACCORD (CAP), TEMOZOLOMIDE HEXAL (CAP), TEMOZOLOMIDE SANDOZ (CAP), TEMOZOLOMIDE SUN (CAP), TEMOZOLOMIDE TEVA (CAP); NAP

Applicants: Accord Healthcare S.L.U. (Temozolomide Accord), Hexal AG (Temozolomide Hexal), medac Gesellschaft fur klinische Spezialpraparate mbH (Temomedac), Merck Sharp & Dohme B.V. (Temodal), Sandoz GmbH (Temozolomide Sandoz), Sun Pharmaceutical Industries Europe B.V. (Temozolomide Sun), Teva B.V. (Temozolomide Teva)

PRAC Rapporteur: Martin Huber

[58] 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

[59] 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

Scope: Signal of progressive multifocal leukoencephalopathy (PML)

EPITT 19814 – New signal

Lead Member State(s): DE

14.2. New signals detected from other sources

14.2.1. Tildrakizumab – ILUMETRI (CAP)

Applicant: Almirall S.A

PRAC Rapporteur: Adam Przybylkowski

Scope: Signal of herpes zoster

EPITT 19801 - New signal

Lead Member State(s): PL

14.3. Signals follow-up and prioritisation

None

14.4. Variation procedure(s) resulting from signal evaluation

14.4.1. Pregabalin - LYRICA (CAP) - EMEA/H/C/000546/WS2261/0118; pregabalin - PREGABALIN PFIZER (CAP) - EMEA/H/C/003880/WS2261/0047

Applicant: Upjohn EESV

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Update of sections 4.4 and 4.8 of the SmPC with a warning regarding Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) as severe cutaneous adverse reactions as requested in the conclusions of the signal procedure (EPITT 19723) adopted in January 2022 (SDA 055). The package leaflet is updated accordingly

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

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

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

15. Annex I – Risk management plans

15.1. Medicines in the pre-authorisation phase

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

15.1.1. Ranibizumab - EMEA/H/C/005617

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

15.1.2. Teriflunomide - EMEA/H/C/005962

Scope: Treatment of multiple sclerosis (MS)

15.1.3. Teriparatide - EMEA/H/C/005793

Scope: Treatment of osteoporosis

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

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

15.2.1. Alogliptin - VIPIDIA (CAP) - EMEA/H/C/002182/WS2191/0029; alogliptin, metformin - VIPDOMET (CAP) - EMEA/H/C/002654/WS2191/0036; alogliptin, pioglitazone - INCRESYNC (CAP) - EMEA/H/C/002178/WS2191/0040

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Menno van der Elst

Scope: Submission of an updated RMP (version 11) in order to consolidate it within a single RMP for Vipidia (alogliptin), Vipdomet (alogliptin/metformin) and Incresync (alogliptin/pioglitazone) as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00010061/202104) finalised in November 2021. The consolidated RMP is also updated in line with revision 2 of GVP module V on 'Risk management systems' and the targeted follow up questionnaires (FUQ) of severe hypersensitivity and skin reactions, pancreatitis, hepatic events and follow up gastrointestinal events and infections is removed. Finally, the removal of the inverted black triangle as agreed other procedures is reflected in the RMP.

15.2.2. Elasomeran - SPIKEVAX (CAP) - EMEA/H/C/005791/II/0062

Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Submission of an updated RMP (version 4.0) in order to remove 'anaphylaxis' as an important identified risk and 'interaction with other vaccines' as a safety concern in study mRNA-1273-P904 (study 1) (listed as a category 3 study in the RMP): a post-authorisation active surveillance safety study using secondary data to monitor real-world safety of Spikevax (COVID-19 mRNA-1273 vaccine) in Europe - an enhanced pharmacovigilance study to provide additional evaluation of adverse events of special interest (AESI) and emerging validated safety signals in European populations and electronic database assessment of use in pregnant women, following the outcome of MEA 004.4 adopted in January 2022; to implement the WHO[60]-approved international non-proprietary name (INN) 'elasomeran'. In addition, the MAH updated the milestones for studies mRNA-1273-P301, mRNA-1273-P203, mRNA-1273-P201, mRNA-1273-P901, mRNA-1273-P903 and mRNA-1273-P910 and added study mRNA-1273-P911 to the RMP. Annex II of the product information is updated accordingly.

15.2.3. Tolvaptan - JINARC (CAP) - EMEA/H/C/002788/II/0036

Applicant: Otsuka Pharmaceutical Netherlands B.V.

PRAC Rapporteur: Amelia Cupelli

Scope: Submission of an updated RMP (version 15.0) in order to reflect the outcome of a substantial amendment to a protocol previously agreed for study 156-12-299 (listed as a category 1 study): a 7.5-year, multicentre, non-interventional PASS to characterise and quantify the identified risk of idiosyncratic liver injury in Jinarc (tolvaptan) treated patients with autosomal dominant polycystic kidney disease (ADPKD) in routine clinical practice, as concluded in procedure PSA/S/0078.1 finalised in February 2021. Annex II is updated accordingly. In addition, the MAH took the opportunity to correct an oversight/editorial error in the package leaflet.

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

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

15.3.1. (1R,2S,5S)-N-((1S)-1-cyano-2-((3S)-2-oxopyrrolidin-3-yl)ethyl)-3-((2S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido) butanoyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide, ritonavir - PAXLOVID (CAP) - EMEA/H/C/005973/II/0007

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Martin Huber

Scope: Submission of the final report from study C4671010 (listed as a category 3 study in the RMP): a phase 1, non-randomized, open label study to assess the pharmacokinetics, safety and tolerability of PF-07321332 boosted with ritonavir (Paxlovid) in adults with moderate hepatic impairment and individuals with normal hepatic function. The RMP (version 2.0) has also been submitted

[60] World Health Organization

15.3.2. Agalsidase alfa - REPLAGAL (CAP) - EMEA/H/C/000369/II/0117

Applicant: Takeda Pharmaceuticals International AG Ireland Branch

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Update of sections 4.2 and 6.6 of the SmPC in order to add self-administration by a trained patient and/or a caregiver as a new method of administration. The package leaflet is updated accordingly. In addition, the MAH took the opportunity to introduce minor editorial changes to the product information. The RMP (version 0.1) is updated accordingly

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

Applicant: CSL Behring GmbH

PRAC Rapporteur: Menno van der Elst

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

15.3.4. Besilesomab - SCINTIMUN (CAP) - EMEA/H/C/001045/II/0015

Applicant: CIS BIO International

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Submission of the final report from study AG-2012 (listed as a category 3 study in the RMP): a non-interventional controlled survey on the impact of Scintimun (besilesomab) administered for scintigraphic imaging on diagnostic thinking and management of patient with suspicion of peripheral osteomyelitis (in fulfilment of MEA 08.4). The RMP (version 15) is updated accordingly

15.3.5. Brexucabtagene autoleucel - TECARTUS (CAP) - EMEA/H/C/005102/II/0019, Orphan

Applicant: Kite Pharma EU B.V., ATMP[61]

PRAC Rapporteur: Menno van der Elst

Scope: Update of sections 4.8 and 5.1 of the SmPC in order to update the safety and efficacy information based on 24-month follow-up data from all treated patients in cohort 1 of pivotal study KTE-C19-102 (ZUMA-2): a phase 2, multicentre, open-label study evaluating the safety and efficacy of KTE-X19 (brexucabtagene autoleucel) in subjects with relapsed or refractory (r/r) mantle cell lymphoma (MCL). This submission is in fulfilment of specific obligation SOB 004 to confirm the long-term efficacy and safety of Tecartus (brexucabtagene autoleucel) in adult patients with r/r MCL. In addition, the MAH took the

[61] Advanced therapy medicinal product

opportunity to make minor editorial changes in the SmPC. The RMP (version 2.1) has also been submitted

15.3.6. Buprenorphine - BUVIDAL (CAP) - EMEA/H/C/004651/II/0017

Applicant: Camurus AB

PRAC Rapporteur: Tiphaine Vaillant

Scope: Extension of indication to include treatment of moderate to severe chronic pain in patients with opioid dependence. As a consequence, sections 4.1, 4.2, 4.5, 5.1 and 6.6 of the SmPC are updated. The package leaflet and the RMP (version 2.1) are updated accordingly

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

Applicant: Kyowa Kirin Holdings B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include treatment of fibroblast growth factor 23 (FGF23)-related hypophosphataemia in tumour-induced osteomalacia (TIO) associated with phosphaturic mesenchymal tumours that cannot be curatively resected or localised in patients aged 1 year and over, based on data from two ongoing open-label clinical studies, namely: 1) study UX023T-CL201: a phase 2 open-label trial to assess the efficacy and safety of burosumab in subjects with TIO or epidermal nevus syndrome (ENS)-associated osteomalacia, 2) study KRN23-002: a phase 2 open-label trial to assess the efficacy and safety of burosumab in patients with TIO or ENS (144-week data and 88-week data respectively). As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 4.0) are updated accordingly. The MAH also applied for one additional year of market protection

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

Applicant: Ablynx NV

PRAC Rapporteur: Jan Neuhauser

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

15.3.9. Carglumic acid - CARBAGLU (CAP) - EMEA/H/C/000461/II/0044

Applicant: Recordati Rare Diseases

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Update of sections 4.2 and 4.4 of the SmPC in order to include information on the impact of renal impairment on systemic exposures to Carbaglu (carglumic acid) based on final results from study A: a phase 1, multicentre, open-label, parallel-group adaptive pharmacokinetic single dose study of oral Carbaglu (carglumic acid) in subjects with normal and varying degrees of impaired renal function. The package leaflet is updated accordingly.

