24 January 2023
EMA/PRAC/938468/2022
Human Medicines Division

Pharmacovigilance Risk Assessment Committee (PRAC)

Minutes of the meeting on 29 August - 01 September 2022

Chair: Sabine Straus – Vice-Chair: Martin Huber

Disclaimers

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

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

Note on access to documents

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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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 current coronavirus (COVID-19 outbreak), and the associated EMA Business Continuity Plan (BCP), the meeting was held remotely.

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

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

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

1.2. Agenda of the meeting on 29 August -01 September 2022

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

1.3. Minutes of the previous meeting on 04-07 July 2022

The minutes will be adopted following a consultation phase and will be published on the EMA website.

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

2.1. Newly triggered procedures

2.1.1. Pholcodine (NAP); pholcodine, biclotymol, chlorphenamine (NAP); pholcodine, chlorphenamine (NAP); pholcodine, chlorphenamine, ephedrine (NAP); pholcodine, diphenhydramine (NAP); pholcodine, dextromethorphan, paracetamol (NAP); pholcodine, diphenhydramine, paracetamol, pseudoephedrine (NAP); pholcodine, guaiacol (NAP); pholcodine, paracetamol, pseudoephedrine (NAP) - EMEA/H/A-107i/1521

Applicant(s): various

PRAC Rapporteur: Željana Margan Koletić; PRAC Co-rapporteur: Lina Seibokiene

Scope: Review of the benefit-risk balance following notification by France of a referral under Article 107i of Directive 2001/83/EC, based on pharmacovigilance data

Pholcodine is a semi-synthetic alkaloid indicated for the treatment of non-productive (dry) cough in children and adults. In combination with other active substances, pholcodine is used for the treatment of symptoms of cold and flu.

The French Medicine Agency (ANSM) sent a letter of notification dated 19 August 2022, along with a scientific background (rationale), triggering an urgent Union procedure under Article 107i of Directive 2001/83/EC for the review of pholcodine-containing products. The review was initiated following the preliminary results of ALPHO[1], a post-authorisation safety study (PASS) imposed as a condition to the marketing authorisations of pholcodine-containing products, following the outcome of a referral procedure under Article 31 of Directive 2001/83/EC in 2011 (EMEA/H/A-31/1292). The preliminary report of the ALPHO study suggests that there is a significant link between exposure to pholcodine during the 12 months preceding surgery and a risk of peri-anaesthetic anaphylactic reaction related to neuromuscular blocking agents (NMBA). In light of these new data, ANSM was of the view that the benefit-risk profile of pholcodine-containing products is no longer favourable and considered to suspend the marketing authorisations of these medicinal products in France. As a consequence, ANSM triggered an urgent Union procedure resulting from pharmacovigilance data, and requested PRAC to assess the impact of the above concerns on the benefit-risk balance of pholcodine-containing products and to give its recommendation as to whether marketing authorisations for these medicinal product(s) should be maintained, varied, suspended, or revoked. For further background, see PRAC minutes January 2022.

Discussion

PRAC noted the notification letter and the scientific background from ANSM.

PRAC appointed Željana Margan Koletić as Rapporteur and Lina Seibokiene as Co-Rapporteur for the procedure.

PRAC discussed the results of the ALPHO study and the need for temporary measures to protect public health as well as lists of questions to be addressed during the procedure together with a timetable for conducting the review. PRAC also discussed the need for a public hearing.

Summary of recommendation(s)/conclusions

- The Committee adopted a list of questions (LoQ) to the MAHs of pholcodine-containing products (EMA/PRAC/704708/2022) and a LoQ to stakeholders (EMA/PRAC/709548/2022). In addition, PRAC adopted a timetable for the procedure (EMA/PRAC/704846/2022).
- PRAC discussed the option to conduct a public hearing in the context of the current procedure according to the pre-defined criteria set out in the rules of procedure[2] (EMA/363479/2015). It was agreed by the Committee that at this stage in the assessment, in light of the currently available data and the need to determine the appropriate approach to stakeholder engagement, a public hearing would not be

[1] Neuromuscular blocking agent anaphylaxis and pholcodine exposure – A case-control study, Central Hospital - Nancy, France, Principal investigator: Pierre Gillet
[2] Rules of procedure on the organisation and conduct of public hearings at PRAC

appropriate. PRAC can reconsider this at a later stage of the procedure, as needed.

See EMA press release (EMA/709083/2022) entitled 'Review of pholcodine medicines started'.

2.2. Ongoing procedures

None

2.3. Procedures for finalisation

None

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

3.1. Newly triggered procedures

3.1.1. Topiramate (NAP); topiramate, phentermine (NAP) - EMEA/H/A-31/1520

Applicant(s): various

PRAC Rapporteur: Ulla Wändel Liminga; PRAC Co-rapporteur: Martin Huber

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

Background

Topiramate is an anticonvulsant indicated for the treatment of partial seizures, generalised tonic clonic seizures, seizures associated with Lennox-Gastaut syndrome and as an adjunctive therapy in partial-onset seizures and for the prophylaxis of migraine. In combination with phentermine, topiramate is indicated in weight management in adults.

The French Medicine Agency (ANSM) sent a letter of notification dated 22 August 2022 of a referral under Article 31 of Directive 2001/83/EC for the review of topiramate-containing products following the results of a publication by *Bjørk et al.*[3] that showed a significant increase of neurodevelopmental disorders, in particular autism spectrum disorders and intellectual disability, in children with prenatal exposure to topiramate. This follows an initial evaluation of the safety issues in the framework of a signal procedure for which PRAC concluded that a thorough review should be conducted for topiramate-containing product(s) to review these risks. For further background, see PRAC minutes July 2022 and see current minutes under 4.3.4.

Given a potentially increased risk of neurodevelopmental disorders highlighted in this study with *in utero* exposure to topiramate and the known risk of congenital malformations, ANSM referred the matter to PRAC in the interest of the Union for further evaluation and requested that it gives its recommendation as to whether the marketing authorisation(s) for topiramate-containing product(s) should be maintained, varied, suspended or revoked.

Discussion

[3] Bjørk M, Zoega H, Leinonen MK, et al. Association of prenatal exposure to antiseizure medication with risk of autism and intellectual disability. JAMA Neurol. Published online May 31, 2022. doi:10.1001/jamaneurol.2022.1269

PRAC noted the notification letter and the scientific background from ANSM.

PRAC appointed Ulla Wändel Liminga as Rapporteur and Martin Huber as Co-Rapporteur for the procedure.

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

Summary of recommendation(s)/conclusions

- The Committee adopted a LoQ to the MAHs (EMA/PRAC/702490/2022) and a timetable for the procedure (EMA/PRAC/702489/2022).
- PRAC discussed the option to conduct a public hearing in the context of the current procedure according to the pre-defined criteria set out in the rules of procedure[4] (EMA/363479/2015). It was agreed by the Committee that at this stage in the assessment, in light of the currently available data and the need to determine the appropriate approach to stakeholder engagement, a public hearing would not be appropriate. PRAC can reconsider this at a later stage of the procedure, as needed.

See EMA press release (EMA/707437/2022) entitled 'PRAC starts review of topiramate use in pregnancy and women of childbearing potential'.

3.2. Ongoing procedures

3.2.1. Janus kinase (JAK) inhibitors[5]: 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. This follows the final results from study A3921133[6] (ORAL surveillance) for Xeljanz (tofacitinib) showing an increased 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

[4] Rules of procedure on the organisation and conduct of public hearings at PRAC
[5] Indicated for the treatment of inflammatory disorders
[6] 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

tofacitinib compared to TNF-inhibitors. This also follows preliminary results from study I4V-MC-B023[7] for Olumiant (baricitinib) suggesting also an increased risk of MACE and VTE in patients with rheumatoid arthritis treated with Olumiant (baricitinib) compared to those treated with TNF-inhibitors. For further background, see PRAC minutes February 2022 and PRAC minutes June 2022.

Summary of recommendation(s)/conclusions

- PRAC adopted an updated list of questions (LoQ) to the ad-hoc expert group (AHEG) meeting to be held on 19 September 2022 and agreed on a draft list of experts for the AHEG.

Post-meeting note: On 19 September 2022, the final list of experts for the AHEG meeting was adopted by written procedure.

3.3. Procedures for finalisation

None

3.4. Re-examination procedures[8]

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

Applicant(s): Artegodan GmbH, Temmler Pharma GmbH

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

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

Background

Following the PRAC recommendation adopted in June 2022 to revoke the marketing authorisation(s) for amfepramone-containing product(s), the MAHs concerned by this referral procedure requested a re-examination. For further background, see PRAC minutes June 2022.

Discussion

PRAC noted the notification letter from the MAHs requesting a re-examination of the recommendation adopted by PRAC in June 2022 as well as the detailed grounds for re-examination of the PRAC recommendation submitted on 29 August 2022.

The PRAC appointed Ulla Wändel Liminga as Rapporteur and Roxana Dondera as Co-Rapporteur for the re-examination procedure.

Summary of recommendation(s)/conclusions

- PRAC adopted a revised timetable (EMA/PRAC/51714/2021 Rev.5) for the re-examination procedure.

[7] A retrospective observational study to compare baricitinib relative to the standard of care
[8] Re-examination of PRAC recommendation under Article 32 of Directive 2001/83/EC

3.5. Others

None

4. Signals assessment and prioritisation[9]

4.1. New signals detected from EU spontaneous reporting systems

See also Annex 14.1.

4.1.1. Tozinameran – COMIRNATY (CAP)

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Signal of histiocytic necrotizing lymphadenitis

EPITT 19835 – New signal

Background

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

During routine signal detection activities, a signal of histiocytic necrotizing lymphadenitis was identified by Spain based on 11 cases retrieved from EudraVigilance.

The Rapporteur confirmed that the signal needed initial analysis and prioritisation by PRAC.

Discussion

Having considered the available evidence in EudraVigilance and the literature, PRAC agreed that further evaluation on the signal of histiocytic necrotizing lymphadenitis with Comirnaty (tozinameran) is warranted.

Summary of recommendation(s)

- In the next PSUR, the MAH for Comirnaty (tozinameran) should include a detailed review of cases of histiocytic necrotizing lymphadenitis, including any relevant data from the literature together with a discussion on probable mechanism(s) of action for the occurrence of vaccine-associated histiocytic necrotizing lymphadenitis following administration of Comirnaty (tozinameran). The MAH should include a proposal to update the product information/RMP as warranted.

4.1.2. Tozinameran – COMIRNATY (CAP)

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

[9] 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

Scope: Signal of vulval ulceration

EPITT 19840 – New signal

Background

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

During routine signal detection activities, a signal of vulval ulceration was identified by Ireland, based on 4 cases reported from national databases, 84 further cases for Comirnaty (tozinameran) from EudraVigilance, and 9 cases with COVID-19 vaccines published in the scientific literature.

The Rapporteur confirmed that the signal needed initial analysis and prioritisation by PRAC.

Discussion

Having considered the available evidence in EudraVigilance, PRAC agreed that further evaluation on the signal of vulval ulceration with Comirnaty (tozinameran) is warranted.

Summary of recommendation(s)

- The MAH for Comirnaty (tozinameran) should submit to EMA, within 60 days, a cumulative review of the signal from all available sources (clinical trials, post-marketing, and literature), including an observed to expected (O/E) analysis and discuss a possible mechanism of action. The MAH should propose the update of the product information/RMP as warranted.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.1.3. Tranexamic acid (NAP)

Applicant(s): various

PRAC Rapporteur: Ronan Grimes

Scope: Signal of incorrect route of product administration

EPITT 19844 – New signal

Background

Tranexamic acid is a synthetic derivative of lysine used as antifibrinolytic and is indicated in adults and children from one year in the prevention and treatment of haemorrhages due to general or local fibrinolysis.

During routine signal detection activities, a signal of incorrect route of product administration was identified by Ireland, based on 29 cases retrieved from EudraVigilance. Ireland confirmed that the signal needed initial analysis and prioritisation by PRAC.

Discussion

Having considered the available evidence from the published literature and EudraVigilance, and taking into account the ongoing worksharing variation (DK/H/xxxx/WS/179) to update the product information regarding the incorrect intrathecal and epidural administration of

tranexamic acid, PRAC agreed that further actions will be considered in the framework of the ongoing worksharing variation as appropriate.

PRAC appointed Ronan Grimes as Rapporteur for the signal.

Summary of recommendation(s)

- PRAC agreed that further assessment and actions will be considered in the framework of the ongoing worksharing variation as appropriate.

4.2. New signals detected from other sources

See also Annex 14.2.

4.3. Signals follow-up and prioritisation

4.3.1. Coronavirus (COVID-19) vaccine (ChAdOx1-S [recombinant]) - VAXZEVRIA (CAP) - EMEA/H/C/005675/SDA/112

Applicant: AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

Scope: Signal of corneal graft rejection

EPITT 19791 – 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 corneal graft rejection and the responses were assessed by the Rapporteur.

Discussion

Having considered the data submitted by the MAH together with the Rapporteur's assessment, PRAC concluded that there is insufficient evidence to establish a causal association between Vaxzevria (coronavirus (COVID-19) vaccine (ChAdOx1-S[recombinant])) and corneal graft rejection at this stage.

Summary of recommendation(s)

- The MAH for Vaxzevria (coronavirus (COVID-19) vaccine (ChAdOx1-S[recombinant])) should continue to monitor cases of corneal graft rejection as part of routine safety surveillance.

4.3.2. Elasomeran - SPIKEVAX (CAP) - EMEA/H/C/005791/SDA/064

Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Signal of corneal graft rejection

EPITT 19792 – 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 corneal graft rejection and the responses were assessed by the Rapporteur.

Discussion

Having considered the data submitted by the MAH together with the Rapporteur's assessment, PRAC concluded that there is insufficient evidence to establish a causal association between Spikevax (elasomeran) and corneal graft rejection at this stage.

Summary of recommendation(s)

- The MAH for Spikevax (elasomeran) should continue to monitor cases of corneal graft rejection as part of routine safety surveillance.

4.3.3. Pneumococcal polysaccharide vaccine (23 serotypes) (NAP)

Applicant(s): various

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Signal of extensive swelling of vaccinated limb

EPITT 19768 – Follow-up March 2022

Background

For background information, see PRAC minutes March 2022.

The MAH MSD Sharp & Dohme GmbH replied to the request for information on the signal of extensive swelling of vaccinated limb and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence in EudraVigilance, the literature, the responses from the MAH together with the Rapporteur's assessment, PRAC agreed that there is sufficient evidence to establish a causal association between extensive swelling of vaccinated limb and pneumococcal polysaccharide vaccine containing 23 serotypes. PRAC noted that injection site cellulitis is already mentioned in the product information as an undesirable effect with a frequency 'rare' and agreed that extensive swelling of the vaccinated limb is a more appropriate term to describe the non-infectious cellulitis-like reactions and the cases reported. Therefore, PRAC agreed that extensive swelling of vaccinated limb should be added to the product information as an undesirable effect with a frequency 'rare'.

Summary of recommendation(s)

- The MAH(s) for pneumococcal polysaccharide vaccine containing 23 serotypes should submit to the relevant National Competent Authorities (NCAs) of the Member States, within 60 days, a variation for amending[10] the product information.

For the full PRAC recommendation, see EMA/PRAC/699721/2022 published on 26 September 2022 on the EMA website.