The RMP (version 2.2) has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the product information

15.3.10. Cemiplimab - LIBTAYO (CAP) - EMEA/H/C/004844/II/0026

Applicant: Regeneron Ireland Designated Activity Company (DAC)

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication to include monotherapy treatment of adult patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 3.0) are updated in accordance

15.3.11. Coronavirus (COVID-19) vaccine (ChAdOx1-S [recombinant]) - VAXZEVRIA (CAP) - EMEA/H/C/005675/II/0075

Applicant: AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

Scope: Update of section 5.1 of the SmPC in order to include updated efficacy information based on the 6 months follow-up analysis from study D8110C00001 (listed as a specific obligation in Annex II): a phase 3 randomised, double-blind, placebo-controlled, multicentre study in adults to determine the safety, efficacy and immunogenicity of Vaxzevria (COVID-19 vaccine (ChAdOx1-S [recombinant])). The RMP (version 5.1) has also been submitted. The MAH removed the important identified risk of anaphylaxis from the list of safety concerns, updated the routine and additional pharmacovigilance activities section and took the opportunity to implement other administrative updates

15.3.12. Dalbavancin - XYDALBA (CAP) - EMEA/H/C/002840/II/0043

Applicant: Allergan Pharmaceuticals International Limited

PRAC Rapporteur: Rugile Pilviniene

Scope: Extension of indication to the paediatric population (aged 3 months to < 18 years) for the treatment of acute bacterial skin and skin structure infections (ABSSSI) based on the interim results from the study DUR001-306: a phase 3, multicentre, open-label, randomized, comparator controlled trial of the safety and efficacy of dalbavancin versus active comparator in paediatric subjects with ABSSSI, together with data from three phase 1 pharmacokinetic studies (A8841004, DUR001-106, and DAL-PK-02). Consequently, the sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 6.6 of the SmPC were updated. The package leaflet is updated accordingly. In addition, the applicant took the opportunity to make minor editorial amendments and to bring the product information in line with the latest quality review of documents (QRD) (version 10.2). The RMP (version 7.0) has also been submitted

15.3.13. Dapivirine - DAPIVIRINE VAGINAL RING 25 MG (Art 58[62]) - EMEA/H/W/002168/II/0016

Applicant: International Partnership for Microbicides Belgium AISBL

PRAC Rapporteur: Jan Neuhauser

Scope: Update of Annex II in order to replace the current post-authorisation efficacy study (PAES) IPM 055 (listed as a category 1 study in the RMP): a phase 4, open label, multicentre efficacy trial in healthy human immunodeficiency virus (HIV)-negative young women aged 18-25 years, with the implementation study: dapivirine vaginal ring implementation in a real-world setting in young women. The RMP (version 0.9) is updated accordingly

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

Applicant: Bayer AG

PRAC Rapporteur: Jan Neuhauser

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

15.3.15. Elasomeran - SPIKEVAX (CAP) - EMEA/H/C/005791/II/0062

Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Extension of indication to include immunisation of paediatric individuals from 6 months through 5 years of age based on results from study P204 (KidCove): a phase 2/3, two-part, open-label, dose-escalation, age de-escalation and randomised, observer-blind, placebo-controlled expansion study to evaluate the safety, tolerability, reactogenicity, and effectiveness of elasomeran (mRNA-1273 SARS-CoV-2) vaccine in healthy children 6 months to less than 12 years of age. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 4.1) are updated in accordance. The MAH also took the opportunity to implement minor editorial changes in the product information

15.3.16. Finerenone - KERENDIA (CAP) - EMEA/H/C/005200/II/0001/G

Applicant: Bayer AG

PRAC Rapporteur: Menno van der Elst

[62] Article 58 of Regulation (EC) No 726/2004 allows the Committee for Medicinal Products for Human Use (CHMP) to give opinions, in co-operation with the World Health Organisation (WHO) on medicinal products for human use that are intended exclusively for markets outside of the European Union (EU)

Scope: Grouped variations consisting of: 1) extension of indication to include the treatment of chronic kidney disease (CKD) and for the prevention of cardiovascular (CV) events in adults with CKD (regardless of the stage of albuminuria) associated with type 2 diabetes mellitus (T2DM), based on results from study 17530 (FIGARO-DKD): a randomized, double-blind, placebo-controlled, parallel-group, multicentre, event-driven phase 3 study to investigate the efficacy and safety of finerenone on the reduction of cardiovascular morbidity and mortality in subjects with T2DM and the clinical diagnosis of diabetic kidney disease in addition to standard of care. As a consequence, sections 4.1, 4.8, 5.1, 5.2 of the SmPC are updated. The package leaflet and the RMP (version 2.1) are updated accordingly. In addition, the MAH took the opportunity to introduce editorial changes in the SmPC; 2) update of section 5.2 of the SmPC based on the results of study 21429: a phase 1 drug interaction study of finerenone with rosuvastatin; 3) submission of the results of study 21325: a phase 1 bioequivalence (BE) study assessing BE between finerenone 2 x 10 mg tablets and 20 mg tablet in Japanese healthy male adult participants

15.3.17. Ibrutinib - IMBRUVICA (CAP) - EMEA/H/C/003791/II/0073

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Extension of indication to include treatment with Imbruvica (ibrutinib) in combination with bendamustine and rituximab (BR) of adult patients with previously untreated mantle cell lymphoma (MCL) who are unsuitable for autologous stem cell transplantation, based on final results from study PCI-32765MCL3002 (SHINE) (listed as a category 3 study in the RMP): a randomized, double-blind, placebo-controlled phase 3 study of ibrutinib in combination with BR in subjects with newly diagnosed MCL. As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 19.1) are updated in accordance

15.3.18. Ivacaftor, tezacaftor, elexacaftor - KAFTRIO (CAP) - EMEA/H/C/005269/II/0024, Orphan

Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Martin Huber

Scope: Update of sections 4.8 and 5.1 of the SmPC in order to update efficacy and safety information based on interim results from clinical study VX17-445-105 (study 105) (listed as a category 3 study in the RMP): a phase III, open label extension study to evaluate the long-term safety and efficacy of Kaftrio (ivacaftor/tezacaftor/elexacaftor) in cystic fibrosis (CF) subjects homozygous for F508del (F/F genotype) or heterozygous for F508del and a minimal function (MF) mutation (F/MF genotypes). The RMP (version 6.1) has also been submitted. In addition, the MAH took the opportunity to implement minor corrections and editorial changes in the product information

15.3.19. Lonoctocog alfa - AFSTYLA (CAP) - EMEA/H/C/004075/II/0042

Applicant: CSL Behring GmbH

PRAC Rapporteur: Sonja Hrabcik

Scope: Update of section 5.1 of the SmPC in order to update efficacy and safety information

based on final results from study 3001 (listed as a category 3 study in the RMP): an open label, multicentre extension study to assess the safety and efficacy of Afstyla (lonoctocog alfa) in subjects with severe haemophilia A. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet. The RMP (version 6.0) is updated accordingly

15.3.20. Lumasiran - OXLUMO (CAP) - EMEA/H/C/005040/II/0008, Orphan

Applicant: Alnylam Netherlands B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of sections 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC in order to clarify administration instructions, remove an existing warning on metabolic acidosis in patients with severe or end stage renal impairment, update the description of adverse reactions injection site reactions, abdominal pain and immunogenicity, update efficacy and pharmacokinetic information based on: 1) interim results from study ALN-GO1-005 (ILLUMINATE-C) (listed as a category 3 study in the RMP): a single arm study to evaluate efficacy, safety, pharmacokinetics, and pharmacodynamics of lumasiran in patients with advanced primary hyperoxaluria type 1 (PH1); 2) available long-term efficacy and safety data from ongoing studies: study ALN-GO1-003 (ILLUMINATE-A): a phase 3 randomized, double-blind, placebo-controlled study with an extended dosing period to evaluate the efficacy and safety of lumasiran in children and adults with PH1 and study ALN-GO1-004 (ILLUMINATE-B): an open-label study to evaluate the efficacy, safety, pharmacokinetics, and pharmacodynamics of lumasiran in infants and young children with primary PH1; 3) study ALN-GO1-002: a phase 2, multicentre, open-label, extension study to evaluate the long-term administration of ALN-GO1 (lumasiran) in patients with PH. The package leaflet and the RMP (version 1.1) are updated in accordance

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

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Jean-Michel Dogné

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

15.3.22. Macitentan - OPSUMIT (CAP) - EMEA/H/C/002697/II/0046, Orphan

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Eva Segovia

Scope: Update of sections 4.6 and 5.3 of the SmPC in order to introduce additional data on male fertility based on literature search and global safety database. The RMP (version 13.1) has also been submitted

15.3.23. Nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/II/0117

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include Opdivo (nivolumab) in combination with platinum-based chemotherapy for neoadjuvant treatment of adult patients with resectable stage IB-IIIA non-small cell lung cancer (NSCLC), based on results from study CA209816: a randomised, open-label, phase 3 trial of nivolumab plus ipilimumab or nivolumab plus platinum-doublet chemotherapy versus platinum-doublet chemotherapy in early-stage NSCLC. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 27.0) are updated in accordance

15.3.24. Obinutuzumab - GAZYVARO (CAP) - EMEA/H/C/002799/II/0047, Orphan

Applicant: Roche Registration GmbH

PRAC Rapporteur: Annika Folin

Scope: Submission of the final report from study BO21223/GALLIUM (listed as a category 3 study in the RMP): an open-label, international, multicentre, randomized, phase 3 study to investigate the efficacy and safety of obinutuzumab administration at standard infusion rate plus chemotherapy followed by obinutuzumab maintenance therapy for responders (G-chemo arm) compared with rituximab plus chemotherapy followed by rituximab maintenance therapy for responders (R-chemo arm) in patients with previously untreated advanced indolent non-Hodgkin’s lymphoma (iNHL).The RMP (version 9.0) has also been submitted

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

Applicant: Bayer AG

PRAC Rapporteur: Brigitte Keller-Stanislawski

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

15.3.26. Pralsetinib - GAVRETO (CAP) - EMEA/H/C/005413/II/0002/G

Applicant: Roche Registration GmbH

PRAC Rapporteur: Annika Folin

Scope: Grouped variations consisting of: 1) extension of indication to include monotherapy treatment of adult and paediatric patients 12 years of age and older with locally advanced or metastatic rearranged during transfection (RET)-mutant medullary thyroid cancer for Gavreto (pralsetinib) based on the efficacy and safety data obtained from pivotal study

BO42863 (ARROW): a phase 1/2 study of the highly-selective RET inhibitor, BLU-667, in patients with thyroid cancer, non-small cell lung cancer (NSCLC) and other advanced solid tumours. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. Furthermore, some minor changes to the product information have been implemented in line with the latest anticancer guidelines recommendations; 2) extension of indication to include monotherapy treatment of adult and paediatric patients 12 years of age and older with locally advanced or metastatic RET fusion-positive thyroid cancer for Gavreto (pralsetinib) based on the efficacy and safety data obtained from pivotal study BO42863 (ARROW). As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The package leaflet and the RMP (version 1.1) are updated accordingly

15.3.27. Ribociclib - KISQALI (CAP) - EMEA/H/C/004213/II/0035

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Update of sections 4.4, 4.8 and 5.1 of the SmPC based on the final overall survival (OS) analysis from study A2301 (MONALEESA-2) (listed as a category 3 study in the RMP): a phase 3, randomized, double-blind, placebo-controlled, multicentre study of ribociclib in combination with letrozole in postmenopausal women with hormonal receptor positive (HR+), human epidermal growth factor receptor-2 negative (HER2-), locoregionally recurrent or metastatic breast cancer who had not received previous systemic therapy for advanced disease, and based on an updated pooled safety dataset including: 1) study MONALEESA-2; 2) study MONALEESA-3: a randomized double-blind, placebo-controlled study of ribociclib in combination with fulvestrant for the treatment of men and postmenopausal women with hormone receptor positive, HER2-negative, advanced breast cancer who have received no or only one line of prior endocrine treatment; 3) study MONALEESA-7: a phase 3 randomized, double-blind, placebo-controlled study of LEE011 or placebo in combination with tamoxifen and goserelin or a non-steroidal aromatase inhibitor (NSAI) and goserelin for the treatment of premenopausal women with hormone receptor positive, HER2-negative, advanced breast cancer (in fulfilment of MEA 004). The package leaflet and the RMP (version 6.0) are updated accordingly

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

Applicant: Stemline Therapeutics B.V.