[10] Update of section 4.8 of the SmPC. The package leaflet is to be updated accordingly. Any existing wording should be adjusted to the recommended product information changes

4.3.4. Topiramate (NAP)

Applicant(s): various

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of neurodevelopmental disorders due to in utero exposure

EPITT 19825 – Follow up to July 2022

Background

For background information, see PRAC minutes July 2022.

The Rapporteur further reviewed the publication by *Bjørk et al.*[11] and presented its assessment for a further recommendation at PRAC.

Discussion

Having considered the available evidence from the publication by *Bjørk et al.*, PRAC agreed that the epidemiological study results suggest a potentially increased risk of neurodevelopmental disorders in addition to the already well-established teratogenic risk associated to prenatal exposure to topiramate. Therefore, PRAC considered that a thorough review should be conducted for topiramate-containing product(s) to review the potential risk of neurodevelopmental disorders due to *in utero* exposure to the substance. Regarding other antiepileptic drugs reviewed in the study, PRAC discussed the relevant data and concluded that no further regulatory action is warranted at present.

Summary of recommendation(s)

- PRAC considered that a thorough review should be conducted for topiramate-containing product(s) regarding the potentially increased risk of neurodevelopmental disorders. PRAC noted the initiation of a procedure under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data. See under 3.1.1. .

4.3.5. Tozinameran - COMIRNATY (CAP) - EMEA/H/C/005735/SDA/055

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Signal of corneal graft rejection

EPITT 19789 – 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 corneal graft rejection and the responses were assessed by the Rapporteur.

Discussion

[11] Bjørk M, Zoega H, Leinonen MK, et al. Association of prenatal exposure to antiseizure medication with risk of autism and intellectual disability. JAMA Neurol. Published online May 31, 2022. doi:10.1001/jamaneurol.2022.1269

Having considered the data submitted by the MAH together with the Rapporteur's assessment, PRAC concluded that there is insufficient evidence to establish a causal association between Comirnaty (tozinameran) and corneal graft rejection at this stage.

Summary of recommendation(s)

- The MAH for Comirnaty (tozinameran) should continue to monitor cases of corneal graft rejection as part of routine safety surveillance.

4.4. Variation procedure(s) resulting from signal evaluation

See Annex 14.3.

5. Risk management plans (RMPs)

5.1. Medicines in the pre-authorisation phase

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

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

See also Annex 15.1.

5.1.1. Abaloparatide - EMEA/H/C/005928

Scope: Treatment of osteoporosis

5.1.2. Cipaglucosidase alfa - EMEA/H/C/005703, Orphan

Applicant: Amicus Therapeutics Europe Limited

Scope: Treatment of adults aged 18 years and older with a confirmed diagnosis of Pompe disease

5.1.3. Miglustat - EMEA/H/C/005695, Orphan

Applicant: Amicus Therapeutics Europe Limited

Scope: Treatment of adults aged 18 years and older with a confirmed diagnosis of Pompe disease

5.1.4. Palovarotene - EMEA/H/C/004867, Orphan

Applicant: Ipsen Pharma

Scope: Treatment of fibrodysplasia ossificans progressiva

5.1.5. Tabelecleucel - EMEA/H/C/004577, PRIME, Orphan

Applicant: Atara Biotherapeutics Ireland Limited, ATMP[12]

Scope: Treatment of Epstein-Barr virus positive post-transplant lymphoproliferative disease (EBV^+ PTLD)

5.1.6. Vadadustat - EMEA/H/C/005131

Scope: Treatment of anaemia

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

See Annex 15.2.

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

See also Annex 16.3.

5.3.1. Elasomeran - SPIKEVAX (CAP) - EMEA/H/C/005791/II/0075/G

Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Grouped application consisting of line extension to add a new strain (Omicron BA.1) resulting in two new Spikevax bivalent Original/Omicron (25 µg elasomeran / 25 µg imelasomeran per dose) 0.1 mg/mL dispersion for injection presentations together with other quality variations. The SmPC, the package leaflet and labelling are updated accordingly. The RMP (version 4.2) has also been submitted.

Background

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

CHMP is evaluating a grouping of type II variations for Spikevax, a centrally authorised product containing elasomeran, including the addition of a new strain (Omicron BA.1) resulting in two new Spikevax bivalent Original/Omicron (25 µg elasomeran / 25 µg imelasomeran per dose) 0.1 mg/mL dispersion for injection presentations. PRAC is responsible for providing advice to CHMP on the necessary updates to the RMP to support these grouped type II variations.

Summary of advice

- The RMP for Spikevax (elasomeran) in the context of the variation procedure under evaluation by CHMP could be considered acceptable provided that an update to RMP version 4.2 is submitted.
- Regarding the pharmacovigilance plan, PRAC considered that the protocols of studies 'P904: a post-authorisation active surveillance safety study using secondary data to monitor real-world safety of the mRNA-1273 vaccine in the EU', 'P905: monitoring

[12] Advanced therapy medicinal product

safety of COVID-19 vaccine Moderna in pregnancy: an observational study using routinely collected health data in five European countries' and 'P910: natural history and clinical outcomes of vaccine associated myocarditis', need to be amended to implement exposure to elasomeran/imelasomeran, including adequate stratification of elasomeran/imelasomeran exposure. Pending authorisation of Spikevax (elasomeran/imelasomeran) in the US, the protocols of study P903: a post-authorisation safety study of SARS-CoV-2 mRNA-1273 vaccine in the US - active surveillance, signal refinement and self-controlled risk interval (SCRI) signal evaluation in HealthVerity, and of study P911: long-term outcomes of myocarditis following administration of Spikevax as well as study P919: an observational study to assess maternal and infant outcomes following exposure to Spikevax during pregnancy, need to be similarly amended. PRAC also considered that routine risk minimisation measures are sufficient to minimise the risks of the medicinal product in the proposed indication(s) in light of the current knowledge.

5.3.2. Tozinameran - COMIRNATY (CAP) - EMEA/H/C/005735/II/0140

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Line extension to add a new strain (Omicron BA.1) resulting in a new Comirnaty bivalent Original/Omicron BA.1 (15 µg tozinameran/ 15 µg riltozinameran per dose) dispersion for injection presentation. The SmPC, the package leaflet and labelling are updated accordingly. The RMP (version 6.0) has also been submitted

Background

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

CHMP is evaluating a type II variation for Comirnaty, a centrally authorised product containing tozinameran, to add a new strain (Omicron BA.1) resulting in a new Comirnaty bivalent Original/Omicron BA.1 (15 µg tozinameran/ 15 µg riltozinameran per dose) dispersion for injection presentation. PRAC is responsible for providing advice to CHMP on the necessary updates to the RMP to support this type II variation.

Summary of advice

- The RMP for Comirnaty (tozinameran) in the context of the variation procedure under evaluation by CHMP could be considered acceptable provided that an update to RMP version 6.1 is submitted within the next regulatory procedure.
- PRAC discussed the risk of medication errors due to possible confusion between different presentations and noted the MAH strategy to distinguish cap colours for different age groups that would mitigate the risk of medication error. PRAC considered that the flip off colour strategy is acceptable. Regarding the pharmacovigilance plan, PRAC agreed that it is important that further safety data on Comirnaty bivalent Original/Omicron BA.1 vaccine as well as on the future modified vaccines is collected in the post-marketing setting and that these need to be included in all ongoing PASSs or justify otherwise. PRAC also considered that routine risk minimisation measures are sufficient to minimise

the risks of the medicinal product in the proposed indication(s) in light of the current knowledge.

5.3.3. Tozinameran - COMIRNATY (CAP) - EMEA/H/C/005735/II/0143

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Addition of a new strain (Omicron BA.4-5) resulting in a new Comirnaty bivalent Original/Omicron BA.4-5 (15 µg / 15 µg per dose) dispersion for injection presentation. The SmPC, the Package Leaflet and Labelling are updated accordingly. The submission includes a revised RMP version 7.0

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 variation to extend the therapeutic indication for Comirnaty, a centrally authorised product containing tozinameran, to add a new strain (Omicron BA.4-5) resulting in a new Comirnaty bivalent Original/Omicron BA.4-5 (15 µg / 15 µg per dose) dispersion for injection presentation.

At an extraordinary meeting convened remotely on 08 September 2022, PRAC reviewed the proposed RMP updates submitted within this procedure. PRAC is responsible for providing advice to CHMP on the necessary updates to the RMP to support the procedure.

Summary of advice

- The RMP version 7.1 for Comirnaty (tozinameran) in the context of the variation under evaluation by CHMP was considered acceptable.
- PRAC endorsed the inclusion of studies C4591031 and C4591044 in the pharmacovigilance plan, as these studies will provide reactogenicity and immunogenicity data. However, PRAC noted the limitations with regard to the sample size. PRAC also agreed that safety data on Comirnaty bivalent Original/Omicron BA.1 vaccine as well as on Comirnaty bivalent Original/Omicron BA.4-5 vaccine are collected in the post-marketing setting and that these need to be included in all ongoing PASSs or justify otherwise. PRAC had discussed the risk of medication errors associated with the introduction of bivalent vaccines in variation procedure EMEA/H/C/005735/II/0140 (addition of a new strain (Omicron BA.1) resulting in a new Comirnaty bivalent Original/Omicron BA.1) and concluded that the MAH's strategy to distinguish cap colours for different age groups is acceptable also with the introduction of a Comirnaty bivalent Original/Omicron BA.4-5 vaccine. PRAC also considered that routine risk minimisation measures are sufficient to minimise the risks of the medicinal product in the proposed indication(s) in light of the current knowledge.

6. Periodic safety update reports (PSURs)

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

See also Annex 16.1.

6.1.1. Bictegravir, emtricitabine, tenofovir alafenamide - BIKTARVY (CAP) - PSUSA/00010695/202202

Applicant: Gilead Sciences Ireland UC

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 Biktarvy, a centrally authorised medicine containing bictegravir/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 Biktarvy (bictegravir/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[13].
- In the next PSUR, the MAH should provide a review on the potential interaction of bictegravir with zinc-containing products and associated lack of efficacy. The MAH should also provide any new relevant data on pure red cell aplasia 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.

6.1.2. Osilodrostat - ISTURISA (CAP) - PSUSA/00010820/202201

Applicant: Recordati Rare Diseases

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

Background

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

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

[13] 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.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Isturisa (osilodrostat) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add myalgia and arthralgia as undesirable effects with a frequency 'very common'. Therefore, the current terms of the marketing authorisation(s) should be varied[14].
- In the next PSUR, the MAH should closely monitor cases of hepatic events (other than transaminases events), cases of serious depression and suicide related events and cases of myalgia with increase of creatine phosphokinase and/or acute renal failure. The MAH should include an analysis of cases of non-Cushing disease (CD) Cushing syndrome (CS). Additionally, pancreatitis should be closely monitored 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.

6.1.3. Remimazolam - BYFAVO (CAP) - PSUSA/00010924/202201

Applicant: PAION Netherlands B.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

Background

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

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Byfavo, a centrally authorised medicine containing remimazolam 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 Byfavo (remimazolam) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add information regarding incompatibilities between remimazolam and co-administered solutions which may result in precipitation/turbidity, which subsequently may cause occlusion of vascular access site. Therefore, the current terms of the marketing authorisation(s) should be varied[15].

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

[14] 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.
[15] Update of SmPC section 6.2. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion.

6.1.4. Umeclidinium bromide - INCRUSE ELLIPTA (CAP); ROLUFTA ELLIPTA (CAP) - PSUSA/00010263/202112

Applicant: GlaxoSmithKline (Ireland) Limited (Incruse Ellipta), GlaxoSmithKline Trading Services Limited (Rolufta Ellipta)

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 PSURs, PRAC reviewed the benefit-risk balance of Incruse Ellipta and Rolufta Ellipta, centrally authorised medicines containing umeclidinium bromide 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 Incruse Ellipta and Rolufta Ellipta (umeclidinium bromide) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add anaphylaxis as an undesirable effect with a frequency 'rare' under hypersensitivity reactions. Therefore, the current terms of the marketing authorisation(s) should be varied[16].
- In the next PSUR, the MAH should continue to monitor cases of medication errors resulting from the confusion on the name of the oral inhaler medicine that use the proprietary name 'Ellipta' and provide a detailed analysis of possible related safety concerns. The MAH should also continue to monitor off-label use, focusing on the use in the asthma indication and related adverse events (AEs).

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. Umeclidinium bromide, vilanterol - ANORO ELLIPTA (CAP); LAVENTAIR ELLIPTA (CAP) - PSUSA/00010264/202112

Applicant: GlaxoSmithKline (Ireland) Limited

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.

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

Based on the assessment of the PSURs, PRAC reviewed the benefit-risk balance of Anoro Ellipta and Laventair Ellipta, centrally authorised medicines containing umeclidinium bromide/vilanterol 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 Anoro Ellipta and Laventair Ellipta (umeclidinium bromide/vilanterol) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add muscle spasm as an undesirable effect with a frequency 'uncommon' and eye pain with a frequency 'rare'. Therefore, the current terms of the marketing authorisation(s) should be varied[17].
- In the next PSUR, the MAH should continue to monitor cases of medication errors resulting from the confusion on the name of the oral inhaler medicine that use the proprietary name 'Ellipta' and provide a detailed analysis of possible related safety concerns. The MAH should also continue to monitor off-label use and provide a review with the outcome of the associated adverse events.

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

6.1.6. Ustekinumab - STELARA (CAP) - PSUSA/00003085/202112

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

Background

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

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Stelara, a centrally authorised medicine containing ustekinumab 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 Stelara (ustekinumab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add lupus-related conditions as a warning, to add cutaneous lupus and lupus-like syndrome as undesirable effects with a frequency 'very rare', and amend the existing warning on opportunistic infections. In addition, the wording regarding breastfeeding in the package leaflet should be

[17] 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.

amended. Therefore, the current terms of the marketing authorisation(s) should be varied[18].

- In the next PSUR, the MAH should provide an updated review of lymphoma including an assessment of the cases according to WHO[19] causality assessment criteria with a specific review of cutaneous T-cell lymphoma. The MAH should also provide a cumulative review of complications of herpes zoster including meningoencephalitis, and ocular or ophthalmic herpes zoster with a detailed discussion of the cases retrieved, as well as cumulative reviews of cases of systemic vasculitis, panniculitis including erythema nodosum, sepsis, pericarditis, pericardial effusion and myocarditis, alopecia, and glomerulonephritis. In addition, the MAH should also provide any new data regarding cases of thrombotic thrombocytopenic purpura from all relevant sources. Moreover, the MAH is requested to discuss whether the important identified risk erythrodermic psoriasis should be included as an undesirable effect in the product information. 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 16.2.

6.2.1. Riluzole - RILUTEK (CAP); RILUZOLE ZENTIVA (CAP); NAP - PSUSA/00002645/202112

Applicant: Sanofi Mature IP (Rilutek), Zentiva, k.s. (Riluzole Zentiva), various

PRAC Rapporteur: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

Background

Riluzole is a benzothiazole indicated to extend life or the time to mechanical ventilation for patients with amyotrophic lateral sclerosis.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of Rilutek and Riluzole Zentiva, centrally authorised medicines containing riluzole and nationally authorised medicines containing riluzole, 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 riluzole-containing products in the approved indication(s) remains unchanged.