PRAC Rapporteur: Menno van der Elst

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

Refer also to 10.1.1.

15.3.29. Tenofovir alafenamide - VEMLIDY (CAP) - EMEA/H/C/004169/II/0038

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Amelia Cupelli

Scope: Submission of the final week 192 report from study GS-US-320-3912 (listed as a category 3 study in the RMP): a phase 2, randomized, open label study to evaluate the efficacy and safety of tenofovir alafenamide (TAF) versus tenofovir disoproxil fumarate (TDF)-containing regimens in subjects with chronic hepatitis B virus (HBV) infection and stage 2 or greater chronic kidney disease who have received a liver transplant'. The RMP (version 8.1) has also been submitted

15.3.30. Tixagevimab, cilgavimab - EVUSHELD (CAP MAA) - EMEA/H/C/005788/II/0001

Applicant: AstraZeneca AB

PRAC Rapporteur: Kimmo Jaakkola

Scope: Extension of indication to include treatment of adults and adolescents aged 12 years and older weighing at least 40 kg with coronavirus (COVID-19), who do not require supplemental oxygen, based on interim results from study D8851C00001 (TACKLE): an ongoing, randomised, double-blind, placebo-controlled, multicentre study assessing the safety and efficacy of a single 600 mg dose of AZD7442 (× 2 intramuscular (IM) injections) compared with matching placebo for the treatment of mild to moderate COVID-19 in non-hospitalised adults. As a consequence, sections 4.1, 4.2, 4.8, 4.9, 5.1, 5.2 and 6.6 of the SmPC are updated. The package leaflet and labelling are updated in accordance. The RMP (version 2 succession 1) has also been submitted

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

Applicant: Daiichi Sankyo Europe GmbH

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

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

15.3.32. Trastuzumab deruxtecan - ENHERTU (CAP) - EMEA/H/C/005124/II/0014

Applicant: Daiichi Sankyo Europe GmbH

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Extension of indication to include treatment of adult patients with unresectable or metastatic human epidermal growth factor receptor 2 (HER2)-positive breast cancer who have received one or more prior anti-HER2-based regimens. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 1.2) are updated accordingly

15.3.33. Upadacitinib - RINVOQ (CAP) - EMEA/H/C/004760/II/0020/G

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Grouped variations consisting of: 1) update of sections 4.4 and 4.8 of the SmPC in order to add a new warning on 'hypersensitivity' and to add it to the list of adverse drug reactions (ADRs) with a frequency not known; 2) update of section 4.8 of the SmPC in order to add 'non-melanoma skin cancer (NMSC)' to the list of adverse drug reactions (ADRs) with a frequency uncommon. The package leaflet and the RMP (version 9.0) are updated accordingly

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

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

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

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

16.1.1. Acalabrutinib - CALQUENCE (CAP) - PSUSA/00010887/202110

Applicant: AstraZeneca AB

PRAC Rapporteur: Željana Margan Koletić

Scope: Evaluation of a PSUSA procedure

16.1.2. Aclidinium bromide, formoterol fumarate dihydrate - BRIMICA GENUAIR (CAP); DUAKLIR GENUAIR (CAP) - PSUSA/00010307/202111

Applicant(s): AstraZeneca AB

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.3. Autologous CD34+ enriched cell fraction that contains CD34+ cells transduced with retroviral vector that encodes for the human adenosine deaminase (ADA) complementary deoxyribonucleic acid (cDNA) sequence - STRIMVELIS (CAP) - PSUSA/00010505/202111

Applicant: Orchard Therapeutics (Netherlands) BV, ATMP[63]

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.4. Benralizumab - FASENRA (CAP) - PSUSA/00010661/202111

Applicant: AstraZeneca AB

PRAC Rapporteur: David Olsen

Scope: Evaluation of a PSUSA procedure

16.1.5. Bezlotoxumab - ZINPLAVA (CAP) - PSUSA/00010576/202110

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.6. Buprenorphine[64] - SIXMO (CAP) - PSUSA/00010778/202111

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

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.7. Ceftaroline fosamil - ZINFORO (CAP) - PSUSA/00010013/202110

Applicant: Pfizer Ireland Pharmaceuticals

PRAC Rapporteur: Maia Uusküla

Scope: Evaluation of a PSUSA procedure

16.1.8. Conestat alfa - RUCONEST (CAP) - PSUSA/00000873/202110

Applicant: Pharming Group N.V

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.1.9. Crizanlizumab - ADAKVEO (CAP) - PSUSA/00010888/202111

Applicant: Novartis Europharm Limited

[63] Advanced therapy medicinal product
[64] Implant(s) only

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

16.1.10. Darifenacin - EMSELEX (CAP) - PSUSA/00000933/202110

Applicant: Zr Pharma& GmbH

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

16.1.11. Dinutuximab beta - QARZIBA (CAP) - PSUSA/00010597/202111

Applicant: EUSA Pharma (Netherlands) B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.12. Dostarlimab - JEMPERLI (CAP) - PSUSA/00010931/202110

Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Evaluation of a PSUSA procedure

16.1.13. Drospirenone, estetrol - DROVELIS (CAP); LYDISILKA (CAP) - PSUSA/00010938/202111

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

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.14. Eculizumab - SOLIRIS (CAP) - PSUSA/00001198/202110

Applicant: Alexion Europe SAS

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

16.1.15. Edoxaban - LIXIANA (CAP); ROTEAS (CAP) - PSUSA/00010387/202110

Applicant(s): Daiichi Sankyo Europe GmbH (Lixiana), Berlin Chemie AG (Roteas)

PRAC Rapporteur: Nathalie Gault

Scope: Evaluation of a PSUSA procedure

16.1.16. Emicizumab - HEMLIBRA (CAP) - PSUSA/00010668/202111

Applicant: Roche Registration GmbH

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.1.17. Etelcalcetide - PARSABIV (CAP) - PSUSA/00010533/202111

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.1.18. Flutemetamol (^{18}F) - VIZAMYL (CAP) - PSUSA/00010293/202110

Applicant: GE Healthcare AS

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.19. Follitropin alfa - BEMFOLA (CAP); GONAL-F (CAP); OVALEAP (CAP) - PSUSA/00001463/202110

Applicant(s): Gedeon Richter Plc. (Bemfola), Merck Europe B.V. (Gonal-f), Theramex Ireland Limited (Ovaleap)

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.20. Follitropin alfa, lutropin alfa - PERGOVERIS (CAP) - PSUSA/00001464/202110

Applicant: Merck Europe B.V.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Evaluation of a PSUSA procedure

16.1.21. Fostamatinib - TAVLESSE (CAP) - PSUSA/00010819/202110

Applicant: Instituto Grifols, S.A.

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.22. Givosiran - GIVLAARI (CAP) - PSUSA/00010839/202111

Applicant: Alnylam Netherlands B.V.

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.23. Glasdegib - DAURISMO (CAP) - PSUSA/00010859/202111

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.24. Hepatitis B surface antigen - HEPLISAV B (CAP) - PSUSA/00010919/202111

Applicant: Dynavax GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.25. Ibrutinib - IMBRUVICA (CAP) - PSUSA/00010301/202111

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Evaluation of a PSUSA procedure

16.1.26. Idarucizumab - PRAXBIND (CAP) - PSUSA/00010435/202110

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.27. Insulin detemir - LEVEMIR (CAP) - PSUSA/00001750/202110

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Evaluation of a PSUSA procedure

16.1.28. Ivacaftor, tezacaftor, elexacaftor - KAFTRIO (CAP) - PSUSA/00010868/202110

Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.29. Ixazomib - NINLARO (CAP) - PSUSA/00010535/202111

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

16.1.30. Ketoconazole[65] - KETOCONAZOLE HRA (CAP) - PSUSA/00010316/202111

Applicant: HRA Pharma Rare Diseases

[65] Centrally authorised product(s) only

PRAC Rapporteur: Željana Margan Koletić

Scope: Evaluation of a PSUSA procedure

16.1.31. Larotrectinib - VITRAKVI (CAP) - PSUSA/00010799/202111

Applicant: Bayer AG

PRAC Rapporteur: Rugile Pilviniene

Scope: Evaluation of a PSUSA procedure

16.1.32. Letermovir - PREVYMIS (CAP) - PSUSA/00010660/202111

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

16.1.33. Lumasiran - OXLUMO (CAP) - PSUSA/00010884/202111

Applicant: Alnylam Netherlands B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.34. Meningococcal group B vaccine (recombinant, adsorbed) - TRUMENBA (CAP) - PSUSA/00010607/202110

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

16.1.35. Midostaurin - RYDAPT (CAP) - PSUSA/00010638/202110

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Evaluation of a PSUSA procedure

16.1.36. Miglustat - ZAVESCA (CAP) - PSUSA/00002062/202110

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.37. Nintedanib[66] - OFEV (CAP) - PSUSA/00010319/202110

Applicant: Boehringer Ingelheim International GmbH

[66] Respiratory indication(s) only

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Evaluation of a PSUSA procedure

16.1.38. Ozanimod - ZEPOSIA (CAP) - PSUSA/00010852/202111

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

16.1.39. Padeliporfin - TOOKAD (CAP) - PSUSA/00010654/202111

Applicant: STEBA Biotech S.A

PRAC Rapporteur: Maia Uusküla

Scope: Evaluation of a PSUSA procedure

16.1.40. Pandemic influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) - FOCLIVIA (CAP); prepandemic influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) - AFLUNOV (CAP) - PSUSA/00010008/202110

Applicant(s): Seqirus S.r.l

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.1.41. Parathyroid hormone - NATPAR (CAP) - PSUSA/00010591/202110

Applicant: Takeda Pharmaceuticals International AG

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

16.1.42. Pazopanib - VOTRIENT (CAP) - PSUSA/00002321/202110

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Evaluation of a PSUSA procedure

16.1.43. Pemigatinib - PEMAZYRE (CAP) - PSUSA/00010923/202110

Applicant: Incyte Biosciences Distribution B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.44. Potassium citrate, potassium hydrogen carbonate - SIBNAYAL (CAP) - PSUSA/00010932/202110

Applicant: Advicenne

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.45. Prasterone[67] - INTRAROSA (CAP) - PSUSA/00010672/202111

Applicant: Endoceutics S.A.