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

- Nevertheless, the product information should be updated to add rash as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisations should be varied[20].

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

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

See also Annex 16.3.

6.3.1. Amino acid combinations, glucose, triglyceride combinations[21], with or without electrolytes, mineral compounds[22] [23] (NAP) - PSUSA/00010190/202112

Applicant(s): various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

Background

Amino acid combinations/glucose/triglyceride combinations/with or without electrolytes/mineral compounds are indicated for parenteral nutrition in paediatric patients when oral or enteral nutrition is not possible, insufficient or contraindicated.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing amino acid combinations/glucose/triglyceride combinations/with or without electrolytes/mineral compounds 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 amino acid combinations/glucose/triglyceride combinations/with or without electrolytes/mineral compounds-containing product(s) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.

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.

Additionally, PRAC considered that the potential risks associated with the formation of 'yellow globules' in the lipid emulsion need to be further assessed, given the potential seriousness of this finding. Further consideration is to be given at the level of CMDh.

[20] 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.
[21] E.g. olive oil, soya bean oil, fish oil
[22] Intravenous (I.V.) application only
[23] Nationally authorised product Numeta only

6.3.2. Botulinum toxin A (NAP) - PSUSA/00000426/202112

Applicant(s): various

PRAC Lead: Ronan Grimes

Scope: Evaluation of a PSUSA procedure

Background

Botulinum toxin A is a purified neurotoxin complex indicated for various indications, such as treatment of blepharospasm and hemifacial spasm, cervical dystonia of a predominantly rotational form (spasmodic torticollis), spasticity of the upper limb, chronic sialorrhea due to neurological disorders, as well as in the temporary improvement of the appearance of upper facial lines when the severity of these lines has an important psychological impact for the patient, subject to certain conditions.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing botulinum toxin A 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 botulinum toxin A-containing product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add Mephisto sign (lateral elevation of eyebrows) as an undesirable effect with a frequency 'common' for the forehead lines and glabellar lines with or without Crow's feet lines indication and with a frequency 'uncommon' for the glabellar lines indication. The MAHs should also add Mephisto sign (lateral elevation of eyebrows) as an undesirable effect with a frequency 'unknown' for the medicinal products containing botulinum toxin A indicated in chronic migraine. Therefore, the current terms of the marketing authorisation(s) should be varied[24].
- In the next PSUR, the MAHs should continue monitoring safety in patients requiring sedative therapy, including effects on bone and muscle health (muscle atrophy and fibrosis) and possible distant spread of toxin (PDSOT).

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

6.3.3. Bupropion (NAP) – PSUSA/00000461/202112

Applicant(s): various

PRAC Lead: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

Background

[24] 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.

Bupropion is a selective inhibitor of the neuronal re-uptake of catecholamines (noradrenaline and dopamine) indicated for the treatment of of major depressive disorder (MDD) and for the treatment of nicotine dependence as an aid to smoking cessation, subject to certain conditions.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing bupropion 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 bupropion-containing product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add a warning regarding Brugada syndrome. Therefore, the current terms of the marketing authorisation(s) should be varied[25].

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

PRAC considered that the warning on Brugada syndrome is also relevant for bupropion-containing products as a single agent or in fixed-dose combinations. Further consideration is to be given at the level of CMDh.

6.3.4. Ciclosporin[26] (NAP) - PSUSA/00000745/202112

Applicant(s): various

PRAC Lead: Maia Uusküla

Scope: Evaluation of a PSUSA procedure

Background

Ciclosporin is a potent immunosuppressive agent, indicated for the following: prevention of graft rejection following kidney, liver, heart, combined heart-lung, lung or pancreas allogeneic transplantation and treatment of transplant rejection in patients previously receiving other immunosuppressive agents, and prevention of graft rejection following bone marrow transplantation. It is also indicated for the prevention or treatment of graft-versus-host disease (GVHD), treatment of endogenous uveitis, nephrotic syndrome, rheumatoid arthritis, psoriasis and atopic dermatitis.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing ciclosporin 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 ciclosporin-containing product(s) 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 CMDh for adoption of a position.
[26] For systemic use only

- Nevertheless, the product information should be updated to add hearing impairment as undesirable effect with frequency 'not known'. 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.

6.3.5. Dexlansoprazole (NAP), lansoprazole (NAP) - PSUSA/00001827/202112

Applicant(s): various

PRAC Lead: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

Background

Dexlansoprazole is a proton pump inhibitor (PPI) indicated for the symptomatic non-erosive gastroesophageal reflux disease and the healing of all grades of erosive oesophagitis. Lansoprazole is also a PPI indicated for the treatment of peptic ulcers of the stomach and duodenum, symptomatic gastroesophageal reflux disease including long-term maintenance therapy, all grades of reflux oesophagitis (prophylaxis and treatment), Zollinger-Ellison syndrome, eradication of Helicobacter pylori, as well as for prophylaxis of relapses of peptic ulcer in patients with ulcers associated to Helicobacter pylori (in combination with oral antibiotics) and prophylaxis and treatment of nonsteroidal anti-inflammatory drug (NSAID)-associated gastric and duodenal ulcers in patients requiring continuous NSAID treatment.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing dexlansoprazole or lansoprazole 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 dexlansoprazole- and lansoprazole-containing products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add tubulointerstitial nephritis (TIN) as a warning and as undesirable effect with a frequency 'rare'. Therefore, the current terms of the marketing authorisation(s) should be varied[28].
- In the next PSUR, the MAHs should continue monitoring major adverse cardiovascular events (MACE), acute kidney injury (AKI), chronic kidney disease (CKD), end stage renal disease (ESRD) and renal failure.

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.

[27] 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.
[28] Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position.

6.3.6. Dexketoprofen, tramadol (NAP) - PSUSA/00010468/202201

Applicant(s): various

PRAC Lead: Eva Segovia

Scope: Evaluation of a PSUSA procedure

Background

Dexketoprofen is a nonsteroidal anti-inflammatory drug (NSAID) and tramadol an opioid. In combination, dexketoprofen/tramadol is indicated for the symptomatic short-term treatment of moderate to severe acute pain in adult patients whose pain is considered to require a combination of dexketoprofen and tramadol.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing dexketoprofen/tramadol 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 dexketorpofen/tramadol-containing product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add a warning on the use of dexketoprofen after pregnancy week 20, due to the risk of 'renal dysfunction, oligohydramnios and neonatal renal impairment' and 'ductus arteriosus constriction'. Therefore, the current terms of the marketing authorisation(s) should be varied[29].
- In the next PSUR, the MAHs should provide a cumulative review on opioid use disorders and discuss the need for an update of the product information as warranted.

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

6.3.7. Terbutaline (NAP) - PSUSA/00002897/202112

Applicant(s): various

PRAC Lead: Melinda Palfi

Scope: Evaluation of a PSUSA procedure

Background

Terbutaline is an adrenergic agonist, which predominantly stimulates beta-2 receptors and is indicated for the treatment of bronchial asthma, chronic bronchitis, emphysema and other lung diseases where bronchospasm or reversible airway obstruction is a complicating factor, as well as for uncomplicated preterm labour to arrest labour between 22 and 37 weeks of gestation in patients with no medical or obstetric contraindication to tocolytic therapy, subject to certain conditions.

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

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing terbutaline 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 terbutaline-containing product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information of terbutaline reliever medications (i.e. the inhalation powder and the nebuliser solution) should be updated to strengthen the warnings regarding the risks of short-acting beta-agonist (SABA) overuse. Therefore, the current terms of the marketing authorisation(s) should be varied[30].
- In the next PSUR, the MAH AstraZeneca should address SABA overuse for the inhalation powder and the nebuliser solution as an important identified 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.

6.3.8. Testosterone[31] (NAP) - PSUSA/00010631/202112

Applicant(s): various

PRAC Lead: Maia Uusküla

Scope: Evaluation of a PSUSA procedure

Background

Testosterone is an androgen indicated for testosterone replacement therapy for male hypogonadism.

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

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 chorioretinopathy (including central serous chorioretinopathy) associated to testosterone replacement therapy needs to be further assessed. Further consideration is to be given at the level of CMDh.

[30] Update of SmPC section 4.4. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position.
[31] For all formulations (apart from topical use)

6.3.9. Testosterone[32] (NAP) - PSUSA/00002908/202112

Applicant(s): various

PRAC Lead: Maia Uusküla

Scope: Evaluation of a PSUSA procedure

Background

Testosterone is an androgen indicated for testosterone replacement therapy for male hypogonadism.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing testosterone 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 testosterone-containing product(s) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAH Endo should provide the results of the following studies, if available: 'consortium post-marketing study to evaluate the effect of testosterone replacement therapy (TRT) on the incidence of major adverse cardiovascular events (MACE)' and 'efficacy measures in hypogonadal men : an open-label, randomised, parallel-group, three treatment arm, multicentre study on hypogonadal males to evaluate the effect on 24-hour ambulatory blood pressure after 16-week continuous administration with marketed testosterone products'.

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 chorioretinopathy (including central serous chorioretinopathy) associated to testosterone replacement therapy needs to be further assessed. Further consideration is to be given at the level of CMDh.

6.3.10. Valaciclovir (NAP) - PSUSA/00003086/202112

Applicant(s): various

PRAC Lead: Jana Lukačišinová

Scope: Evaluation of a PSUSA procedure

Background

Valaciclovir is an antiviral indicated for the treatment of herpes zoster, varicella zoster, herpes labialis and other herpes simplex infections of the skin and mucous membranes, including initial and recurrent genital herpes, as well as for the prevention (suppression) of recurrent herpes simplex infections of the skin and mucous membranes, including genital

[32] Topical use only

herpes and prophylaxis of cytomegalovirus (CMV) infection and disease, following organ transplantation.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing valaciclovir 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 valaciclovir-containing product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add tubulointerstitial nephritis as undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[33].

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 16.4.

6.5. Variation procedure(s) resulting from PSUSA evaluation

See also Annex 16.5.

6.5.1. Tozinameran - COMIRNATY (CAP) - EMEA/H/C/005735/II/0141

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Update of sections 4.4 and 4.8 of the SmPC in order to update the occurrence of myocarditis because more information is available in the age group 5-11 years; and to update the statement in the SmPC section 4.4 regarding the risk of myocarditis after a third dose of Comirnaty based on real-world evidence requested by PRAC following the assessment of MEA/002.13 procedure concluded in June 2022. The package leaflet is updated accordingly. In addition, the MAH took the opportunity to implement editorial changes in section 4.4 of the SmPC

Background

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

Following the evaluation of the summary safety review (SSR) finalised in June 2022 for the above-mentioned medicine(s), the MAH submitted to EMA a variation to amend the existing warning on myocarditis. For background information, see PRAC minutes June 2022. PRAC is responsible for adopting an outcome based on the assessment report from the PRAC

[33] 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

Rapporteur, to be further considered at the level of CHMP, responsible for adopting an opinion on this variation.

Summary of recommendation(s)

- Based on the available data and the Rapporteur's assessment, PRAC agreed with the proposed amendments[34] to the product information in order to amend the wording on myocarditis based on literature data.
- The MAH should continue to closely monitor any accumulating evidence on this matter and discuss the need for updating the product information as warranted.

6.6. Expedited summary safety reviews[35]

See Annex 16.5.

7. Post-authorisation safety studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)[36]

See also Annex 17.1.

7.1.1. Ciltacabtagene autoleucel - CARVYKTI (CAP) - EMEA/H/C/PSP/S/0099

Applicant: Janssen-Cilag International NV, ATMP

PRAC Rapporteur: Jo Robays

Scope: A long-term follow-up study for participants previously treated with ciltacabtagene autoleucel to collect data on delayed adverse events after administration of cilta-cel, and to characterise and understand the long-term safety profile of cilta-cel

Background

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

In order to fulfil the specific obligation to conduct a PASS (Annex II-D) imposed in accordance with Article 107n(3) of Directive 2001/83/EC, the MAH Janssen-Cilag International NV submitted to EMA a protocol for a study entitled: 'Long-term follow-up study for participants previously treated with ciltacabtagene autoleucel' for review by PRAC. PRAC is responsible for evaluating the PASS protocol.

Endorsement/Refusal of the protocol

- Having considered the draft protocol version May 2022 in accordance with Article 107n of Directive 2001/83/EC, PRAC objected to the draft protocol for the above listed medicinal product(s). PRAC agreed that the study design does not fulfil the study objectives at this stage.

[34] Update of sections 4.4 and 4.8 of the SmPC. The package is updated accordingly.
[35] 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
[36] In accordance with Article 107n of Directive 2001/83/EC

- PRAC considered that, although the study is classified as interventional, the milestones and planned deadlines for all interim reports, as well as progress reports for monitoring enrolment progression, identification of potential data quality issues and planning remedial actions should be included in the updated protocol. In addition, a discussion on the power of the study to measure side effects adequate precision should be provided. The MAH should update the protocol accordingly.
- The MAH should submit a revised PASS protocol within 60 days to EMA. A 60 day-assessment timetable will be followed.

7.1.2. Fenfluramine - FINTEPLA (CAP) - EMEA/H/C/PSP/S/0093.3

Applicant: Zogenix ROI Limited

PRAC Rapporteur: Martin Huber

Scope: MAH's response to PSP/0093.2 [an observational registry to provide data on long-term safety of fenfluramine in routine practice, with a focus on characterising and quantifying the important potential risks VHD and PAH (primary objective), and growth retardation (secondary objective). In addition, data on the frequency of echocardiographic monitoring will contribute to assess the effectiveness of risk minimisation measures] as per the request for supplementary information (RSI) adopted in April 2022

Background

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

In order to fulfil the specific obligation to conduct a PASS (Annex II-D) imposed in accordance with Article 107n(3) of Directive 2001/83/EC, the MAH Zogenix ROI Limited submitted to EMA a protocol version 1.0 for a study entitled: 'a registry of subjects with Dravet syndrome treated with fenfluramine' for review by PRAC in order to assess long-term cardiac safety of fenfluramine prescribed in routine practice. PRAC is responsible for evaluating the PASS protocol and the responses from the MAH to a request for supplementary information adopted in April 2022. For further background information, see PRAC minutes April 2022.

Endorsement/Refusal of the protocol

- Having considered the protocol version 4.0 in accordance with Article 107n of Directive 2001/83/EC, PRAC confirmed that the study is non-interventional and the PASS protocol is endorsed.
- In order to maintain the overall study duration, PRAC agreed with the proposed delay to provide the final study report by Q1 2034.
- The MAH should submit to EMA a variation to update the requirements of the condition to the marketing authorisation(s) of Fintepla (Fenfluramine) to amend the due date for the final study report.

7.2. Protocols of PASS non-imposed in the marketing authorisation(s)[37]

See also Annex 17.2.

7.2.1. Fenfluramine - FINTEPLA (CAP) - EMEA/H/C/003933/MEA 005.3

Applicant: Zogenix ROI Limited

PRAC Rapporteur: Martin Huber

Scope: MAH's response MEA 005.2 [protocol for study ZX008-2102: a drug utilisation study (DUS) in Europe to describe fenfluramine use in routine clinical practice [final report expected in August 2025] (from initial opinion/marketing authorisation)] as per the request for supplementary information (RSI) adopted in April 2022

Background

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

As part of the RMP of Fintepla (fenfluramine), the MAH was requested to conduct a drug utilisation study (DUS) to describe fenfluramine use in routine clinical practice with a focus on its use in epilepsies other than Dravet syndrome, if any. PRAC is requested to provide advice to CHMP on the protocol submitted by the MAH and the responses from the MAH to a request for supplementary information adopted in April 2022. For further background, see PRAC minutes April 2022.

Summary of advice

- PRAC confirmed that the proposed study is non-interventional but does not meet its objectives at this stage. Therefore, the MAH should submit a revised protocol and satisfactory responses to the request for supplementary information (RSI) agreed by PRAC. PRAC noted that the list of countries in which the DUS is to be conducted may still be subject to further revision according to market uptake and agreed that the MAH should provide a brief discussion on this list in each PSUR. In addition, PRAC agreed that all eligible study sites should be contacted and invited to participate in the DUS, and not only those participating in the Fintepla registry study.

7.3. Results of PASS imposed in the marketing authorisation(s)[38]

7.3.1. Rivaroxaban – XARELTO (CAP) - EMEA/H/C/PSR/S/0027

Applicant: Bayer AG

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Final study report comprising the pharmacoepidemiological study programme of rivaroxaban use and potential adverse outcomes in routine clinical practice in the United Kingdom (UK), Germany, the Netherlands and Sweden

Background

[37] 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
[38] In accordance with Article 107p-q of Directive 2001/83/EC

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.

Xarelto, a centrally authorised medicine containing rivaroxaban, was authorised in 2008. In 2013, the indication(s) were extended to the prevention of atherothrombotic events after acute coronary syndrome (ACS). As a result, the MAH was imposed to conduct a PASS (Annex II-D) to explore whether the characteristics of patients who are prescribed rivaroxaban for the ACS indication in a clinical setting are different to the patients included in the pivotal study, especially with regards to bleeding risk, and to monitor drug utilisation in a hospital setting. Following PRAC assessment, it was agreed that the ongoing and planned studies of the already existing PASS programme were expanded to include the ACS indication, and the full PASS programme was consequently re-classified to category 1 studies.

PRAC discussed the final study report of the non-interventional pharmacoepidemiological programme comprised of drug utilisation (DUS) and specific adverse outcomes studies for prevention of stroke and systemic embolism in non-valvular atrial fibrillation[39] and ACS in routine clinical practice, which has been undertaken in data sources in the UK, Germany, the Netherlands and Sweden. PRAC is responsible for issuing a recommendation on the final study results.

For background, see PRAC minutes March 2021, PRAC minutes October 2021[40] and PRAC minutes May 2022.

Summary of recommendation(s) and conclusions

- Based on the review of the final report of the non-interventional pharmacoepidemiological study programme of rivaroxaban use and potential adverse outcomes in routine clinical practice, PRAC considered that the benefit-risk balance of Xarelto (rivaroxaban) remains unchanged.
- PRAC recommended that the terms of the marketing authorisation(s) for Xarelto (rivaroxaban) should be varied to update the product information[41] to reflect the key findings of the PASS DUS programme and to remove the PASS programme as an obligation to the marketing authorisation(s) from Annex II-D on 'Conditions or restrictions with regard to the safe and effective use of the medicinal product', as the obligation to perform the PASS is now considered fulfilled. In addition, PRAC agreed that Xarelto (rivaroxaban) should be removed from the 'List of medicines under additional monitoring'. Finally, PRAC agreed on RMP version 13.4, in which the RMP was updated to remove some safety concerns as they are considered as further characterised as part of this PASS programme.

7.4. Results of PASS non-imposed in the marketing authorisation(s)[42]

See also Annex 17.4.

[39] Deep vein thrombosis (DVT-T), pulmonary embolism (PE-T), stroke prevention in non-valvular AF (SPAF)
[40] Held 27-30 September 2021
[41] Update of SmPC section 5.1
[42] In accordance with Article 61a (6) of Regulation (EC) No 726/2004, in line with the revised variations regulation for any submission as of 4 August 2013

7.4.1. Cobimetinib - COTELLIC (CAP) - EMEA/H/C/003960/II/0027

Applicant: Roche Registration GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Update of sections 4.4 and 5.1 of the SmPC in order to update information based on final results from study ML39302 listed as a category 3 study in the RMP in order to fulfil MEA/003.5; this is a non-interventional PASS study to investigate the effectiveness, safety and utilisation of cobimetinib and vemurafenib in patients with and without brain metastasis with BRAF V600 mutant melanoma under real world conditions. The RMP version 5.0 has also been submitted

Background

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

As stated in the RMP of Cotellic (cobimetinib), the MAH conducted a non-imposed non-interventional PASS to investigate the effectiveness, safety and utilisation of cobimetinib and vemurafenib in patients with and without brain metastasis with BRAF V600 mutant melanoma under real world conditions. The Rapporteur assessed the MAH's final study report together with the necessary updates to the RMP.

Summary of advice

- Based on the available data and the Rapporteur's review, PRAC considered that further information was necessary before the ongoing variation assessing the final study report can be recommended for approval. In addition, the RMP for Cotellic (cobimetinib) could be considered acceptable provided that an update to RMP version 5.0 is submitted.
- The MAH should provide more information on the cases under MedDRA SOC[43] nervous system disorders, as well as a literature review on whether incidence/severity of nervous system disorders could increase following exposure to BRAF/MEK inhibitors, either alone or in combination with stereotactic radiosurgery. As a consequence, the MAH should address a request for supplementary information (RSI) before a conclusion can be drawn.

7.4.2. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/II/0095

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: Submission of the final report from study PSOLAR (C0168Z03) (listed as a category 3 study in the RMP): a multicentre, open registry of patients with psoriasis who are candidates for systemic therapy including biologics: PSOLAR. The RMP (version 22.2) is updated accordingly

Background

[43] Medical dictionary for regulatory activities – System Organ Class

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

As stated in the RMP of Stelara (ustekinumab), the MAH conducted a non-imposed non-interventional PASS PSOLAR (C0168Z03) (listed as a category 3 study in the RMP): a multicentre, open registry of patients with psoriasis who are candidates for systemic therapy including biologics. The Rapporteur assessed the MAH's final study report together with the necessary updates to the RMP.

Summary of advice

- Based on the available data and the Rapporteur's review, PRAC considered that further information is necessary before the ongoing variation assessing the final study report can be recommended for approval. In addition, the RMP for Stelara (ustekinumab) could be considered acceptable provided that an update to RMP version 22.2 is submitted.
- PRAC supported updating of product information with a warning on cardiovascular events, and amending the existing information on risk of malignancy and risk of infections. However, PRAC agreed that the MAH should submit cumulative reviews of the association of Stelara (ustekinumab) with all-cause mortality and with malignancy, including data from clinical trials and literature. PRAC also agreed with removing the study PSOLAR as a category 3 study from the RMP.

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

See also Annex 17.5.

7.5.1. Influenza vaccine (live attenuated, nasal) - FLUENZ TETRA (CAP) - EMEA/H/C/002617/MEA 004.13

Applicant: AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

Scope: Annual report for the passive enhanced safety surveillance (ESS) D2560C00008: a post-marketing non-interventional cohort study of the safety of live attenuated influenza vaccine (LAIV) in subjects 2 through 17 years of age for the 2021-2022 influenza season

Background

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

In line with the 'Interim guidance on enhanced safety surveillance for seasonal influenza vaccines in the EU' and according to the RMP, the MAH for Fluenz Tetra (influenza vaccine (live attenuated, nasal)) had committed to conduct a passive enhanced safety surveillance (ESS). The results of the non-interventional study to monitor the safety of live attenuated influenza vaccine (LAIV) in subjects 2 through 17 years of age for the 2021-2022 influenza season were assessed by the Rapporteur for PRAC review.

Summary of advice

- PRAC discussed the annual report for the ESS described in the RMP as a routine pharmacovigilance activity. PRAC concluded that the ESS study conducted in the flu season 2021-2022, did not lead to the identification of new safety signals related to the vaccination of children and adolescents with Fluenz Tetra (influenza vaccine (live attenuated, nasal)).
- PRAC agreed that the last interim results for this study should be submitted to EMA for the vaccination campaign of the flu season 2022-2023. After that, safety surveillance will continue passively and safety data will be assessed in future PSURs. The RMP should be updated accordingly.

7.6. Others

See Annex 17.6.

7.7. New Scientific Advice

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

7.8. Ongoing Scientific Advice

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

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

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

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

8.1. Annual reassessments of the marketing authorisation

See Annex 18.1.

8.2. Conditional renewals of the marketing authorisation

See Annex 18.2.

8.3. Renewals of the marketing authorisation

See Annex 18.3.

9. Product related pharmacovigilance inspections

9.1. List of planned pharmacovigilance inspections

None

9.2. Ongoing or concluded pharmacovigilance inspections

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

9.3. Others

None

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

10.1. Safety related variations of the marketing authorisation

10.1.1. Ranibizumab - LUCENTIS (CAP) – EMEA/H/C/000715/II/0098

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: PRAC consultation on a variation to update section 4.6 of the SmPC regarding breastfeeding as requested in the conclusions of the PSUSA procedure (PSUSA/00002609/202010) adopted by PRAC in May 2021, based on a cumulative assessment of pre-clinical studies, pharmacokinetic data, published literature and post-marketing spontaneous reports. The package leaflet is updated accordingly

Background

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

A type II variation proposing to update the product information of Lucentis (ranibizumab) on breastfeeding as requested in the conclusions of the PSUSA procedure (PSUSA/00002609/202010) adopted by PRAC in May 2021 is under evaluation at CHMP. For background, see PRAC minutes May 2021. The PRAC was requested to provide advice on this variation.

Summary of advice

- Based on the review of the available information, PRAC noted the limited data regarding excretion of ranibizumab into breastmilk and potential effects on vascular endothelial growth factor-A (VEGF-A) levels.
- PRAC advised that an update of the product information on breastfeeding is 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

None

11.2. Other requests

None

12. Mandate and organisation of PRAC

12.1.1. PRAC membership

The Chair welcomed Mari Thörn as the new alternate for Sweden (mandate started on 15 July 2022) and Jo Robays as the new alternate for Belgium (mandate started on 26 July 2022). The Chair also announced that Gudrun Thengilsdottir is the new alternate for Iceland (mandate started on 02 September 2022) and that Eva Segovia was to step down from PRAC as the member for Spain following the current meeting (mandate ended on 02 September 2022). The Chair thanked her for her contribution to PRAC.

12.1.2. Vote by proxy

None

12.1.3. PRAC working group - Best practice guide on using PRAC plenary time efficiently and effectively – update on the implementation of quantitative goals – Q2 2022

In line with the adopted PRAC best practice guidance (BPG) on Committee efficiency (see PRAC minutes May 2016 and PRAC minutes June 2018) and the adopted implementation plan for the BPG including goals to measure compliance with the recommendations (see PRAC minutes June 2016 and PRAC minutes June 2018), at the organisational, regulatory and methodological matters (ORGAM) meeting on 15 September 2022, the EMA secretariat

informed PRAC about the quantitative measures collected for Q2 2022 of PRAC meetings. For previous update, see PRAC minutes April 2022.

12.2. Coordination with EMA Scientific Committees or CMDh-v

None

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

None

12.4. Cooperation within the EU regulatory network

12.4.1. Coronavirus (COVID-19) pandemic - update

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

12.5. Cooperation with International Regulators

None

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

None

12.7. PRAC work plan

12.7.1. PRAC work plan 2022 - update

PRAC lead: Sabine Straus, Martin Huber

At the organisational, regulatory and methodological matters (ORGAM) meeting on 15 September 2022, the EMA Secretariat presented to PRAC a mid-year status update on the activities described in the PRAC work plan 2022. PRAC will initiate its work plan for 2023 taking into account the activities completed, progress made, priorities identified at the level of the Committee, EMA, Heads of Medicines Agencies (HMA) and EU network.

12.8. Planning and reporting

12.8.1. EU Pharmacovigilance system - quarterly workload measures and performance indicators – Q2 2022 and predictions

At the organisational, regulatory and methodological matters (ORGAM) meeting on 15 September 2022, the EMA Secretariat presented to PRAC an overview of the quarterly

figures on the EMA pharmacovigilance system-related workload and performance indicators. For previous update, see PRAC minutes May 2022.

12.8.2. PRAC workload statistics – Q2 2022

At the organisational, regulatory and methodological matters (ORGAM) meeting on 15 September 2022, the EMA secretariat presented to PRAC the quarterly and cumulative figures to estimate the evolution of the workload of the PRAC for Q2 2022, by reflecting on the number of procedures and agenda items covered at each PRAC plenary meeting. For previous update, see PRAC minutes May 2022.

12.9. Pharmacovigilance audits and inspections

12.9.1. Pharmacovigilance systems and their quality systems

None

12.9.2. Pharmacovigilance inspections

None

12.9.3. Pharmacovigilance audits

None

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

12.10.1. Periodic safety update reports

None

12.10.2. Granularity and Periodicity Advisory Group (GPAG)

PRAC lead: Menno van der Elst, Maia Uusküla

The topic was postponed to October 2022.

12.10.3. PSURs repository

None

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

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

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

12.11. Signal management

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

PRAC lead: Menno van der Elst

The topic was postponed to October 2022.

12.12. Adverse drug reactions reporting and additional monitoring

12.12.1. Management and reporting of adverse reactions to medicinal products

None

12.12.2. Additional monitoring

None

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

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

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

12.13. EudraVigilance database

12.13.1. Activities related to the confirmation of full functionality

None

12.14. Risk management plans and effectiveness of risk minimisations

12.14.1. Risk management systems

None

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

None

12.14.3. Coronavirus (COVID-19) pandemic - coreRMP19: update

PRAC lead: Jean-Michel Dogné, Brigitte Keller-Stanislawski, Zane Neikena, Marie Louise Schougaard Christiansen, Anette Kirstine Stark, Menno van der Elst, Ulla Wändel Liminga

The EMA secretariat presented to PRAC an update of the 'Consideration on core requirements for RMPs of COVID-19 vaccines' to address the initial summary safety reviews (SSR) submission requirements for approved vaccines that are not yet used in mass-vaccination campaigns. PRAC supported the changes brought to the guidance.

Post-meeting note: On 01 September 2022, the coreRMP19 guidance version 3.1 (EMA/PRAC/709308/2022) was published on EMA website.

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

12.15.3. Good pharmacovigilance practices (GVP) module VIII on 'Post-authorisation safety studies (PASS)' – Revision

At the organisational, regulatory and methodological matters (ORGAM) meeting on 15 September 2022, the EMA Secretariat presented to PRAC the initiative to start the revision of GVP module VIII on 'Post-authorisation safety studies (PASS)'. The EMA Secretariat presented the rationale for this future revision, as well as the timelines for this project. The EMA Secretariat launched a call for volunteers to be part of the authors team either as a PRAC rapporteur or as co-authors. Members were invited to express interest by 07 October 2022.

Post-meeting note: The following members expressed interest in being part of the authors team: Nathalie Gault, Patricia McGettigan, Nikica Mirošević Skvrce, Maria del Pilar Rayon.