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.46. Prucalopride - RESOLOR (CAP) - PSUSA/00002568/202110

Applicant: Takeda Pharmaceuticals International AG

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.47. Ebola Zaire vaccine (live, attenuated) - ERVEBO (CAP) - PSUSA/00010834/202111

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.48. Relugolix, estradiol, norethisterone acetate - RYEQO (CAP) - PSUSA/00010942/202111

Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.49. Rurioctocog alfa pegol - ADYNOVI (CAP) - PSUSA/00010663/202111

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.50. Selpercatinib - RETSEVMO (CAP) - PSUSA/00010917/202111

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.51. Setmelanotide - IMCIVREE (CAP) - PSUSA/00010941/202111

Applicant: Rhythm Pharmaceuticals Netherlands B.V.

[67] Pessary, vaginal use only

PRAC Rapporteur: Marek Juracka

Scope: Evaluation of a PSUSA procedure

16.1.52. Sotagliflozin - ZYNQUISTA[68] - PSUSA/00010766/202110

Applicant: Guidehouse Germany GmbH

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.53. Stiripentol - DIACOMIT (CAP) - PSUSA/00002789/202111

Applicant: Biocodex

PRAC Rapporteur: Maia Uusküla

Scope: Evaluation of a PSUSA procedure

16.1.54. Susoctocog alfa - OBIZUR (CAP) - PSUSA/00010458/202111

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.55. Talazoparib - TALZENNA (CAP) - PSUSA/00010781/202110

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Evaluation of a PSUSA procedure

16.1.56. Talimogene laherparepvec - IMLYGIC (CAP) - PSUSA/00010459/202110

Applicant: Amgen Europe B.V., ATMP[69]

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.57. Trastuzumab - HERCEPTIN (CAP); HERZUMA (CAP); KANJINTI (CAP); OGIVRI (CAP); ONTRUZANT (CAP); TRAZIMERA (CAP); ZERCEPAC (CAP) - PSUSA/00003010/202109

Applicant(s): Accord Healthcare S.L.U. (Zercepac), Amgen Europe B.V., BREDA (Kanjinti), Celltrion Healthcare Hungary Kft. (Herzuma), Pfizer Europe MA EEIG (Trazimera), Roche Registration GmbH (Herceptin), Samsung Bioepis NL B.V. (Ontruzant), Viatris Limited (Ogivri)

PRAC Rapporteur: Brigitte Keller-Stanislawski

[68] European Commission (EC) decision on the withdrawal of the marketing authorisation (MA) for Zynquista dated 22 March 2022

[69] Advanced therapy medicinal product

Scope: Evaluation of a PSUSA procedure

16.1.58. Tucatinib - TUKYSA (CAP) - PSUSA/00010918/202110

Applicant: Seagen B.V.

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

16.1.59. Vestronidase alfa - MEPSEVII (CAP) - PSUSA/00010709/202111

Applicant: Ultragenyx Germany GmbH

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

16.1.60. Volanesorsen - WAYLIVRA (CAP) - PSUSA/00010762/202111

Applicant: Akcea Therapeutics Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.61. Zinc acetate dihydrate - WILZIN (CAP) - PSUSA/00003145/202110

Applicant: Recordati Rare Diseases

PRAC Rapporteur: Rhea Fitzgerald

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. Bosentan - STAYVEER (CAP); TRACLEER (CAP); NAP - PSUSA/00000425/202111

Applicants: Janssen-Cilag International N.V. (Stayveer, Tracleer), various

PRAC Rapporteur: Nathalie Gault

Scope: Evaluation of a PSUSA procedure

16.2.2. Carbidopa, entacapone, levodopa - CORBILTA (CAP); LEVODOPA/CARBIDOPA/ENTACAPONE ORION (CAP); STALEVO (CAP); NAP - PSUSA/00000547/202110

Applicants: Orion Corporation (Corbilta, Levodopa/Carbidopa/Entacapone Orion, Stalevo), various

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

16.2.3. Posaconazole - NOXAFIL (CAP); NAP - PSUSA/00002480/202110

Applicants: Merck Sharp & Dohme B.V. (Noxafil), various

PRAC Rapporteur: Nathalie Gault

Scope: Evaluation of a PSUSA procedure

16.2.4. Sevelamer - RENAGEL (CAP); RENVELA (CAP); SEVELAMER CARBONATE WINTHROP (CAP); NAP - PSUSA/00002697/202110

Applicants: Genzyme Europe BV (Renagel, Renvela, Sevelamer Carbonate Winthrop), various

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

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

16.3.1. ^{13}C-methacetin (NAP) - PSUSA/00010846/202110

Applicant(s): various

PRAC Lead: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.3.2. Acetylsalicylic acid, bisoprolol (NAP) - PSUSA/00010287/202111

Applicant(s): various

PRAC Lead: Anna Mareková

Scope: Evaluation of a PSUSA procedure

16.3.3. Acitretin (NAP) - PSUSA/00000051/202110

Applicant(s): various

PRAC Lead: Marie Louise Schougaard Christiansen

Scope: Evaluation of a PSUSA procedure

16.3.4. Amlodipine, perindopril (NAP) - PSUSA/00000179/202110

Applicant(s): various

PRAC Lead: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

16.3.5. Azelastine, fluticasone (NAP) - PSUSA/00010067/202110

Applicant(s): various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.3.6. Benzalkonium chloride, chlorhexidine digluconate (NAP) - PSUSA/00010070/202111

Applicant(s): various

PRAC Lead: Rugilė Pilvinienė

Scope: Evaluation of a PSUSA procedure

16.3.7. Benzydamine (NAP) - PSUSA/00000375/202110

Applicant(s): various

PRAC Lead: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.3.8. Brimonidine[70] (NAP) - PSUSA/00000430/202109

Applicant(s): various

PRAC Lead: Ronan Grimes

Scope: Evaluation of a PSUSA procedure

16.3.9. Brimonidine, timolol (NAP) - PSUSA/00000431/202109

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.3.10. Clevidipine (NAP) - PSUSA/00010288/202111

Applicant(s): various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.3.11. Clindamycin (NAP) - PSUSA/00000795/202110

Applicant(s): various

PRAC Lead: Sonja Hrabcik

Scope: Evaluation of a PSUSA procedure

16.3.12. Dexketoprofen (NAP) - PSUSA/00000997/202110

Applicant(s): various

PRAC Lead: Eva Segovia

[70] Non-centrally authorised product(s) only

Scope: Evaluation of a PSUSA procedure

16.3.13. Dextromethorphan (NAP) - PSUSA/00001009/202111

Applicant(s): various

PRAC Lead: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

16.3.14. Diclofenac, omeprazole (NAP) - PSUSA/00010461/202109

Applicant(s): various

PRAC Lead: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

16.3.15. Drospirenone (NAP) - PSUSA/00010853/202111

Applicant(s): various

PRAC Lead: Annika Folin

Scope: Evaluation of a PSUSA procedure

16.3.16. Erythromycin, tretinoin (NAP) - PSUSA/00001259/202110

Applicant(s): various

PRAC Lead: Anna Mareková

Scope: Evaluation of a PSUSA procedure

16.3.17. Ethinylestradiol, norgestimate (NAP) - PSUSA/00001313/202110

Applicant(s): various

PRAC Lead: Marie Louise Schougaard Christiansen

Scope: Evaluation of a PSUSA procedure

16.3.18. Human coagulation factor VIII, human von Willebrand factor (NAP) – PSUSA/00001621/202110

Applicant(s): various

PRAC Lead: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.3.19. Hydrochlorothiazide, olmesartan (NAP) - PSUSA/00002209/202110

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.3.20. Isopropyl alcohol, propyl alcohol, mecetronium ethyl sulfate (NAP) - PSUSA/00010108/202109

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.3.21. Lacidipine (NAP) - PSUSA/00001815/202110

Applicant(s): various

PRAC Lead: Maia Uusküla

Scope: Evaluation of a PSUSA procedure

16.3.22. Letrozole (NAP) - PSUSA/00001842/202110

Applicant(s): various

PRAC Lead: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

16.3.23. Magnesium hydroxide (NAP) - PSUSA/00001926/202110

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.3.24. Meningococcal group C polysaccharide conjugate vaccine (NAP) - PSUSA/00001971/202110

Applicant(s): various

PRAC Lead: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

16.3.25. Milrinone (NAP) - PSUSA/00002064/202110

Applicant(s): various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.3.26. Olmesartan (NAP) - PSUSA/00002207/202110

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.3.27. Phloroglucinol (NAP), phloroglucinol, trimethylphloroglucinol (NAP) - PSUSA/00010355/202109

Applicant(s): various

PRAC Lead: Nathalie Gault

Scope: Evaluation of a PSUSA procedure

16.3.28. Piretanide (NAP) - PSUSA/00002433/202110

Applicant(s): various

PRAC Lead: Nathalie Gault

Scope: Evaluation of a PSUSA procedure

16.3.29. Polystyrene sulfonate (NAP) - PSUSA/00002472/202110

Applicant(s): various

PRAC Lead: Jana Lukačišinová

Scope: Evaluation of a PSUSA procedure

16.3.30. Rubidium (^{82}Rb) chloride (NAP) - PSUSA/00010806/202110

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.3.31. Tiotropium (NAP) - PSUSA/00002972/202110

Applicant(s): various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.3.32. Zidovudine (NAP) - PSUSA/00003143/202109

Applicant(s): various

PRAC Lead: Jana Lukačišinová

Scope: Evaluation of a PSUSA procedure

16.4. Follow-up to PSUR/PSUSA procedures

16.4.1. Alectinib - ALECENSA (CAP) - EMEA/H/C/004164/LEG 004

Applicant: Roche Registration GmbH

PRAC Rapporteur: Jana Lukacisinova

Scope: Cumulative review of cases of QT prolongation reported with alectinib

administration, including post-marketing, clinical trials and literature data, as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00010581/202107) adopted in February 2022

16.4.2. Coronavirus (COVID-19) vaccine (Ad26.COV2-S, recombinant) - JCOVDEN (CAP) - EMEA/H/C/005737/LEG 051

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Cumulative review of cases of coronary artery disease including myocardial infarction based on data from clinical trials, post-marketing data and literature, including (age) stratified observed/expected (O/E) analyses following the publication of an epidemiological study based on data from French national databases (EPI-Phare) suggesting a slightly increased risk for myocardial infarction with Jcovden (COVID-19 vaccine (Ad26.COV2-S, recombinant)), as requested in the conclusions of the ninth summary safety report (SSR) adopted in March 2022

16.4.3. Coronavirus (COVID-19) vaccine (ChAdOx1-S [recombinant]) - VAXZEVRIA (CAP) - EMEA/H/C/005675/LEG 103

Applicant: AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

Scope: Cumulative review of cases of pulmonary embolism (PE) and coronary artery disease including myocardial infarction based on data from clinical trials, post-marketing data and literature, including (age) stratified observed/expected (O/E) analyses following the publication of an epidemiological study based on data from French national databases (EPI-Phare), together with a justification of used background rates.

16.4.4. Laronidase - ALDURAZYME (CAP) - EMEA/H/C/000477/LEG 056

Applicant: Genzyme Europe BV

PRAC Rapporteur: Nathalie Gault

Scope: Detailed review of cases of hypersensitivity reactions, immunogenicity, infusion-site reaction, overdose, cases suggestive of overdose and use of laronidase by intrathecal route, as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00010581/202107) adopted in December 2021

16.5. Variation procedure(s) resulting from PSUSA evaluation

16.5.1. Dolutegravir - TIVICAY (CAP) - EMEA/H/C/002753/WS2268/0079; dolutegravir, abacavir, lamivudine - TRIUMEQ (CAP) - EMEA/H/C/002754/WS2268/0104; dolutegravir, lamivudine - DOVATO (CAP) - EMEA/H/C/004909/WS2268/0031; dolutegravir, rilpivirine - JULUCA (CAP) - EMEA/H/C/004427/WS2268/0044

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Martin Huber

Scope: Update of section 4.8 of the SmPC to add 'weight increased' with a frequency

common based on available data/results from study RESPOND (International Cohort Consortium of Infectious Disease): a prospective, multi-cohort collaboration study of people living with human immunodeficiency virus (HIV) across Europe and Australia as requested in the conclusions of the post-authorisation measures (LEG procedures) adopted in February 2022 that followed a request adopted in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00010075/202101) finalised in September 2021. The package leaflet is updated accordingly. In addition, the MAH took the opportunity to implement a minor editorial change in the German SmPC for Juluca (dolutegravir/rilpivirine)

16.6. Expedited summary safety reviews[71]

16.6.1. Coronavirus (COVID-19) vaccine (recombinant, adjuvanted) - NUVAXOVID (CAP) - EMEA/H/C/005808/MEA 014.2

Applicant: Novavax CZ, a.s.

PRAC Rapporteur: Brigitte Keller-Stanislawski

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

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

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

17.1. Protocols of PASS imposed in the marketing authorisation(s)[72]

17.1.1. Lomitapide - LOJUXTA (CAP) - EMEA/H/C/PSA/S/0083.1

Applicant: Amryt Pharmaceuticals DAC

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to PSA/S/0083 [substantial amendment to a protocol previously agreed in November 2013 for lomitapide observational worldwide evaluation registry to evaluate the occurrence and outcomes of pregnancy in females of reproductive potential treated with lomitapide] as per the request for supplementary information (RSI) adopted in March 2022

17.1.2. Teduglutide - REVESTIVE (CAP) - EMEA/H/C/PSA/S/0082.1

Applicant: Shire Pharmaceuticals Ireland Limited

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: MAH's response to PSA/S/0082 [substantial amendment to a protocol previously

[71] 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
[72] In accordance with Article 107n of Directive 2001/83/EC

agreed in July 2019 (PSA/S/0040) for study TED-R13-002: a prospective, multicentre registry for patients with short bowel syndrome] as per the request for supplementary information (RSI) adopted in February 2022

17.1.3. Valproate[73] (NAP) - EMEA/H/N/PSP/J/0074.5

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

PRAC Rapporteur: Jean-Michel Dogné

Scope: MAH's response to PSP/J/0074.4 [interim report for a joint observational study to evaluate and identify the best practices for switching of valproate in clinical practice, as required in the outcome of the referral procedure under Article 31 of Directive 2001/83/EC on valproate-containing products completed in February 2018 (EMEA/H/A-31/1454)] as per the request for supplementary information (RSI) adopted in January 2022

17.2. Protocols of PASS non-imposed in the marketing authorisation(s)[74]

17.2.1. Crizanlizumab - ADAKVEO (CAP) - EMEA/H/C/004874/MEA 004.1

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Jean-Michel Dogné

Scope: MAH's response to MEA 004 [protocol for study CSEG101A2405 (listed as a category 3 study in the RMP): a non-interventional PASS - registry-based study to assess long-term safety and pregnancy outcomes in patients with sickle cell disease (SCD) using crizanlizumab] as per the request for supplementary information (RSI) adopted in December 2021

17.2.2. Eptinezumab – VYEPTI (CAP) – EMEA/H/C/005287/MEA 004

Applicant: H. Lundbeck A/S

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Protocol for study 19756N: a long-term cardiovascular safety and real-world use of eptinezumab - an observational, historical cohort study of patients initiating eptinezumab in routine clinical practice

17.2.3. Linaclotide - CONSTELLA (CAP) - EMEA/H/C/002490/MEA 009.5

Applicant: Allergan Pharmaceuticals International Limited

PRAC Rapporteur: Martin Huber

Scope: Substantial amendment to a protocol previously agreed for PASS EVM-18888: linaclotide safety study assessing the complications of diarrhoea and associated risk factors in selected European populations with irritable bowel syndrome with constipation (IBS-C) for Constella (linaclotilde) 290µg capsule (protocol version 10.0)

[73] Valproic acid, sodium valproate, valproate pivoxil, valproate semisodium, valpriomide, valproate bismuth, calcium valproate, valproate magnesium
[74] 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. Lonapegsomatropin - LONAPEGSOMATROPIN ASCENDIS PHARMA (CAP) - EMEA/H/C/005367/MEA 001

Applicant: Ascendis Pharma Endocrinology Division A/S

PRAC Rapporteur: Martin Huber

Scope: Protocol for study VV-SUB-056752: a prospective, non-interventional, long-term, safety study of patients treated with lonapegsomatropin to further characterise the potential long-term safety risks of lonapegsomatropin in patients treated with under real-world conditions in the post-marketing setting [final results expected in July 2033]

17.2.5. Neratinib - NERLYNX (CAP) - EMEA/H/C/004030/MEA 003.2

Applicant: Pierre Fabre Medicament

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to MEA 003.1 [protocol for study PUMA-NER-7402: a non-interventional study exploring the safety of neratinib among breast cancer patients to characterise the incidence and duration of diarrhoea in a real world setting, to describe patient characteristics, incidence rates and duration of diarrhoea, to describe use of loperamide and other concomitant anti-diarrhoeal medication, describe adherence to neratinib therapy, assess the impact of neratinib therapy on patient self-reported, health related quality of life and their ability to perform their activities of daily living and to further assess and characterise adverse events hepatic, cardiac, pulmonary, reproductive and developmental toxicity] as per the request for supplementary information (RSI) adopted in May 2020

17.2.6. Patisiran - ONPATTRO (CAP) - EMEA/H/C/004699/MEA 003.3

Applicant: Alnylam Netherlands B.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: MAH's response to MEA 003.2 [update to a previously agreed protocol and interim study report for study ALN-TTR02-010: patisiran- lipid nanoparticle (LNP) pregnancy surveillance programme (PSP) to collect primary data on pregnant women from the US, the United Kingdom (UK), France, Spain, Italy, Portugal and Germany, and other potential countries, who have been exposed to patisiran during the exposure window, defined as 12 weeks prior to their last menstrual period (LMP), or at any time during pregnancy as well as to collect and analyse information pertaining to pregnancy complications and birth outcomes in women exposed to patisiran during pregnancy] as per the request for supplementary information (RSI) adopted in January 2022

17.2.7. Ponesimod - PONVORY (CAP) - EMEA/H/C/005163/MEA 001.1

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Anette Kirstine Stark

Scope: MAH's response to MEA 001 [protocol for study PCSNSP004001 (listed as a category 3 study in the RMP): ponesimod pregnancy outcomes enhanced monitoring (POEM) - pregnancy outcomes programme utilising enhanced pharmacovigilance monitoring to

evaluate the potential risk of reproductive and embryofetal toxicity in pregnant women exposed to ponesimod (from initial opinion/marketing authorisation)] as per the request for supplementary information (RSI) adopted in January 2022

17.2.8. Ponesimod - PONVORY (CAP) - EMEA/H/C/005163/MEA 004.1

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Anette Kirstine Stark

Scope: MAH's response to MEA 004 [protocol for study PCSNSP003693 (listed as a category 3 study in the RMP): a survey among healthcare professionals (neurologists treating patients with multiple sclerosis (MS) along with MS specialist nurses) in selected European countries to evaluate knowledge and behaviours required for the safe use of ponesimod] as per the request for supplementary information (RSI) adopted in December 2021

17.2.9. Rivaroxaban - XARELTO (CAP) - EMEA/H/C/000944/MEA 049.2

Applicant: Bayer AG

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Protocol for study 22195 (listed as a category 3 study in the RMP): an observational, longitudinal, multi-source drug utilisation safety study to evaluate the drug use patterns and safety of rivaroxaban oral suspension in children under two years with venous thromboembolism (feasibility report assessed by PRAC in July 2021 (MEA 049))

17.2.10. Sacubitril, valsartan - ENTRESTO (CAP) - EMEA/H/C/004062/MEA 002.8

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Anette Kirstine Stark

Scope: Substantial protocol amendment and fifth interim report for study CLCZ696B2014 (PASS 1) (listed as a category 3 study in the RMP): a non-interventional post-authorisation European multi-database safety study to characterise the risk of angioedema and other specific safety events of interest in association with the use of Entresto/Neparvis (sacubitril/valsartan) in adult patients with heart failure

17.2.11. Sacubitril, valsartan - NEPARVIS (CAP) - EMEA/H/C/004343/MEA 002.5

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Anette Kirstine Stark

Scope: Substantial protocol amendment and fifth interim report for study CLCZ696B2014 (PASS 1) (listed as a category 3 study in the RMP): a non-interventional post-authorisation European multi-database safety study to characterise the risk of angioedema and other specific safety events of interest in association with the use of Entresto/Neparvis (sacubitril/valsartan) in adult patients with heart failure

17.2.12. Tozinameran - COMIRNATY (CAP) - EMEA/H/C/005735/MEA 017.3

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to MEA 017.2 [substantial amendment to a protocol previously agreed in June 2021 for study C4591021 (previously known as vACcine Covid-19 monitoring readinESS/Vaccine monitoring Collaboration for Europe (ACCESS/VAC4EU)): an assessment of potential increased risk of adverse events of special interest (AESI), including myocarditis/pericarditis after being vaccinated with COVID-19 messenger ribonucleic acid (mRNA) vaccine estimating the time trend, in relation to DHPC letter dissemination, of the proportion of individuals who received real-world clinical assessments for myocarditis/pericarditis following Comirnaty (tozinameran) vaccination together with a statistical analysis plan (SAP)] as per the request for supplementary information (RSI) adopted in March 2022

17.2.13. Tozinameran - COMIRNATY (CAP) - EMEA/H/C/005735/MEA 041.1

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to MEA 041 [protocol for study C4591036 (former paediatric heart network study): a safety surveillance study of myocarditis and myopericarditis associated with Comirnaty (tozinameran) in persons less than 21 years of age to characterize the clinical course, risk factors, long-term sequelae, and quality of life in children and young adults under 21 years with acute post-vaccine myocarditis] as per the request for supplementary information (RSI) adopted in February 2022