12.16. Community procedures

12.16.1. Referral procedures for safety reasons

None

12.17. Renewals, conditional renewals, annual reassessments

None

12.18. Risk communication and transparency

12.18.1. Public participation in pharmacovigilance

None

12.18.2. Safety communication

None

12.19. Continuous pharmacovigilance

12.19.1. Incident management

None

12.20. Impact of pharmacovigilance activities

None

12.21. Others

12.21.1. EMA Scientific Committees support – organisational adjustments

At the organisational, regulatory and methodological matters (ORGAM) meeting on 15 September 2022, the EMA Secretariat presented to PRAC an overview of the organisational changes related to EMA Scientific Committees support.

13. Any other business

None

14. Annex I – Signals assessment and prioritisation[44]

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[45].

14.1.1. Dabrafenib - TAFINLAR (CAP); trametinib - MEKINIST (CAP)

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of haemophagocytic lymphohistiocytosis

EPITT 19824 – New signal

[44] 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

[45] 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

14.1.2. Voxelotor– OXBRYTA (CAP)

Applicant: Global Blood Therapeutics Netherlands B.V.

PRAC Rapporteur: Jean-Michel Dogné

Scope: Signal of drug reaction with eosinophilia and systemic symptoms (DRESS)

EPITT 19833 – New signal

14.2. New signals detected from other sources

14.2.1. Regorafenib - STIVARGA (CAP)

Applicant: Bayer AG

PRAC Rapporteur: Menno van der Elst

Scope: Signal of thrombotic microangiopathy

EPITT 19832 – New signal

14.3. Variation procedure(s) resulting from signal evaluation

14.3.1. Obinutuzumab - GAZYVARO (CAP) - EMEA/H/C/002799/II/0051, Orphan

Applicant: Roche Registration GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of section 4.8 of the SmPC in line with the SmPC Guideline following the recommendation by PRAC in the outcome for the signal assessment of non-overt disseminated intravascular coagulation (DIC) (EPITT 19711). The package leaflet is updated accordingly

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. Melatonin - MELATONIN NEURIM (CAP MAA) - EMEA/H/C/005603

Scope: Treatment of primary insomnia

15.1.2. Sugammadex - SUGAMMADEX - AMOMED (CAP MAA) - EMEA/H/C/005935

Scope: Reversal of neuromuscular blockade induced by rocuronium or vecuronium

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

Applicant: Clinuvel Europe Limited

PRAC Rapporteur: Martin Huber

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

15.2.2. Caspofungin - CANCIDAS (CAP) - EMEA/H/C/000379/II/0078

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Jo Robays

Scope: Submission of an updated RMP version 4.1 in order to remove safety concerns and align it with the GVP Module V (Revision 2)

15.2.3. Micafungin - MYCAMINE (CAP) - EMEA/H/C/000734/II/0047

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Martin Huber

Scope: Update of Annex II and the RMP to version 23.0 to include the results of the non-interventional PASS 9463-PV-0002: effectiveness check of the prescriber checklist for Mycamine (micafungin)

15.2.4. Ropeginterferon alfa-2b - BESREMI (CAP) - EMEA/H/C/004128/II/0025

Applicant: AOP Orphan Pharmaceuticals GmbH

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Submission of an updated RMP version 1.1 for Besremi to revise the list of safety concerns according to GVP Module V (Revision 2)

15.2.5. 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

15.2.6. Voriconazole - VFEND (CAP); NAP - EMEA/H/C/000387/WS2270/0147

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Update of Annex II and RMP to version 6.0 to include the results from final clinical study report (CSR) following the completion of a non-interventional (NI) post-authorisation safety study (PASS) A1501103: an active safety surveillance program to monitor selected events in patients with long-term voriconazole use - MEA091. In addition, MAH is also taking this opportunity to introduce editorial changes

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-randomised, 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

15.3.2. Abrocitinib - CIBINQO (CAP) - EMEA/H/C/005452/II/0001

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Update of sections 4.4 and 4.8 of the SmPC based on updated safety data from the Full Cumulative Pool (April 2021 data cut) from the ongoing long-term extension study B7451015. The RMP version v1.0 has also been submitted. In addition, MAH took the opportunity to implement editorial changes in the SmPC and to update the contact details of the local representatives in the package leaflet

15.3.3. Baloxavir marboxil - XOFLUZA (CAP) - EMEA/H/C/004974/X/0008/G

Applicant: Roche Registration GmbH

PRAC Rapporteur: Sonja Hrabcik

Scope: Grouped variations consisting of: 1) extension application to introduce a new

pharmaceutical form associated with new strength (2 mg/mL granules for oral suspension); 2) extension of indication to add a paediatric indication applicable to the new presentation, as well as to all approved presentations (EU/1/20/1500/001 and 002). The RMP (version 2.0) is updated in accordance

15.3.4. Axicabtagene ciloleucel - YESCARTA (CAP) - EMEA/H/C/004480/II/0046, Orphan

Applicant: Kite Pharma EU B.V., ATMP[46]

PRAC Rapporteur: Anette Kirstine Stark

Scope: Extension of indication to include treatment of adult patients with relapsed or refractory (r/r) diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL). 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 5.3) are updated in accordance. In addition, the MAH took the opportunity to update the product information with minor editorial changes

15.3.5. Bictegravir, emtricitabine, tenofovir alafenamide - BIKTARVY (CAP) - EMEA/H/C/004449/X/0040/G

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Grouped application consisting of: 1) extension application to introduce a new strength 30/120/15 mg; 2) extension of indication to include a paediatric indication by adding the use in patients of 2 years of age and older and weighing at least 14 kg. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC and the package leaflet are updated to support the extension of indication. The RMP (version 3.1) is updated in accordance

15.3.6. Budesonide - JORVEZA (CAP) - EMEA/H/C/004655/II/0015, Orphan

Applicant: Dr. Falk Pharma GmbH

PRAC Rapporteur: Zane Neikena

Scope: Update of section 4.8 of the SmPC in order to update the list of adverse drug reactions based on final results from long-term maintenance study BUL-2/EER: a double-blind, randomised, placebo-controlled, phase 3 study on the efficacy and tolerability of a 48-week treatment with two different doses of budesonide effervescent tablets vs. placebo for maintenance of clinico-pathological remission in adult patients with eosinophilic esophagitis. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet. The package leaflet and RMP (version 3.0) are updated accordingly. The MAH also submitted the final report of study BUL-6/BIO: an open-label, randomised, 3-period, 3-sequence, single dose change-over trial in 18 male and female healthy volunteers, previously assessed within procedure X/0007/G concluded in March 2020

[46] Advanced therapy medicinal product

15.3.7. Cannabidiol - EPIDYOLEX (CAP) - EMEA/H/C/004675/II/0020, Orphan

Applicant: GW Pharma (International) B.V.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Extension of indication to include treatment with Epidyolex (cannabidiol) in monotherapy as adjunctive therapy of seizures associated with Lennox Gastaut syndrome (LGS) or Dravet syndrome (DS) for patients 2 years of age and older without the restriction for use only in conjunction with clobazam (CLB), based on the previously generated data in patients treated without CLB in LGS and DS pivotal studies re-evaluated in the context of the more recent evidence from study GWEP1521: a double-blind, randomised, placebo-controlled study to investigate the efficacy and safety of cannabidiol as add-on therapy in patients with tuberous sclerosis complex (TCS) who experience inadequately-controlled seizures. As a consequence, sections 4.1, 4.5, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The package leaflet is updated in accordance. In addition, the MAH took the opportunity to implement editorial changes in the product information. The RMP (version 2.1) has also been submitted

15.3.8. 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

15.3.9. Dapivirine - DAPIVIRINE VAGINAL RING 25 MG (Art 58[47]) - EMEA/H/W/002168/II/0015/G

Applicant: International Partnership for Microbicides Belgium AISBL

PRAC Rapporteur: Jan Neuhauser

Scope: Grouped variations consisting of submission of four addenda from studies (listed as category 3 studies in the RMP): 1) IPM 007 (RING study): a phase 3, randomised study exploring dapivirine ring long-term safety and efficacy; 2) study MTN-015: a multisite, prospective, observational cohort study of women following human immunodeficiency virus type 1 (HIV-1) seroconversion in microbicide trials of antiretroviral (ARV)-based microbicides or oral pre-exposure prophylaxis (PrEP); 3) studies IPM 032 and MTN-025: phase 3b open-label extension (OLE) dapivirine ring trials. The data presented in the addenda are the results of retrospective next generation sequencing (NGS) and phenotype

[47] 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 Organization (WHO) on medicinal products for human use that are intended exclusively for markets outside of the European Union (EU)

susceptibility testing on blood samples to further assess the potential development of non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance in women with unrecognized or acute HIV-1 infection. The RMP (version 0.9) is updated accordingly. Additionally, the MAH took the opportunity to update the EMA on other commitments outlined in the RMP as additional risk minimisation measures. These include the development of a healthcare professional guide (HCP guide) and a user guide with agreed objectives and key messages

15.3.10. 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 randomised, 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

15.3.11. Darolutamide - NUBEQA (CAP) - EMEA/H/C/004790/II/0012

Applicant: Bayer AG

PRAC Rapporteur: Jan Neuhauser

Scope: Submission of the final report of carcinogenicity study T104877-7 listed as a category 3 study in the RMP. This is a non-clinical study to assess the carcinogenic potential in mice. The study evaluates the effects of daily oral administration of darolutamide for a period of 6 months in Tg-rasH2 transgenic mouse model. The updated RMP version 3.1 has also been submitted

15.3.12. Darunavir, cobicistat, emtricitabine, tenofovir alafenamide - SYMTUZA (CAP) - EMEA/H/C/004391/II/0045

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Submission of the interim report from study GS-US-292-0106 listed as a category 3 study in the RMP. This is a Phase II/III, open-label study to evaluate of the pharmacokinetics, safety, tolerability, and antiviral activity of the Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (E/C/F/TAF) single tablet regimen in HIV-1 infected antiretroviral treatment-naive adolescents and virologically suppressed HIV-infected children. The RMP version 8.1 has also been submitted

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

Applicant: Otsuka Novel Products GmbH

PRAC Rapporteur: Jo Robays

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

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

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Martin Huber

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

15.3.15. Dolutegravir - TIVICAY (CAP) - EMEA/H/C/002753/WS2323/0081; dolutegravir, abacavir, lamivudine - TRIUMEQ (CAP) -EMEA/H/C/002754/WS2323/0106; dolutegravir, rilpivirine - JULUCA (CAP) - EMEA/H/C/004427/WS2323/0045

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Nathalie Gault

Scope: Submission of the final report from study 200336 (listed as a category 3 study in the RMP): a prospective, interventional pharmacokinetic and safety study of dolutegravir (DTG)/abacavir (ABC)/lamivudine (3TC) in pregnant women. The summary of objective of this PASS study is to investigate the use of DTG during pregnancy and address the safety concerns of pregnant/breastfeeding women. The RMP versions 18.0, 20.0 and 4.0 for Tivicay, Triumeq and Juluca, respectively, have also been submitted

15.3.16. Dostarlimab - JEMPERLI (CAP) - EMEA/H/C/005204/II/0013

Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Update of section 5.1 of the SmPC in order to update efficacy and safety information based on interim results from study 4010-01-001 (GARNET) listed as a specific obligation in the Annex II; This is a single-arm, open-label, phase I trial of intravenous dostarlimab in advanced solid tumors. In addition, the MAH took the opportunity to update section E of Annex II. The RMP version 1.2 has also been submitted

15.3.17. Eltrombopag - REVOLADE (CAP) - EMEA/H/C/001110/II/0068

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Eva Segovia

Scope: Extension of indication to include treatment of adult patients with primary immune thrombocytopenia (ITP) who are refractory to other treatments (e.g. corticosteroids, immunoglobulins) irrespective of time since initial diagnosis, based on an ad-hoc analysis of

study TAPER (CETB115J2411): an ongoing phase 2, open-label, prospective, single-arm study in adult ITP patients who are refractory or relapsed after first-line steroids. As a consequence, sections 4.1 and 5.1 of the SmPC have been updated. In addition, the MAH took the opportunity to make some minor amendments in section 4.8 of the SmPC for increased consistency. The RMP (version 54.0) is updated accordingly

15.3.18. Filgotinib - JYSELECA (CAP) - EMEA/H/C/005113/II/0018

Applicant: Galapagos N.V.

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Update of sections 4.4, 4.6 and 5.1 of the SmPC in order to update information on fertility based on interim results from studies GLPG0634-CL-227 (MANTA Ray) and GS-US-418-4279 (MANTA) listed as a category 3 study in the RMP. The package leaflet and Annex II are updated accordingly. The RMP version 4.1 has also been submitted

15.3.19. Fluticasone furoate, vilanterol - RELVAR ELLIPTA (CAP) - EMEA/H/C/002673/WS2274/0054; REVINTY ELLIPTA (CAP) - EMEA/H/C/002745/WS2274/0052

Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Submission of the final report from study HZA114971 (listed as a category 3 study in the RMP): a multicentre randomised, double-blind, placebo-controlled, parallel-group study to evaluate the effects of a one-year regimen of orally inhaled fluticasone furoate 50 mcg once daily on growth velocity in prepubertal, paediatric subjects with asthma. The RMP version 11.1 has also been submitted

15.3.20. Human thrombin, human fibrinogen - TACHOSIL (CAP) - EMEA/H/C/000505/II/0117

Applicant: Corza Medical GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include treatment of children aged 1 month to 18 years, based on available bibliographical data, results from study TC-2402-040-SP which compared TachoSil with Surgicel Original as adjunct to primary surgical treatment in both adult and paediatric subjects, and results from Study TC-019-IN: a prospective, uncontrolled study in paediatric subjects. As a consequence, sections 4.1, 4.2, and 5.1 of the SmPC are updated. The package leaflet is updated in accordance. In addition, the MAH took the opportunity to implement minor editorial changes in the product information. Version 0.1 of the RMP has also been submitted

15.3.21. Inclisiran - LEQVIO (CAP) - EMEA/H/C/005333/II/0013

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Kimmo Jaakkola

Scope: Submission of the final report from ORION-3 study (CKJX839A12201E1 or MDCO-PCS-16-01) listed as a category 3 study in the RMP. This is an open label, active

comparator extension trial to assess the effect of long-term dosing of inclisiran and evolocumab given as subcutaneous injections in subjects with high cardiovascular risk and elevated LDL-C. The RMP version 2.0 has also been submitted

15.3.22. Ipilimumab - YERVOY (CAP) - EMEA/H/C/002213/WS2187/0098; nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/WS2187/0121

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of section 4.8 of the SmPC in alignment with the recommendations made by the CHMP to revise the pooling approach used to describe immune related adverse reactions and tabulated summaries of adverse drug reactions (ADRs) following II/0096. Individual study data included within this application has been previously reviewed by the CHMP. The updated Opdivo RMP version 29.0 and Yervoy RMP version 37.0 have also been submitted. The MAH took the opportunity to introduce editorial changes. The package leaflet was updated accordingly

15.3.23. 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

15.3.24. Lisocabtagene maraleucel - BREYANZI (CAP) - EMEA/H/C/004731/II/0005

Applicant: Bristol-Myers Squibb Pharma EEIG, ATMP[48]

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include treatment of adult patients with Second-line (2L) Transplant Intended (TI) Large B-Cell Lymphoma (LBCL) for BREYANZI, based on interim analyses from pivotal study JCAR017-BCM-003: a global randomised multicentre phase III trial to compare the efficacy and safety of JCAR017 to standard of care in adult subjects with high-risk, transplant-eligible relapsed or refractory aggressive B-cell Non-Hodgkin Lymphomas (TRANSFORM). As a consequence, sections 4.1, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet is updated in accordance. Version 2.0 of the RMP has also been submitted

[48] Advanced therapy medicinal product

15.3.25. Lorlatinib - LORVIQUA (CAP) - EMEA/H/C/004646/II/0022

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Submission of an updated RMP version 5.0 to revise plans for conduct of hepatic impairment studies. The RMP is updated to reflect the termination of the hepatic impairment study B7461009: a phase 1 study to evaluate the effect of hepatic impairment on the pharmacokinetics and safety of Lorlatinib in advanced cancer patients and to include new hepatic impairment study B7461040: a phase 1, open-label, single-dose, parallel-group study to evaluate the plasma pharmacokinetics and safety of Lorlatinib in participants with moderate and severe hepatic impairment relative to participants with normal hepatic function

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

Applicant: Alnylam Netherlands B.V.