17.2.14. Tozinameran - COMIRNATY (CAP) - EMEA/H/C/005735/MEA 047.1

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to MEA 047 [protocol for study C4591038 (listed as a category 3 study in the RMP): a post conditional approval active surveillance study among individuals in Europe receiving the Pfizer BioNTech coronavirus disease 2019 (COVID-19) vaccine to investigate natural history of post-vaccination myocarditis and pericarditis] as per request for supplementary information (RSI) adopted in May 2022

17.3. Results of PASS imposed in the marketing authorisation(s)[75]

17.3.1. Valproate (NAP) - EMEA/H/N/PSR/J/0036

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

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: MAH's response to PSR/J/0036 [results for a joint survey among healthcare professionals (HCP) to assess knowledge of HCP and behaviour with regards to pregnancy prevention programme (PPP) as well as receipt/use of a direct healthcare professional communication (DHPC) and educational materials (EM) and survey among patients to assess knowledge of the patients with regards to PPP as well as receipt/use of EM, as required in the outcome of the referral procedure under Article 31 of Directive 2001/83/EC

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

on valproate-containing products completed in February 2018 (EMEA/H/A-31/1454)] as per the request for supplementary information (RSI) adopted in October 2021

17.4. Results of PASS non-imposed in the marketing authorisation(s)[76]

17.4.1. Alirocumab - PRALUENT (CAP) - EMEA/H/C/003882/II/0068

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of section 4.8 of the SmPC based on the final results from study OBS14697 (listed as a category 3 study in the RMP): a non-interventional, retrospective drug utilisation study (DUS) to assess in Europe the effectiveness of the dosing recommendation and to describe patterns of alirocumab utilisation in real world clinical practice (in fulfilment of MEA 019.8). In addition, the MAH took the opportunity to implement editorial changes in the product information

17.4.2. Crizotinib - XALKORI (CAP) - EMEA/H/C/002489/II/0075

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Tiphaine Vaillant

Scope: Submission of the final report for study A8081062 (listed as a category 3 study in the RMP): a non-interventional, descriptive study of potential sight threatening event and severe visual loss following exposure to crizotinib (in fulfilment of MEA 024)

17.4.3. Empagliflozin - JARDIANCE (CAP) - EMEA/H/C/002677/WS2196/0063; empagliflozin, linagliptin - GLYXAMBI (CAP) - EMEA/H/C/003833/WS2196/0042; empagliflozin, metformin - SYNJARDY (CAP) - EMEA/H/C/003770/WS2196/0060

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Eva Segovia

Scope: Update of section 4.4 of the SmPC to delete the warning on lower limb amputations based on the results from the final meta-analysis report of study 1245.171 (listed as a category 3 study in the RMP): a meta-analysis of amputation risk in empagliflozin studies, namely: 1) study 1245.25 (EMPA-REG OUTCOME): a study in patients with type 2 diabetes mellitus (T2DM) and increased cardiovascular risk; 2) study 1245.110 (EMPEROR- HFpEF): a study in patients with chronic heart failure (HF) with preserved ejection fraction; 3) study 1245.121 (EMPEROR- HFrEF): a study in patients with chronic HF with reduced ejection fraction. The package leaflet and the RMP (version 17 for Jardiance, version 11 for Synjardy and version 6 for Glyxambi) are updated accordingly. The conduct of this meta-analysis was requested to MAHs of all sodium-glucose co-transporter-2 (SGLT2)-containing products as part of the outcome of the referral procedure (EMEA/H/A-20/1419) under Article 20 of Regulation (EC) No 726/2004 finalised in 2016

[76] 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

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

Applicant: GE Healthcare AS

PRAC Rapporteur: Martin Huber

Scope: Submission of the final report from study GE067-027 (listed as a category 3 study in the RMP): a non-interventional PASS to evaluate the effectiveness of Vizamyl (flutemetamol (^{18}F)) reader training in Europe. The submission also includes a comprehensive root-cause analysis on the contributing factors having an impact on reader performance as requested by PRAC. The RMP (version 3.1) is updated accordingly and includes relevant updates to reflect the completion of study GE067-028 on the use pattern of Vizamyl (flutemetamol (^{18}F)) in post-authorisation setting in the EU, as previously assessed in MEA 003.3

17.4.5. Hepatitis B surface antigen - HEPLISAV B (CAP) - EMEA/H/C/005063/II/0015

Applicant: Dynavax GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Submission of the final report from study HBV-26 (listed as a category 3 study in the RMP): a post-marketing observational surveillance study to evaluate the incidence of new-onset immune-mediated diseases, herpes zoster, and anaphylaxis in recipients of Heplisav B (hepatitis B surface antigen) with recipients of another hepatitis B vaccine. The RMP (version 1.3) is updated accordingly

17.4.6. Meningococcal group B vaccine (recombinant, adsorbed) - TRUMENBA (CAP) - EMEA/H/C/004051/II/0040

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Jean-Michel Dogné

Scope: Submission of the final report from study B1971052 (listed as a category 3 study in the RMP): a population-based, non-interventional cohort study utilising administrative healthcare claims data assessing pregnancy and birth outcome after exposure to Trumenba (meningococcal group B vaccine (recombinant, adsorbed)) (in fulfilment of MEA 001)

17.4.7. Naltrexone hydrochloride, bupropion hydrochloride - MYSIMBA (CAP) - EMEA/H/C/003687/II/0054

Applicant: Orexigen Therapeutics Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: Submission of the final report from study NB-542 (listed as a category 3 study in the RMP): a cross-sectional survey aimed to evaluate the effectiveness of the Mysimba (naltrexone hydrochloride/bupropion hydrochloride) physician prescribing checklist (PPC) among physicians in the EU. The RMP (version 12.6) is updated accordingly

17.4.8. Rotavirus vaccine (live, oral) - ROTARIX (CAP) - EMEA/H/C/000639/II/0125

Applicant: GlaxoSmithKline Biologicals S.A.

PRAC Rapporteur: Jean-Michel Dogné

Scope: Submission of the final report from study EPI-ROTA-052 BOD EU SUPP (201433) (listed as a category 3 study in the RMP): an observational community-based strain surveillance study to monitor the potential emergence and spread of novel rotavirus (RV) strains throughout Europe. The RMP (version 23) is updated accordingly

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

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: Submission of the final safety registry report from study CNTO1275PSO4007: pregnancy research initiative - exposure to ustekinumab during pregnancy: a review and analysis of birth outcomes from the Swedish, Danish, and Finnish medical birth registers (in fulfilment of MEA 024). The RMP (version 22.1) is updated accordingly

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

17.5.1. Abatacept - ORENCIA (CAP) - EMEA/H/C/000701/MEA 048.10

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Kimmo Jaakkola

Scope: Annual update report on recruitment for study IM101240 (listed as a category 3 study in the RMP): an observational registry of abatacept in patients with juvenile idiopathic arthritis (JIA registry) to explore the long-term safety of abatacept treatment for JIA in routine clinical practice by quantifying the incidence rates of serious infections, autoimmune disorders and malignancies [final registry report expected by 2029]

17.5.2. Adalimumab - HUMIRA (CAP) - EMEA/H/C/000481/MEA 065.12

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Thirteenth interim annual report for study P10-023, a psoriasis patient registry: a 10-year, post-marketing observational study to assess the long-term safety of Humira (adalimumab) in adult patients with chronic plaque psoriasis (PS)

17.5.3. Alemtuzumab - LEMTRADA (CAP) - EMEA/H/C/003718/MEA 007.12

Applicant: Sanofi Belgium

PRAC Rapporteur: Anette Kirstine Stark

Scope: Seventh annual progress report for study OBS13434: a prospective, multicentre, observational PASS to evaluate the long-term safety profile of Lemtrada (alemtuzumab) treatment in patients with relapsing forms of multiple sclerosis (MS) and to determine the incidence of adverse events of special interest (AESIs)

17.5.4. Cangrelor - KENGREXAL (CAP) - EMEA/H/C/003773/MEA 002.5

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Amelia Cupelli

Scope: MAH's response to MEA 002.4 [second interim report for study DFIDM-1801 (ARCANGELO (itAlian pRospective study on CANGrELOr)): a multicentre prospective observational study of acute coronary syndrome patients undergoing percutaneous coronary intervention (PCI) who receive cangrelor and transition to either clopidogrel, prasugrel or ticagrelor] as per the request for supplementary information (RSI) adopted in January 2022

17.5.5. Filgrastim - FILGRASTIM HEXAL (CAP) - EMEA/H/C/000918/MEA 007.12

Applicant: Hexal AG

PRAC Rapporteur: Menno van der Elst

Scope: Eleventh annual report for study EP06-501 (SMART): a non-interventional, prospective, long-term safety data collection of Zarzio/Filgrastim Hexal (filgrastim) in healthy unrelated stem cell donors undergoing peripheral blood progenitor cell (PBPC) mobilisation

17.5.6. Filgrastim - ZARZIO (CAP) - EMEA/H/C/000917/MEA 007.12

Applicant: Sandoz GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Eleventh annual report for study EP06-501 (SMART): a non-interventional, prospective, long-term safety data collection of Zarzio/Filgrastim Hexal (filgrastim) in healthy unrelated stem cell donors undergoing peripheral blood progenitor cell (PBPC) mobilisation

17.5.7. Inclisiran - LEQVIO (CAP) - EMEA/H/C/005333/MEA 004.1

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Kimmo Jaakkola

Scope: First annual interim report for study CKJX839A12011: a non-interventional PASS to estimate the proportion of major congenital malformations among pregnancies exposed to inclisiran during pregnancy reported to Novartis amongst (i) live births and (ii) live births plus still births plus termination of pregnancy for foetal anomaly (TOPFA) - Inclisiran pregnancy outcomes intensive monitoring (PRIM)

17.5.8. Mercaptamine - CYSTADROPS (CAP) - EMEA/H/C/003769/MEA 001.4

Applicant: Recordati Rare Diseases

PRAC Rapporteur: Eva Segovia

Scope: Second annual report for study CYT-DS-001 (listed as a category 3 study in the RMP): an open-label longitudinal PASS to assess the safety of Cystadrops (mercaptamine) in paediatric and adult cystinosis patients in long term use

17.5.9. Ofatumumab - KESIMPTA (CAP) - EMEA/H/C/005410/MEA 003

Applicant: Novartis Ireland Limited

PRAC Rapporteur: Amelia Cupelli

Scope: First annual interim report for COMB157G2399 (ALITHIOS) study (listed as a category 3 study in the RMP): an open-label, single arm, multicentre extension study evaluating long-term safety, tolerability and effectiveness of ofatumumab in subjects with relapsing multiple sclerosis

17.5.10. Romosozumab - EVENITY (CAP) - EMEA/H/C/004465/MEA 001.4

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Tiphaine Vaillant

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

17.5.11. Romosozumab - EVENITY (CAP) - EMEA/H/C/004465/MEA 002.4

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Tiphaine Vaillant

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

17.5.12. Sarilumab - KEVZARA (CAP) - EMEA/H/C/004254/MEA 002.6

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Eva Segovia

Scope: Third interim report for a safety surveillance programme using existing EU rheumatoid arthritis (RA) registries conducted in four countries: Germany (German Register for Rheumatoid Arthritis Observation of Biologic Therapy (RABBIT) (OBS15180)), Spain (Spanish Registry for Adverse Events for Biological Therapy in Rheumatic Diseases (BIOBASASER) (6R88-RA-1720)), Sweden (Register for Antirheumatic Therapies in Sweden (ARTIS) (OBS15220)) and UK (British Society for Rheumatology Biologicals Register (BSRBR) (6R88-RA-1634)

17.5.13. Selexipag - UPTRAVI (CAP) - EMEA/H/C/003774/MEA 001.7

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Nathalie Gault

Scope: Fifth annual interim report for PASS AC-065A401 (EXPOSURE): an observational

cohort study of pulmonary arterial hypertension (PAH) patients newly treated with either Uptravi (selexipag) or any other PAH-specific therapy in routine clinical practice

17.5.14. Teriflunomide - AUBAGIO (CAP) - EMEA/H/C/002514/MEA 005.4

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Martin Huber

Scope: MAH's response to MEA 005.3 [1) eighth annual progress report for pregnancy registry OBS13499 (US/CA): teriflunomide pregnancy outcome exposure registry: a 'teratology information specialists (OTIS)' autoimmune diseases in pregnancy project, 2) fifth annual progress report for OBS12751 (international): an international pregnancy exposure registry of women with multiple sclerosis (MS) exposed to Aubagio (teriflunomide)] as per request for supplementary information (RSI) adopted in February 2022

17.5.15. Tisagenlecleucel - KYMRIAH (CAP) - EMEA/H/C/004090/ANX 003.8

Applicant: Novartis Europharm Limited, ATMP[77]

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Fifth semi-annual report for study CCTL019B2401: a non-interventional PASS to further characterise the safety, including long-term safety, of Kymriah (tisagenlecleucel) based on data from a disease registry in acute lymphoblastic leukaemia (ALL) and diffuse large B-cell lymphoma (DLBCL) patients (European Society for Blood and Marrow Transplant Society Registry (EBMT) data only)

17.5.16. Tozinameran - COMIRNATY (CAP) - EMEA/H/C/005735/MEA 011.5

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

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

17.5.17. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/MEA 045.8

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: MAH's response to MEA 045.7 [second interim report for study RRA-20745: an observational PASS to describe the safety of ustekinumab and other Crohn's disease treatments in a cohort of patients with Crohn's disease] as per the request for supplementary information (RSI) adopted in January 2022

17.5.18. Venetoclax - VENCLYXTO (CAP) - EMEA/H/C/004106/MEA 002.9

Applicant: AbbVie Deutschland GmbH & Co. KG

[77] Advanced therapy medicinal product

PRAC Rapporteur: Eva Jirsová

Scope: Second interim analysis report and fourth study progress report for study P16 -562 (listed as a category 3 study in the RMP): a prospective observational study to assess the long-term safety profile of venetoclax in a Swedish cohort of chronic lymphocytic leukaemia (CLL) patients

17.6. Others

17.6.1. Coronavirus (COVID-19) vaccine (ChAdOx1-S [recombinant]) - VAXZEVRIA (CAP) - EMEA/H/C/005675/MEA 007.5

Applicant: AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

Scope: MAH's response to MEA 007.4 [statistical analysis plan (SAP) for study D8111R00006: a post-authorisation/post-marketing observational study using existing secondary health data sources to evaluate the association between exposure to Vaxzevria (AZD1222) and safety concerns] as per the request for supplementary information adopted in February 2022

17.6.2. Fentanyl - INSTANYL (CAP) - EMEA/H/C/000959/LEG 028.5

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Tiphaine Vaillant

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

17.6.3. Natalizumab - TYSABRI (CAP) - EMEA/H/C/000603/MEA 071.1

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: MAH's response to MEA 071 [feasibility assessment for study OXON 214-04 (listed as a category 3 study in the RMP): an observational study utilising data from EU national multiple sclerosis (MS) registries to estimate the incidence of anti-natalizumab antibody among patients who receive subcutaneous administration (SC) of natalizumab for treatment of relapsing remitting MS in order to investigate immunogenic potential of SC administration (from X/0116)] as per the request for supplementary information (RSI) adopted in December 2021

17.6.4. Reslizumab - CINQAERO (CAP) - EMEA/H/C/003912/MEA 005.7

Applicant: Teva B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Submission of an updated feasibility report for study C38072-AS-50027 as a MAH's response to MEA 005.6 [protocol for study C38072-AS-50027 (listed as category 3 study in the RMP): a long-term non-interventional study comparing the potential risk of malignancy

in severe asthma patients treated with reslizumab and patients not treated with reslizumab using secondary administrative healthcare data] as per the request for supplementary information (RSI) adopted in March 2020

17.7. New Scientific Advice

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

17.8. Ongoing Scientific Advice

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

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

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

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

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

18.1. Annual reassessments of the marketing authorisation

18.1.1. Velmanase alfa - LAMZEDE (CAP) - EMEA/H/C/003922/S/0025 (without RMP)

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Jan Neuhauser

Scope: Annual reassessment of the marketing authorisation

18.2. Conditional renewals of the marketing authorisation

18.2.1. Crizanlizumab - ADAKVEO (CAP) - EMEA/H/C/004874/R/0008 (without RMP)

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Jean-Michel Dogné

Scope: Conditional renewal of the marketing authorisation

18.2.2. Larotrectinib - VITRAKVI (CAP) - EMEA/H/C/004919/R/0024 (without RMP)

Applicant: Bayer AG

PRAC Rapporteur: Rugile Pilviniene

Scope: Conditional renewal of the marketing authorisation

18.3. Renewals of the marketing authorisation

18.3.1. Concentrate of proteolytic enzymes enriched in bromelain - NEXOBRID (CAP) - EMEA/H/C/002246/R/0056 (without RMP)

Applicant: MediWound Germany GmbH

PRAC Rapporteur: Martin Huber

Scope: 5-year renewal of the marketing authorisation

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

Applicant: sanofi-aventis groupe

PRAC Rapporteur: Kimmo Jaakkola

Scope: 5-year renewal of the marketing authorisation

18.3.3. Lacosamide - LACOSAMIDE ACCORD (CAP) - EMEA/H/C/004443/R/0015 (without RMP)

Applicant: Accord Healthcare S.L.U.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: 5-year renewal of the marketing authorisation

18.3.4. Letermovir - PREVYMIS (CAP) - EMEA/H/C/004536/R/0027 (with RMP)

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Kirsti Villikka

Scope: 5-year renewal of the marketing authorisation

18.3.5. Miglustat - MIGLUSTAT GEN.ORPH (CAP) - EMEA/H/C/004366/R/0022 (with RMP)

Applicant: Gen.Orph

PRAC Rapporteur: Ulla Wändel Liminga

Scope: 5-year renewal of the marketing authorisation

18.3.6. Padeliporfin - TOOKAD (CAP) - EMEA/H/C/004182/R/0019 (without RMP)

Applicant: STEBA Biotech S.A

PRAC Rapporteur: Maia Uusküla

Scope: 5-year renewal of the marketing authorisation

18.3.7. Ritonavir - RITONAVIR MYLAN (CAP) - EMEA/H/C/004549/R/0015 (without RMP)

Applicant: Mylan Pharmaceuticals Limited

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: 5-year renewal of the marketing authorisation

18.3.8. Tacrolimus – TACFORIUS (CAP) – EMEA/H/C/004435/R/0010 (with RMP)

Applicant: Teva B.V.

PRAC Rapporteur: Ronan Grimes

Scope: 5-year renewal of the marketing authorisation

18.3.9. Trientine - CUPRIOR (CAP) - EMEA/H/C/004005/R/0018 (without RMP)

Applicant: Orphalan

PRAC Rapporteur: Ana Sofia Diniz Martins

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 07-10 June 2022 meeting (marked as "[a]") and the 21 June 2022 ORGAM TC (marked as "[b]").

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Sabine Straus [a, b]	Chair	The Netherlands	No interests declared	
Jan Neuhauser [a, b]	Member	Austria	No interests declared	
Sonja Hrabcik [a, b]	Alternate	Austria	No interests declared	
Jean-Michel Dogné [a]	Member	Belgium	No interests declared	
Maria Popova-Kiradjieva [a, b]	Member	Bulgaria	No interests declared	
Nikica Mirošević Skvrce [a]	Member	Croatia	No interests declared	
Željana Margan Koletić [a, b]	Alternate	Croatia	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Elena Kaisis [b]	Member	Cyprus	No interests declared	
Panagiotis Psaras [a, b]	Alternate	Cyprus	No interests declared	
Eva Jirsová [a, b]	Member	Czechia	No interests declared	
Jana Lukacisinova [a, b]	Alternate	Czechia	No interests declared	
Anette Kirstine Stark [a, b]	Member	Denmark	No interests declared	
Marie Louise Schougaard Christiansen [a, b]	Alternate	Denmark	No interests declared	
Maia Uusküla [a]	Member	Estonia	No interests declared	
Krõõt Aab [a]	Alternate	Estonia	No interests declared	
Kirsti Villikka [a, b]	Member	Finland	No interests declared	
Kimmo Jaakkola [a]	Alternate	Finland	No interests declared	
Tiphaine Vaillant [a, b]	Member	France	No interests declared	
Nathalie Gault [a, b]	Alternate	France	No interests declared	
Martin Huber [a, b]	Member (Vice-Chair)	Germany	No interests declared	
Brigitte Keller-Stanislawski [a]	Alternate	Germany	No interests declared	
Sofia Trantza [a, b]	Member	Greece	No interest declared	
Georgia Gkegka [a]	Alternate	Greece	No interest declared	
Julia Pallos [a]	Member	Hungary	No participation in final deliberations and voting on:	4.1.2. Codeine, ibuprofen (NAP) 4.1.3. Ipilimumab - YERVOY (CAP); nivolumab - OPDIVO (CAP) 15.3.20. Luspatercept - REBLOZYL (CAP) -