PRAC Rapporteur: Mari Thörn

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 randomised, 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

15.3.27. Meningococcal group A, C, W-135 and Y conjugate vaccine - MENQUADFI (CAP) - EMEA/H/C/005084/II/0018/G

Applicant: Sanofi Pasteur

PRAC Rapporteur: Jean-Michel Dogné

Scope: Update of sections 4.2, 4.5, 4.8 and 5.1 of the SmPC in order to add long term antibody persistence at least 3 years after primary vaccination, immunogenicity and safety of a booster dose of MenQuadfi in adolescents, adults, and older adults, as well as co-administration data with meningococcal serogroup B vaccine in adolescents and adults, in order to fulfil ANX/002 and ANX/003 based on final results from studies MET59 and MEQ00066, respectively, listed as specific obligations in the Annex II. MET59 is a phase 3b, open-label, partially randomised, parallel-group, active-controlled, multicentre study evaluating the immunogenicity and safety of a booster dose of an investigational

quadrivalent MenACYW conjugate vaccine in adolescents and adults, while MEQ00066 is a phase 3, two-stage, randomised, open-label, multicentre trial evaluating the safety and immunogenicity of a single dose of MenACYW conjugate vaccine at least 3 years following initial vaccination with either Menomune vaccine or MenACYW conjugate vaccine in older adults. The Annex II and package leaflet are updated accordingly. The RMP version 1.1 has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the product information

15.3.28. Mirabegron - BETMIGA (CAP) - EMEA/H/C/002388/X/0039/G

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Grouped variations consisting of: 1) extension application to introduce a new pharmaceutical form associated with new strength (8 mg/mL prolonged-release granules for oral suspension); 2) extension of indication to include treatment of neurogenic detrusor overactivity (NDO) in paediatric patients aged 3 to less than 18 years. The RMP (version 9.0) is updated accordingly

15.3.29. Naltrexone hydrochloride, bupropion hydrochloride - MYSIMBA (CAP) - EMEA/H/C/003687/II/0056

Applicant: Orexigen Therapeutics Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: Submission of an updated study design and a protocol synopsis for study CVOT-2 (listed as a category 1 study in Annex II-D (ANX/001.7)): a multicentre, randomised, double-blind, placebo-controlled phase 4 study to assess the effect of naltrexone extended release (ER)/bupropion ER on the occurrence of major adverse cardiovascular events (MACE) in overweight and obese subjects with cardiovascular disease, as requested by CHMP in the conclusions of procedure ANX 001.6 adopted in April 2021. Annex II and the RMP (version 13) are updated accordingly

15.3.30. Pitolisant - WAKIX (CAP) - EMEA/H/C/002616/II/0030, Orphan

Applicant: Bioprojet Pharma

PRAC Rapporteur: Kirsti Villikka

Scope: Extension of indication to include treatment of narcolepsy with or without cataplexy in adolescents and children from the age of 6 years, based on results from Study P11-06; an ongoing phase III, double-blind, multicentre, randomised, placebo-controlled trial undertaken to evaluate safety and efficacy of pitolisant in children from 6 to less than 18 years with narcolepsy with/without cataplexy. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet is updated in accordance. Version 7.0 of the RMP has also been submitted

15.3.31. Pneumococcal polysaccharide conjugate vaccine (20-valent, adsorbed) - APEXXNAR (CAP) - EMEA/H/C/005451/II/0006

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Jean-Michel Dogné

Scope: Update of sections 4.5, 4.8 and 5.1 of the SmPC based on final results from study B7471026 (listed as a category 3 study in the RMP): a phase III, randomised, double-blind trial to describe the safety and immunogenicity of 20-valent pneumococcal conjugate vaccine when coadministered with a booster dose of BNT162b2 in adults 65 years of age and older. The package leaflet and the RMP (version 2.0) were updated accordingly

15.3.32. Pneumococcal polysaccharide conjugate vaccine (adsorbed) - VAXNEUVANCE (CAP) - EMEA/H/C/005477/II/0001

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include treatment of infants, children and adolescents from 6 weeks to less than 18 years of age for active immunisation for the prevention of invasive disease, pneumonia and acute otitis media for Vaxneuvance, based on final results from: 1) study V114-008: a phase 2, double-blind, randomised, multicentre trial to evaluate the safety, tolerability, and immunogenicity of V114 (pneumococcal polysaccharide conjugate vaccine (adsorbed)) compared to Prevenar 13 (pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed)) in healthy infants; 2) seven phase 3 studies (V114-023, V114-024, V114-025, V114-027, V114-029, V114-030, V114-031): interventional studies to evaluate the safety, tolerability and immunogenicity of V114 (pneumococcal polysaccharide conjugate vaccine (adsorbed)) in healthy and immunocompromised infants, children and adolescents. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8 and 5.1 of the SmPC are updated. The package leaflet is updated in accordance. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet and to include editorial changes in the product information. The RMP (version 1.1) is updated accordingly

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

Applicant: Roche Registration GmbH

PRAC Rapporteur: Ulla Wändel Liminga

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

15.3.34. Remdesivir - VEKLURY (CAP) - EMEA/H/C/005622/II/0035/G

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Eva Jirsová

Scope: Grouped variations consisting of: 1) extension of indication for treatment of paediatric patients (at least 4 weeks of age and weighing at least 3 kg) with pneumonia requiring supplemental oxygen (low- or high-flow oxygen) or other non-invasive ventilation at start of treatment based on interim results from study GS-US-540-5823: a phase 2/3 single-arm, open-label study to evaluate the safety, tolerability, pharmacokinetics and efficacy of remdesivir in participants from birth to <18 years of age with coronavirus (COVID-19); 2) extension of indication for treatment of paediatric patients (weighing at least 40 kg) who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19 based on data from 8 adolescent patients who were included in study GS-US-540-9012: a phase 3 randomised, double-blind placebo-controlled trial to evaluate the efficacy and safety of remdesivir treatment of COVID-19 in an outpatient setting. As a consequence, sections 4.1, 4.2, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated. The package leaflet and the RMP (version 3.2) are updated accordingly

15.3.35. Ripretinib - QINLOCK (CAP) - EMEA/H/C/005614/II/0004, Orphan

Applicant: Deciphera Pharmaceuticals (Netherlands) B.V.

PRAC Rapporteur: Željana Margan Koletić

Scope: Update of sections 4.2 and 5.2 of the SmPC in order to change posology recommendations in patients with hepatic impairment and update the description of pharmacokinetics based on final results from study DCC-2618-01-004: a phase 1 study of the pharmacokinetics, safety, and tolerability of ripretinib in subjects with hepatic impairment compared to healthy control subjects. The package leaflet and the RMP (version 2.0) are updated accordingly

15.3.36. Risankizumab - SKYRIZI (CAP) - EMEA/H/C/004759/X/0020/G

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Grouped variations consisting of: 1) extension of application to introduce a new pharmaceutical form (concentrate for solution for infusion), a new strength (600 mg) and a new route of administration (intravenous use); 2) extension of application to add a new strength of 360 mg (150 mg/mL) for risankizumab solution for injection (in cartridge) for subcutaneous use. The new presentations are indicated for the treatment of patients 16 years and older with moderately to severely active Crohn’s disease who have had an inadequate response to, lost response to, or were intolerant to conventional therapy or a biologic therapy, or if such therapies are not advisable. The RMP (version 4.0) is updated in accordance

15.3.37. Rituximab - RIXATHON (CAP) - EMEA/H/C/003903/WS2307/0062; RIXIMYO (CAP) - EMEA/H/C/004729/WS2307/0063

Applicant: Sandoz GmbH

PRAC Rapporteur: Anette Kirstine Stark

Scope: Update of section 4.1 of the SmPC in order to include the rapid infusion regimen (90 minutes) for second and subsequent infusions in the label for patients with non-Hodgkin's lymphoma (NHL) or chronic lymphocytic leukaemia (CLL) based on non-interventional PASS CGP2013ES01R and scientific literature. The RMP version 7.0 has also been submitted

15.3.38. Secukinumab - COSENTYX (CAP) - EMEA/H/C/003729/II/0090

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Eva Segovia

Scope: Extension of indication to include treatment of hidradenitis suppurativa (HS) for COSENTYX, based on interim results from two phase III studies CAIN457M2301 (SUNSHINE) and CAIN457M2302 (SUNRISE). These studies are ongoing, multicentre, randomised, double-blind, placebo-controlled, parallel group phase 3 studies conducted to assess the short (16 weeks) and long-term (up to 52 weeks) efficacy and safety of two secukinumab dose regimens (Q2W or Q4W) compared to placebo in adult subjects with moderate to severe HS. 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 11) are updated accordingly

15.3.39. Teduglutide - REVESTIVE (CAP) - EMEA/H/C/002345/II/0054/G, Orphan

Applicant: Takeda Pharmaceuticals International AG Ireland Branch

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Grouped variations consisting of: 1) extension of indication to include patients from 4 months corrected gestational aged 1 year and above. Consequently, sections 4.1, 4.2, 4.8, 5.1 and 5.2 are updated. The package leaflet and the RMP (version 9.1) are updated accordingly; 2) update of Annex II-D on 'Conditions or restrictions with regards to the safe and effective use of the medicinal product' to amend the date of completion of the imposed post authorisation study: an international short bowel syndrome registry, from Q3 2031 to Q2 2032. In addition, the MAH took the opportunity to amend the list of local representatives

15.3.40. Tenofovir alafenamide - VEMLIDY (CAP) - EMEA/H/C/004169/II/0040

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Valentina Di Giovanni

Scope: Extension of indication to include treatment of chronic hepatitis B-infected children from 6 years and older and weighing at least 25 kilograms for Vemlidy, based on the interim results from Week 24 clinical study report (CSR) for Cohort 1 and Cohort 2 Group 1 and supporting modular summaries for the category 3 study GS-US-320-1092, 'A randomised, double-blind evaluation of the pharmacokinetics, safety, and antiviral efficacy of tenofovir alafenamide (TAF) in children and adolescent subjects with chronic hepatitis B virus infection'. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet is updated in accordance. In addition, the MAH took the opportunity to update the wording in section 4.6 of the SmPC related to breastfeeding and pregnancies exposed to TAF, and to update the contact details of the local representative in

Romania in the package leaflet. The RMP (version 8.2) is updated accordingly

15.3.41. Tisagenlecleucel - KYMRIAH (CAP) - EMEA/H/C/004090/II/0060, Orphan

Applicant: Novartis Europharm Limited, ATMP[49]

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of section 4.2 of the SmPC in order to update the paediatric statement for the B-cell ALL indication and section 4.4 to update the warning on 'prior treatment with anti-CD19 therapy' as well as sections 4.4 and 4.8 in order to update safety data to reflect the pool of the 3 studies B2202, B2205J and B2001X. The proposed changes are in line with the request of the CHMP following the assessment of P46/012. The package leaflet is updated accordingly. In addition, the MAH took the opportunity to correct the Complete Response Rate (CRR) 95% Confidence Interval (CI) on Enrolled set for E2202 study presented in Table 8 in section 5.1 of the SmPC. The RMP version 5.0 has also been submitted

15.3.42. Trastuzumab deruxtecan - ENHERTU (CAP) - EMEA/H/C/005124/II/0022

Applicant: Daiichi Sankyo Europe GmbH

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Extension of indication to include treatment of unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer who have received a prior systemic therapy in the metastatic setting or developed disease recurrence during or withing 6 months of completing adjuvant chemotherapy. Patients with hormone receptor positive (HR+) breast cancer must additionally have received or be ineligible for endocrine therapy; for ENHERTU, based on final results from study DS8201-A-U303 (DESTINY-Breast04). This is a phase III, multicentre, randomised, open-label, active-controlled trial of Trastuzumab Deruxtecan (T-DXd), an Anti-HER2-antibody Drug Conjugate (ADC), versus treatment of physician's choice for HER2-low, unresectable and/or metastatic breast cancer subjects. 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 1.4) are updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to update section 4.4 of the SmPC to update the dosing recommendation for corticosteroid treatment (e.g. prednisolone) with a daily dose

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

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

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

[49] Advanced therapy medicinal product

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

16.1.1. Amifampridine - FIRDAPSE (CAP) - PSUSA/00000141/202112

Applicant: SERB SA

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.2. Avapritinib - AYVAKYT (CAP) - PSUSA/00010878/202201

Applicant: Blueprint Medicines (Netherlands) B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.3. Belantamab mafodotin - BLENREP (CAP) - PSUSA/00010869/202202

Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.4. Birch bark extract[50] - EPISALVAN[51] - PSUSA/00010446/202201

Applicant: Amryt GmbH

PRAC Rapporteur: Zane Neikena

Scope: Evaluation of a PSUSA procedure

16.1.5. Brexucabtagene autoleucel - TECARTUS (CAP) - PSUSA/00010903/202201

Applicant: Kite Pharma EU B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.6. Bulevirtide - HEPCLUDEX (CAP) - PSUSA/00010873/202201

Applicant: Gilead Sciences Ireland Unlimited Company

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.7. Botulinum toxin type A - NUCEIVA (CAP) - PSUSA/00010796/202201

Applicant: Evolus Pharma B.V.