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				EMEA/H/C/004444/II/0009, Orphan 15.3.22. Nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/II/0117 16.1.38. Ozanimod - ZEPOSIA (CAP) - PSUSA/00010852/202111 17.5.1. Abatacept - ORENCIA (CAP) - EMEA/H/C/000701/MEA 048.10
Melinda Palfi [a]	Alternate	Hungary	No interest declared	
Guðrún Stefánsdóttir [a]	Member	Iceland	No participation in final deliberations and voting on:	4.1.1. Adalimumab - AMGEVITA (CAP), AMSPARITY (CAP), HEFIYA (CAP), HUMIRA (CAP), HULIO (CAP), HUKYNDRA (CAP), HYRIMOZ (CAP), IDACIO (CAP), IMRALDI (CAP), LIBMYRIS (CAP), YUFLYMA (CAP) 6.1.8. Denosumab - PROLIA (CAP) - PSUSA/00000954/202109 16.1.17. Etelcalcetide - PARSABIV (CAP) - PSUSA/00010533/202111 16.1.56. Talimogene laherparepvec - IMLYGIC (CAP) - PSUSA/00010459/202110 16.1.57. Trastuzumab - HERCEPTIN (CAP); HERZUMA (CAP); KANJINTI (CAP); OGIVRI (CAP);

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				ONTRUZANT (CAP); TRAZIMERA (CAP); ZERCEPAC (CAP) - PSUSA/00003010/202109
Rhea Fitzgerald [b]	Member	Ireland	No interests declared	
Ronan Grimes [a, b]	Alternate	Ireland	No interests declared	
Amelia Cupelli [a, b]	Member	Italy	No interests declared	
Zane Neikena [a]	Member	Latvia	No interests declared	
Rugile Pilviniene [a]	Member	Lithuania	No interests declared	
Lina Seibokiene [a]	Alternate	Lithuania	No participation in discussion, final deliberations and voting on:	7.2.1. Rivaroxaban - XARELTO (CAP) - EMEA/H/C/000944/MEA 049.1 17.2.9. Rivaroxaban - XARELTO (CAP) - EMEA/H/C/000944/MEA 049.2
John Joseph Borg [a, b]	Member	Malta	No interests declared	
Menno van der Elst [a, b]	Member	The Netherlands	No interests declared	
Liana Gross-Martirosyan [a, b]	Alternate	The Netherlands	No interests declared	
David Olsen [a]	Member	Norway	No participation in final deliberations and voting on:	7.2.1. Rivaroxaban - XARELTO (CAP) - EMEA/H/C/000944/MEA 049.1 15.3.14. Darolutamide - NUBEQA (CAP) - EMEA/H/C/004790/II/0009 15.3.15. Finerenone - KERENDIA (CAP) - EMEA/H/C/005200/II/0001/G 15.3.24. Octocog alfa - KOVALTRY (CAP) - EMEA/H/C/003825/II/0038

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				16.1.31. Larotrectinib - VITRAKVI (CAP) - PSUSA/00010799/202111 16.3.7. Benzydamine (NAP) - PSUSA/00000375/202110 16.3.13. Dextromethorphan (NAP) - PSUSA/00001009/202111 7.2.1. Rivaroxaban - XARELTO (CAP) - EMEA/H/C/000944/MEA 049.2 18.2.2. Larotrectinib - VITRAKVI (CAP) - EMEA/H/C/004919/R/0024 (without RMP)
Karen Pernille Harg [a, b]	Alternate	Norway	No interests declared	
Adam Przybylkowski [a]	Member	Poland	No interests declared	
Katarzyna Ziolkowska [b]	Alternate	Poland	No interests declared	
Ana Diniz Martins [a, b]	Member	Portugal	No interests declared	
Marcia Sofia Sanches de Castro Lopes Silva [a]	Alternate	Portugal	No interests declared	
Roxana Dondera [a, b]	Member	Romania	No interests declared	
Alexandra - Maria Spurni [a]	Alternate	Romania	No interests declared	
Marek Juracka [a]	Member	Slovakia	No interests declared	
Anna Mareková [a, b]	Alternate	Slovakia	No interests declared	
Polona Golmajer [a, b]	Member	Slovenia	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Eva Segovia [a, b]	Member	Spain	No interests declared	
Maria del Pilar Rayon [a]	Alternate	Spain	No interests declared	
Ulla Wändel Liminga [a]	Member	Sweden	No interests declared	
Annika Folin [a, b]	Alternate	Sweden	No interests declared	
Annalisa Capuano [a]	Member	Independent scientific expert	No interests declared	
Milou Daniel Drici [a, b]	Member	Independent scientific expert	No interests declared	
Maria Teresa Herdeiro [a]	Member	Independent scientific expert	No interests declared	
Patricia McGettigan [a]	Member	Independent scientific expert	No interests declared	
Hedvig Nordeng [a]	Member	Independent scientific expert	No interests declared	
Roberto Frontini [a, b]	Member (Mandate as member for Healthcare Professionals' Representatives extended on 01/05/2022)	Healthcare Professionals' Representative	No restrictions applicable to the meeting	
Declan Noone [a]	Member (Mandate as alternate for	Patients' Organisation Representative	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
	Healthcare Professionals' Representatives started on 01/05/2022)			
Marko Korenjak [a]	Alternate (Mandate as alternate for Patients' Organisation Representatives started on 01/05/2022)	Patients' Organisation Representative	No restrictions applicable to the meeting	
Christelle Bizimungu [a]	Expert	Belgium	No restrictions applicable to this meeting	
Laurence de Fays [a]	Expert	Belgium	No interests declared	
Jamila Hamdani [a]	Expert	Belgium	No interests declared	
Martine Sabbe [a]	Expert	Belgium	No interests declared	
Françoise Wuillaume [a]	Expert	Belgium	No interests declared	
Nina Lalić [a]	Expert	Croatia	No restrictions applicable to this meeting	
Ivana Ljubičić [a]	Expert	Croatia	No restrictions	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			applicable to this meeting	
Lara Miletić [a]	Expert	Croatia	No restrictions applicable to this meeting	
Petra Kaftanová [a]	Expert	Czechia	No interests declared	
Anna Kroupová [a]	Expert	Czechia	No interests declared	
Hanna Belcik Christensen [a]	Expert	Denmark	No restrictions applicable to this meeting	
Annette Cleveland Nielsen [a]	Expert	Denmark	No restrictions applicable to this meeting	
Kirsten Egebjerg Juul [a]	Expert	Denmark	No interests declared	
Karin Susanne Erneholm [a]	Expert	Denmark	No restrictions applicable to this meeting	
Marianne Hald Clemmensen [a]	Expert	Denmark	No restrictions applicable to this meeting	
Katrine Damkjær Madsen [a]	Expert	Denmark	No restrictions applicable to this meeting	
Peter Horskjær Rose [a]	Expert	Denmark	No interests declared	
Ebru Gulsun Karakoc Madsen [a]	Expert	Denmark	No restrictions applicable to this meeting	
Pernille Lynge Gammelgaard [a]	Expert	Denmark	No interests declared	
Line Michan [a]	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
Chau Minh Tran [a]	Expert	Denmark	No interests declared	
Astrid Munch Hestbæk [a]	Expert	Denmark	No restrictions applicable to this meeting	
Emma Louise Nautrup Ravn Stadsbjerg [a]	Expert	Denmark	No interests declared	
Moritz Sander [a]	Expert	Denmark	No interests declared	
Aynur Sert [a]	Expert	Denmark	No interests declared	
Dara Sevkan Akdag [a]	Expert	Denmark	No interests declared	
Josiane Uwera [a]	Expert	Denmark	No restrictions applicable to this meeting	
Tiina Karonen [a]	Expert	Finland	No interests declared	
Jenni Keskitalo [a]	Expert	Finland	No restrictions applicable to this meeting	
Outi Mäki-Ikola [a]	Expert	Finland	No restrictions applicable to this meeting	
Liisa Tenkanen [a]	Expert	Finland	No restrictions applicable to this meeting	
Laura Andreoli [a]	Expert	France	No interests declared	
Samuel Crommelynck [a]	Expert	France	No restrictions applicable to this meeting	
Elsa Grangier [a]	Expert	France	No interests declared	
Vincent Gazin [a]	Expert	France	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Leo Lambart [a]	Expert	France	No restrictions applicable to this meeting	
Marie-Caroline Pesquidous [a]	Expert	France	No restrictions applicable to this meeting	
Dina Sanctussy [a]	Expert	France	No interests declared	
Youssef Shaim [a]	Expert	France	No restrictions applicable to this meeting	
Jelena Katic [a]	Expert	Germany	No interests declared	
Dennis Lex [a, b]	Expert	Germany	No restrictions applicable to this meeting	
Tania Meier [a]	Expert	Germany	No interests declared	
Karin Seifert [a]	Expert	Germany	No restrictions applicable to this meeting	
Sheena Kennedy [a]	Expert	Ireland	No restrictions applicable to this meeting	
Eamon O'Murchu [a]	Expert	Ireland	No interests declared	
Ruchika Sharma [a]	Expert	Ireland	No restrictions applicable to this meeting	
Armando Genazzani [a]	Expert	Italy	No restrictions applicable to this meeting	
Negar Babae [a]	Expert	The Netherlands	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Paul ten Berg [a]	Expert	The Netherlands	No interests declared	
André Elferink [a]	Expert	The Netherlands	No interests declared	
Jakob Fransen [a]	Expert	The Netherlands	No interests declared	
Lisa Heltzel [a]	Expert	The Netherlands	No interests declared	
Marianne Klanker [a]	Expert	The Netherlands	No interests declared	
Marcel Kwa [a]	Expert	The Netherlands	No interests declared	
Lotte Minnema [a]	Expert	The Netherlands	No interests declared	
Jacobus Romme [a]	Expert	The Netherlands	No restrictions applicable to this meeting	
Stephany Suoth [a]	Expert	The Netherlands	No restrictions applicable to this meeting	
Justine van Tongeren [a]	Expert	The Netherlands	No interests declared	
Maria Vanenburg [a]	Expert	The Netherlands	No interests declared	
Susanne Dertz [a]	Expert	Norway	No interests declared	
Lars Peter Engeset Austdal [a]	Expert	Norway	No interests declared	
Ewa Bałkowiec-Iskra [a]	Expert	Poland	No restrictions applicable to this meeting	
Fernanda Inês Carvalho Pereira Ribeiro Vaz [a]	Expert	Portugal	No interests declared	
Carla Torre [a]	Expert	Portugal	No restrictions applicable to this meeting	
Charlotte Backman [a]	Expert	Sweden	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Karin Bolin [a]	Expert	Sweden	No restrictions applicable to this meeting	
Karin Hellgren [a]	Expert	Sweden	No restrictions applicable to this meeting	
Gunilla Sjölin-Forsberg [a]	Expert	Sweden	No restrictions applicable to this meeting	
Anna Vikerfors [a]	Expert	Sweden	No restrictions applicable to this meeting	
A representative from the European Commission attended the meeting				
Meeting run with support from relevant EMA staff				

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

20. Annex III - List of acronyms and abbreviations

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

21. Explanatory notes

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

EU Referral procedures for safety reasons: Urgent EU procedures and Other EU referral procedures
(Items 2 and 3 of the PRAC minutes)

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

Signals assessment and prioritisation
(Item 4 of the PRAC minutes)

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

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

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

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

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

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

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

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

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

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