[50] Centrally authorised product(s) only
[51] European Commission (EC) decision on the marketing authorisation (MA) withdrawal of Episalvan dated 07 June 2022

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.8. Casirivimab, imdevimab - RONAPREVE (CAP) - PSUSA/00010963/202201

Applicant: Roche Registration GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.9. Dapivirine - DAPIVIRINE VAGINAL RING 25 MG (Art 58[52]) - EMEA/H/W/002168/PSUV/0019

Applicant: International Partnership for Microbicides Belgium AISBL

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUR procedure

16.1.10. Darolutamide - NUBEQA (CAP) - PSUSA/00010843/202201

Applicant: Bayer AG

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.1.11. Defatted powder of Arachis hypogaea L., semen (peanuts) - PALFORZIA (CAP) - PSUSA/00010902/202201

Applicant: Aimmune Therapeutics Ireland Limited

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

16.1.12. Elbasvir, grazoprevir - ZEPATIER (CAP) - PSUSA/00010519/202201

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.1.13. Entacapone - COMTAN (CAP); COMTESS (CAP); ENTACAPONE ORION (CAP) - PSUSA/00001223/202201

Applicant: Orion Corporation

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

[52] 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 Organization (WHO) on medicinal products for human use that are intended exclusively for markets outside of the European Union (EU)

16.1.14. Ertugliflozin - STEGLATRO (CAP) - PSUSA/00010682/202112

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.15. Ertugliflozin, metformin – SEGLUROMET (CAP); ertugliflozin, sitagliptin - STEGLUJAN (CAP) - PSUSA/00010784/202112

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.16. Fostemsavir - RUKOBIA (CAP) - PSUSA/00010911/202202

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

16.1.17. Glucagon[53] - BAQSIMI (CAP); OGLUO (CAP) - PSUSA/00010826/202201

Applicant: Eli Lilly Nederland B.V. (BAQSIMI), Tetris Pharma B.V. (Ogluo)

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

16.1.18. Imipenem, cilastatin, relebactam - RECARBRIO (CAP) - PSUSA/00010830/202201

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.19. Inclisiran - LEQVIO (CAP) - PSUSA/00010904/202112

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

16.1.20. L-lysine hydrochloride, L-arginine hydrochloride - LYSAKARE (CAP) - PSUSA/00010786/202201

Applicant: Advanced Accelerator Applications

PRAC Rapporteur: Adam Przybylkowski

[53] Centrally authorised product(s) only

Scope: Evaluation of a PSUSA procedure

16.1.21. Lonoctocog alfa - AFSTYLA (CAP) - PSUSA/00010559/202201

Applicant: CSL Behring GmbH

PRAC Rapporteur: Sonja Hrabcik

Scope: Evaluation of a PSUSA procedure

16.1.22. Macimorelin - GHRYVELIN (CAP) - PSUSA/00010746/202201

Applicant: Consilient Health Limited

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

16.1.23. Metreleptin - MYALEPTA (CAP) - PSUSA/00010700/202201

Applicant: Amryt Pharmaceuticals DAC

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.24. Odevixibat - BYLVAY (CAP) - PSUSA/00010949/202201

Applicant: Albireo

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.25. Paclitaxel albumin - ABRAXANE (CAP) - PSUSA/00010123/202201

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.26. Perflutren - LUMINITY (CAP); OPTISON (CAP) - PSUSA/00002350/202112

Applicant: GE Healthcare AS (Optison), Lantheus EU Limited (Luminity)

PRAC Rapporteur: Mari Thörn

Scope: Evaluation of a PSUSA procedure

16.1.27. Pneumococcal polysaccharide conjugate vaccine (adsorbed) - VAXNEUVANCE (CAP) - PSUSA/00010975/202201

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.28. Quadrivalent influenza vaccine (recombinant, prepared in cell culture) - SUPEMTEK (CAP) - PSUSA/00010886/202201

Applicant: Sanofi Pasteur

PRAC Rapporteur: Nathalie Gault

Scope: Evaluation of a PSUSA procedure

16.1.29. Ravulizumab - ULTOMIRIS (CAP) - PSUSA/00010787/202112

Applicant: Alexion Europe SAS

PRAC Rapporteur: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

16.1.30. Regdanvimab - REGKIRONA (CAP) - PSUSA/00010964/202202

Applicant: Celltrion Healthcare Hungary Kft.

PRAC Rapporteur: Valentina Di Giovanni

Scope: Evaluation of a PSUSA procedure

16.1.31. Risdiplam - EVRYSDI (CAP) - PSUSA/00010925/202202

Applicant: Roche Registration GmbH

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.1.32. Romosozumab - EVENITY (CAP) - PSUSA/00010824/202201

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

16.1.33. Salmeterol, fluticasone propionate[54] - BROPAIR SPIROMAX (CAP); SEFFALAIR SPIROMAX (CAP) - PSUSA/00010928/202201

Applicant: Teva B.V.

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.1.34. Smallpox vaccine and monkeypox (live, modified vaccinia virus Ankara) - IMVANEX (CAP) - PSUSA/00010119/202201

Applicant: Bavarian Nordic A/S

PRAC Rapporteur: Brigitte Keller-Stanislawski

[54] Centrally authorised product(s) only

Scope: Evaluation of a PSUSA procedure

16.1.35. Sodium phenylbutyrate - AMMONAPS (CAP); PHEBURANE (CAP) - PSUSA/00002758/202112

Applicant: Immedica Pharma AB, Eurocept International B. V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

16.1.36. Tafasitamab - MINJUVI (CAP) - PSUSA/00010951/202201

Applicant: Incyte Biosciences Distribution B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.37. Tagraxofusp - ELZONRIS (CAP) - PSUSA/00010896/202201

Applicant: Stemline Therapeutics B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.38. Vericiguat - VERQUVO (CAP) - PSUSA/00010950/202201

Applicant: Bayer AG

PRAC Rapporteur: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

16.1.39. Verteporfin - VISUDYNE (CAP) - PSUSA/00003110/202112

Applicant: CHEPLAPHARM Arzneimittel GmbH

PRAC Rapporteur: Nathalie Gault

Scope: Evaluation of a PSUSA procedure

16.1.40. Vonicog alfa - VEYVONDI (CAP) - PSUSA/00010714/202112

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.41. Ziconotide - PRIALT (CAP) - PSUSA/00003142/202112

Applicant: ESTEVE Pharmaceuticals GmbH

PRAC Rapporteur: Jo Robays

Scope: Evaluation of a PSUSA procedure

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

16.2.1. Caspofungin - CANCIDAS (CAP); NAP - PSUSA/00000576/202112

Applicant: Merck Sharp & Dohme B.V. (Cancidas), various

PRAC Rapporteur: Jo Robays

Scope: Evaluation of a PSUSA procedure

16.2.2. Nitric oxide - INOMAX (CAP); NAP - PSUSA/00002172/202112

Applicant: Linde Healthcare AB (INOmax), various

PRAC Rapporteur: Jo Robays

Scope: Evaluation of a PSUSA procedure

16.2.3. Paclitaxel - APEALEA (CAP); NAP - PSUSA/00002264/202112

Applicant: Inceptua AB (Apealea), various

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.2.4. Sildenafil[55] - VIAGRA (CAP); NAP - PSUSA/00002699/202112

Applicant: Upjohn EESV (Viagra), various

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

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

16.3.1. Alitretinoin[56] (NAP) - PSUSA/00010710/202201

Applicant(s): various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.3.2. Alpha amylase (NAP) PSUSA/00000104/202201

Applicant(s): various

PRAC Lead: Nathalie Gault

Scope: Evaluation of a PSUSA procedure

[55] Erectile dysfunction indication only
[56] Oral use only

16.3.3. Amlodipine, lisinopril (NAP) - PSUSA/00010192/202112

Applicant(s): various

PRAC Lead: Zane Neikena

Scope: Evaluation of a PSUSA procedure

16.3.4. Anthrax vaccine (NAP) - PSUSA/00010771/202112

Applicant(s): various

PRAC Lead: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.3.5. Beclometasone (NAP) - PSUSA/00000306/202112

Applicant(s): various

PRAC Lead: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.3.6. Beclomethasone, salbutamol (NAP) - PSUSA/00000309/202201

Applicant(s): various

PRAC Lead: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.3.7. Bendamustine hydrochloride (NAP) - PSUSA/00003162/202201

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.3.8. Betula verrucosa[57] [58] (NAP) - PSUSA/00010815/202201

Applicant(s): various

PRAC Lead: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

16.3.9. Botulinum neurotoxin type A (150 kD) free from complexing proteins (NAP) - PSUSA/00009084/202112

Applicant(s): various

PRAC Lead: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

[57] Allergen for therapy
[58] Sublingual tablet(s) only

16.3.10. Botulinum toxin A-haemagglutinin complex (NAP) - PSUSA/00000427/202112

Applicant(s): various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.3.11. Camellia sinensis, leaf, dry extract refined[59] [60](NAP) - PSUSA/00010569/202112

Applicant(s): various

PRAC Lead: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.3.12. Cefotaxime (NAP) - PSUSA/00000599/202112

Applicant(s): various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.3.13. Citalopram (NAP) - PSUSA/00000779/202112

Applicant(s): various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.3.14. Escitalopram (NAP) - PSUSA/00001265/202112

Applicant(s): various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.3.15. Flumazenil (NAP) - PSUSA/00001413/202112

Applicant(s): various

PRAC Lead: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

16.3.16. Flunitrazepam (NAP) - PSUSA/00001418/202201

Applicant(s): various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

[59] Derived from Camellia sinensis, L.O.KUNTZE
[60] Topical use only

16.3.17. Levobunolol[61] (NAP) - PSUSA/00010109/202201

Applicant(s): various

PRAC Lead: Eva Jirsová

Scope: Evaluation of a PSUSA procedure

16.3.18. Methohexital (NAP) - PSUSA/00010656/202201

Applicant(s): various

PRAC Lead: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

16.3.19. Niflumic acid (NAP) - PSUSA/00002157/202112

Applicant(s): various

PRAC Lead: Melinda Palfi

Scope: Evaluation of a PSUSA procedure

16.3.20. Octenidine dihydrochloride, phenoxyethanol (NAP) - PSUSA/00002199/202201

Applicant(s): various

PRAC Lead: Rugilė Pilvinienė

Scope: Evaluation of a PSUSA procedure

16.3.21. Roxithromycin (NAP) - PSUSA/00002669/202112

Applicant(s): various

PRAC Lead: Valentina Di Giovanni

Scope: Evaluation of a PSUSA procedure

16.3.22. Topiramate (NAP) - PSUSA/00002996/202201

Applicant(s): various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.3.23. Typhoid vaccine (live, attenuated) - PSUSA/00003067/202112

Applicant(s): various

PRAC Lead: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

[61] Ophthalmic indication only

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

16.4.1. Alglucosidase alfa - MYOZYME (CAP) - EMEA/H/C/000636/LEG 053.8

Applicant: Genzyme Europe BV

PRAC Rapporteur: Nathalie Gault

Scope: Cumulative review of the impact of immunogenicity testing on the safety and efficacy of the product in line with the conclusions of the PSUR single assessment (PSUSA) procedure for algluclosidase alfa (PSUSA/00000086/202109) adopted in June 2022

16.4.2. Dolutegravir - TIVICAY (CAP) - EMEA/H/C/002753/LEG 015.1

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Martin Huber

Scope: MAH's response to LEG 010 [submission of all available data/results for 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 PSUR single assessment (PSUSA) procedure] as per the request for supplementary information (RSI) adopted in February 2022

16.4.3. Dolutegravir, abacavir, lamivudine - TRIUMEQ (CAP) - EMEA/H/C/002754/LEG 010.1

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Martin Huber

Scope: MAH's response to LEG 010 [submission of all available data/results for 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 PSUR single assessment (PSUSA) procedure] as per the request for supplementary information (RSI) adopted in February 2022

16.4.4. Dolutegravir, lamivudine - DOVATO (CAP) - EMEA/H/C/004909/LEG 005.1

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: David Olsen

Scope: MAH's response to LEG 010 [Submission of all available data/results for 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 PSUR single assessment (PSUSA) procedure] as per the request for supplementary information (RSI) adopted in February 2022

16.5. Follow-up to PSUR/PSUSA procedures

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[62]

16.6.1. Coronavirus (COVID-19) vaccine (recombinant, adjuvanted) - NUVAXOVID (CAP) - EMEA/H/C/005808/MEA 014.4

Applicant: Novavax CZ, a.s.

PRAC Rapporteur: Brigitte Keller-Stanislawski

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

On 01 August 2022, the PRAC assessment report including its outcome was adopted by written procedure.

16.6.2. Coronavirus (COVID-19) vaccine (recombinant, adjuvanted) - NUVAXOVID (CAP) - EMEA/H/C/005808/MEA 014.5

Applicant: Novavax CZ, a.s.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Sixth 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

[62] 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 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)[63]

17.1.1. Alemtuzumab - LEMTRADA (CAP) - EMEA/H/C/PSA/S/0088

Applicant: Sanofi Belgium

PRAC Rapporteur: Anette Kirstine Stark

Scope: Substantial amendment to a non-interventional post-authorisation safety study to investigate drug utilisation and safety monitoring patterns for Lemtrada (alemtuzumab)

17.1.2. Belimumab - BENLYSTA (CAP) - EMEA/H/C/PSA/S/0085

Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: A 5-Year prospective observational registry to assess adverse events of interest and effectiveness in adults with active, autoantibody-positive systemic lupus erythematosus treated with or without belimumab

17.1.3. Blinatumomab - BLINCYTO (CAP) - EMEA/H/C/PSA/S/0084

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Eva Jirsová

Scope: An observational study of blinatumomab safety and effectiveness, utilisation, and treatment practices to characterise the safety of Blincyto in routine clinical practice. Blincyto efficacy, medication errors, and utilisation and select healthcare resource use while using Blincyto will also be described. Safety and efficacy of Blincyto in specified subgroups of patients will also be assessed

17.1.4. Methylphenidate hydrochloride (NAP) - EMEA/H/N/PSA/S/0074.1

Applicant: MEDICE Arzneimittel Pütter GmbH & Co. KG

PRAC Rapporteur: Martin Huber

Scope: Interim study report for a protocol previously agreed in September 2021 (PSA/S/0074): a multicentre, observational, prospective PASS to evaluate the safety concerns of long-term cardiovascular and psychiatric risks within the adult attention deficit/hyperactivity disorder (ADHD) population taking Medikinet Retard (methylphenidate hydrochloride) according to normal standard clinical practice

17.2. Protocols of PASS non-imposed in the marketing authorisation(s)[64]

17.2.1. (1R,2S,5S)-N-((1S)-1-Cyano-2-((3s)-2-oxopyrrolidin-3-yl)ethyl)-3-((2S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido) butanoyl)-6,6-dimethyl-3-

[63] In accordance with Article 107n of Directive 2001/83/EC
[64] 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

azabicyclo[3.1.0]hexane-2-carboxamide, ritonavir - PAXLOVID (CAP) - EMEA/H/C/005973/MEA 009

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Martin Huber

Scope: Protocol for study C4671037: use and safety of Paxlovid during pregnancy and among patients with moderate or severe hepatic or renal impairment

17.2.2. Abrocitinib - CIBINQO (CAP) - EMEA/H/C/005452/MEA 002

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Protocol for study B7451084: an active surveillance study to monitor the real-world safety of abrocitinib among patients with atopic dermatitis (AD) in the EU. The objective of the study is to estimate the incidence rates of safety endpoints of interest among AD patients receiving abrocitinib and AD patients receiving appropriate systemic treatments including dupilumab for AD in a real-world setting

17.2.3. Abrocitinib - CIBINQO (CAP) - EMEA/H/C/005452/MEA 003

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Protocol for study B7451085: a drug utilisation study to evaluate the effectiveness of risk minimisation measures (RMMs) for abrocitinib in the EU using electronic healthcare data. The study objectives will be to evaluate indicators of HCP's adherence to the risk minimisation measures in accordance with the abrocitinib SmPC and prescriber brochure

17.2.4. Abrocitinib - CIBINQO (CAP) - EMEA/H/C/005452/MEA 004

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Protocol for study B7451015: an adolescent imaging substudy to evaluate if abrocitinib has any clinically meaningful effects on bone growth and development

17.2.5. Brexucabtagene autoleucel - TECARTUS (CAP) - EMEA/H/C/005102/MEA 005.3

Applicant: Kite Pharma EU B.V.

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to MEA 005.2 [protocol for study KT-EU-472-5966: a prescriber survey to assess prescribers' understanding of the risks of Tecartus (KTE-X19) to evaluate the effectiveness of risk minimisation activities, namely healthcare professional (HCP) educational materials and patient alert card (PAC) [final study report expected in September 2023] (from initial opinion/marketing authorisation(s) (MA))] as per the request for supplementary information (RSI) adopted in May 2022

17.2.6. Daratumumab - DARZALEX (CAP) - EMEA/H/C/004077/MEA 011.2

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: MAH's response to MEA 011.1 [protocol for study AMY2009: a multicentre, prospective study of daratumumab-based therapy in newly diagnosed patients with light-chain amyloidosis (AL) (from variation II/0043)] as per the request for supplementary information (RSI) adopted in March 2022

17.2.7. Diroximel fumarate - VUMERITY (CAP) - EMEA/H/C/005437/MEA 001.1

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Martin Huber

Scope: MAH's response MEA 001 [protocol for study 272MS401: Vumerity (diroximel fumarate) prospective multiple sclerosis (MS) pregnancy exposure registry] as per the request for supplementary information (RSI) adopted in April 2022

17.2.8. Elasomeran - SPIKEVAX (CAP) - EMEA/H/C/005791/MEA 034.4

Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: MAH's response 034.2 [protocol for a study monitoring the safety of Spikevax (COVID-19 vaccine) in pregnancy: an observational study using routinely collected health data in five European countries] as per the request for supplementary information (RSI) adopted in April 2022 together with a statistical analysis plan (SAP)

17.2.9. Lenalidomide - REVLIMID (CAP) - EMEA/H/C/000717/MEA 046.5

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Tiphaine Vaillant

Scope: Substantial amendment (version 5.0) to a protocol previously endorsed in November 2017 for study CC-5013-MCL-005 to further investigate and characterise the association of lenalidomide and tumour flare reaction (TFR)/high tumour burden following the extension of indication for the treatment of adult patients with relapsed and/or refractory mantle cell lymphoma (RRMCL)

17.2.10. Mepolizumab - NUCALA (CAP) - EMEA/H/C/003860/MEA 015.1

Applicant: GlaxoSmithKline Trading Services Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: MAH's response to MEA 015 [protocol for study 218065: a PASS to describe real-world safety and effectiveness of mepolizumab in paediatric eosinophilic granulomatosis with polyangiitis (EGPA) patients in Europe] as per the request for supplementary information (RSI) adopted in May 2022

17.2.11. Naltrexone hydrochloride, bupropion hydrochloride - MYSIMBA (CAP) - EMEA/H/C/003687/MEA 003.13

Applicant: Orexigen Therapeutics Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: Submission of the 4th feasibility report and final study protocol for PASS NB-451: an observational retrospective drug utilisation study (DUS) of Mysimba (naltrexone hydrochloride/bupropion hydrochloride) in Europe and the United States to describe the demographic and baseline characteristics of users of Mysimba (naltrexone hydrochloride/bupropion hydrochloride), evaluate patterns of Mysimba (naltrexone hydrochloride/bupropion hydrochloride) initiation and use)

17.2.12. Ozanimod - ZEPOSIA (CAP) - EMEA/H/C/004835/MEA 005

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Protocol for study IM0471037: a post-authorisation safety study (PASS) titled 'Long-term real-world safety of ozanimod – A post-authorisation safety study (PASS) in patients diagnosed with ulcerative colitis'. This study is a category 3 study (required additional pharmacovigilance activity - UC indication) listed in the RMP version 3.0

17.2.13. Pegcetacoplan - ASPAVELI (CAP) - EMEA/H/C/005553/MEA 002

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Kimmo Jaakkola

Scope: Protocol for study Sobi.PEGCET-301: a PASS using registry data for pegcetacoplan to evaluate the occurrence of serious infections in patients with paroxysmal nocturnal hemoglobinuria (PNH) treated with pegcetacoplan

17.2.14. Pegcetacoplan - ASPAVELI (CAP) - EMEA/H/C/005553/MEA 003

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Kimmo Jaakkola

Scope: Protocol for study Sobi.PEGCET-302: a post-authorisation safety study for assessment of pregnancy outcomes in patients with paroxysmal nocturnal hemoglobinuria (PNH) exposed to pegcetacoplan during pregnancy

17.2.15. Rimegepant - VYDURA (CAP) - EMEA/H/C/005725/MEA 001

Applicant: Biohaven Pharmaceutical Ireland DAC

PRAC Rapporteur: Anette Kirstine Stark

Scope: Protocol for study BHV3000-402: rimegepant pregnancy registry study together with a statistical analysis plan (SAP)

17.2.16. Rimegepant - VYDURA (CAP) - EMEA/H/C/005725/MEA 002

Applicant: Biohaven Pharmaceutical Ireland DAC

PRAC Rapporteur: Anette Kirstine Stark

Scope: Protocol for study BHV3000-403: a rimegepant pregnancy outcomes study together with a statistical analysis plan (SAP)

17.2.17. Tebentafusp - KIMMTRAK (CAP) - EMEA/H/C/004929/MEA 002

Applicant: Immunocore Ireland Limited

PRAC Rapporteur: Menno van der Elst

Scope: Protocol for a physician's survey to evaluate the effectiveness of additional risk minimisation measure for (educational materials) cytokine release syndrome (CRS) associated with Kimmtrak administration

17.2.18. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/MEA 017.2

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: MAH's response to MEA 017.1 [protocol for study A3921352: an active surveillance, post-authorisation study to characterise the safety of tofacitinib in patients with moderately to severely active ulcerative colitis in the real-world setting using data from the united registries for clinical assessment and research (UR-CARE) in the European Union (EU)] as per the request for supplementary information (RSI) adopted in March 2022

17.2.19. Upadacitinib - RINVOQ (CAP) - EMEA/H/C/004760/MEA 012.1

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: MAH's response to MEA 012 [protocol for study P21-825: an evaluation of the effectiveness of additional risk minimisation measures for upadacitinib in the treatment of atopic dermatitis] as per request for supplementary information (RSI) adopted in February 2022

17.2.20. Upadacitinib - RINVOQ (CAP) - EMEA/H/C/004760/MEA 014.1

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: MAH's response to MEA 014 [protocol for study P21-824: a study of growth and development in adolescents with atopic dermatitis who receive upadacitinib] as per request for supplementary information (RSI) adopted in March 2022

17.2.21. Venetoclax - VENCLYXTO (CAP) - EMEA/H/C/004106/MEA 015

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Eva Jirsová

Scope: Protocol for study P22-907 (listed as category 3 study in the RMP): a one-time, cross-sectional survey study evaluating the effectiveness of the DHPC and of the revised venetoclax SmPC among haematologists in select European countries

17.2.22. Venetoclax - VENCLYXTO (CAP) - EMEA/H/C/004106/MEA 016

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Eva Jirsová

Scope: Protocol for study P22-905 (listed as category 3 study in the RMP): a one-time, cross-sectional survey study to evaluate effectiveness of the patient card among adult patients recently treated with venetoclax for CLL per usual care in select European countries

17.2.23. Zanamivir - DECTOVA (CAP) - EMEA/H/C/004102/MEA 003.1

Applicant: GlaxoSmithKline Trading Services Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: MAH's response to MEA 003 [protocol for study 208140: an intravenous (IV) zanamivir pregnancy registry to evaluate pregnancy outcomes among women exposed to IV zanamivir at any time during pregnancy (from initial marketing authorisation/opinion)]

17.3. Results of PASS imposed in the marketing authorisation(s)[65]

None

17.4. Results of PASS non-imposed in the marketing authorisation(s)[66]

17.4.1. Coronavirus (COVID-19) vaccine (ChAdOx1-S [recombinant]) - VAXZEVRIA (CAP) - EMEA/H/C/005675/II/0038

Applicant: AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

Scope: Submission of the final report from study MS1222-0003 (listed as a category 3 study in the RMP) as assessment of anti-platelet factor 4 (PF4) antibodies prior to, and following, vaccination with AZD1222: a study where sera of vaccinated individuals in study D8110C00001 are tested to elucidate whether vaccination with Vaxzevria (COVID-19 vaccine) leads to increased levels of circulating anti-PF4 antibodies, a key component of the hypothesised mechanism underlying thrombosis with thrombocytopenia syndrome (TTS)

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

Applicant: GE Healthcare AS

PRAC Rapporteur: Martin Huber

[65] In accordance with Article 107p-q of Directive 2001/83/EC
[66] 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

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

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

Applicant: Ferrer Internacional s.a.

PRAC Rapporteur: Liana Gross-Martirosyan

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

17.4.4. Romiplostim - NPLATE (CAP) - EMEA/H/C/000942/II/0083

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Eva Segovia

Scope: Submission of the final report from study 20070797 (listed as a category 3 study in the RMP): an observational study assessing the long-term safety of romiplostim treatment in real-life clinical practice in three Nordic countries. The RMP (version 21.0) is updated accordingly

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

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Tiphaine Vaillant

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

17.4.6. Talimogene laherparepvec - IMLYGIC (CAP) - EMEA/H/C/002771/II/0056

Applicant: Amgen Europe B.V., ATMP[67]

[67] Advanced therapy medicinal product

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Submission of the final report from study 20120139 (listed as a category 3 study in the RMP): is a multicentre, observational registry study to evaluate the survival and long-term safety of subjects who previously received talimogene laherparepvec in Amgen or BioVEX sponsored clinical trials [in fulfilment of MEA/004]

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

17.5.1. Alglucosidase alfa - MYOZYME (CAP) - EMEA/H/C/000636/MEA 024.17

Applicant: Genzyme Europe BV

PRAC Rapporteur: Nathalie Gault

Scope: MAH's response to MEA 024.16 [annual report (covering period from 04 July 2020 to 02 July 2021) on adverse events and/or lack of efficacy, immunological data, follow-up growth disturbances in children and data on urinary hexose tetrasaccharide (Hex4) from the Pompe registry: a global, multicentre, observational and voluntary programme designed to collect uniform and meaningful clinical data related to the onset, progression, and treated course of patients with Pompe disease irrespective of treatment] as per the request for supplementary information (RSI) adopted in March 2022

17.5.2. Alglucosidase alfa - MYOZYME (CAP) - EMEA/H/C/000636/MEA 025.17

Applicant: Genzyme Europe BV

PRAC Rapporteur: Nathalie Gault

Scope: MAH's response to MEA 025.16 [annual report (covering period from 04 July 2020 to 02 July 2021) on data on patients with renal or hepatic insufficiency from the Pompe registry: a global, multicentre, observational and voluntary programme designed to collect uniform and meaningful clinical data related to the onset, progression, and treated course of patients with Pompe disease irrespective of treatment status] as per the request for supplementary information (RSI) adopted in March 2022

17.5.3. Apremilast - OTEZLA (CAP) - EMEA/H/C/003746/MEA 008.2

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Eva Segovia

Scope: Third yearly report for study CC 10004 PSA-012: evaluation of the long-term safety and safety outcomes for psoriatic arthritis patients treated with Otezla (apremilast) in the British Society for Rheumatology Psoriatic Arthritis Register (BSRBR-PsA) [final clinical study report (CSR) expected in Q2 2026]

17.5.4. Beclometasone, formoterol, glycopyrronium bromide - TRIMBOW (CAP) - EMEA/H/C/004257/MEA 002.2

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Jan Neuhauser

Scope: First progress report for study CLI-05993BA1-05 (TRIBE): a multinational database cohort study to assess adverse cardiovascular and cerebrovascular outcomes in patients with chronic obstructive pulmonary disease initiating a fixed triple therapy containing beclometasone dipropionate, formoterol fumarate and glycopyrronium administered via dry powder inhaler (DPI) compared to pressurised metered dose inhaler (pMDI) and MAH's response to MEA 002.1 as per the request for supplementary information (RSI) adopted in December 2021

17.5.5. Dimethyl fumarate - TECFIDERA (CAP) - EMEA/H/C/002601/MEA 007.5

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Martin Huber

Scope: MAH's response to MEA 007.3 and MEA 007.4 [amendment to a protocol previously agreed in November 2017 for study 109MS401 (ESTEEM): a multicentre, global, observational study to collect information on safety and to document the drug utilisation of Tecfidera (dimethyl fumarate) when used in routine medical practice in the treatment of relapsing multiple sclerosis] as per the request for supplementary information (RSI) adopted in April 2021, together with the seventh annual progress report for the study

17.5.6. Fingolimod - GILENYA (CAP) - EMEA/H/C/002202/MEA 012.11

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Tiphaine Vaillant

Scope: Eleventh annual interim report for study D2404: a multinational pregnancy exposure registry in patients with multiple sclerosis (MS) taking Gilenya (fingolimod) from the pregnancy intensive monitoring programme (PRIM)

17.5.7. Ipilimumab - YERVOY (CAP) - EMEA/H/C/002213/MEA 036.4

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Menno van der Elst

Scope: Submission of the progress report for study CA184557: Long-term follow-up of ipilimumab treated paediatric patients enrolled in the Dutch melanoma treatment registry (DMTR)

17.5.8. Lutetium (^{177}Lu) oxodotreotide - LUTATHERA (CAP) - EMEA/H/C/004123/MEA 001.11

Applicant: Advanced Accelerator Applications

PRAC Rapporteur: Adam Przybylkowski

Scope: Fifth 6-monthly progress report for study A-LUT-T-E02-402 (SALUS): an international, non-interventional, post-authorisation long-term safety study of Lutathera (lutetium (^{177}Lu) oxodotreotide) in patients with unresectable or metastatic, well-differentiated, somatostatin receptor positive, gastroenteropancreatic neuroendocrine tumours together with MAH's response to MEA 001.9 as pr the request for supplementary information (RSI) adopted in March 2022

17.5.9. Octocog alfa - KOVALTRY (CAP) - EMEA/H/C/003825/MEA 005.4

Applicant: Bayer AG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Annual interim report 2021 for epidemiological study 15689: an evaluation of adverse events of special interest (AESI) in the European PEDiatric NETwork (PedNet) for haemophilia management registry

17.5.10. Sacubitril, valsartan - ENTRESTO (CAP) - EMEA/H/C/004062/MEA 002.9

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Anette Kirstine Stark

Scope: Submission of the final results for the validation sub study to assess the positive predictive value of the identification of specific primary safety events of interest (angioedema, acute pancreatitis, hepatotoxicity, and myotoxicity) for the post-authorisation multi-database safety LCZ696B2014: a non-interventional, post-authorisation, multi-database safety study to characterize the risk of angioedema and other specific safety events of interest in association with initiation of Entresto (sacubitril/valsartan) or use of an ACE inhibitor in adult patients with heart failure (HF)

17.5.11. Sacubitril, valsartan - ENTRESTO (CAP) - EMEA/H/C/004062/MEA 004.12

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Anette Kirstine Stark

Scope: Submission of the final results for the validation sub study to assess the positive predictive value of the identification of specific primary safety events of interest (angioedema, acute pancreatitis, hepatotoxicity, and myotoxicity) for the post-authorisation multi-database safety study LCZ696B2015: a non-interventional, post-authorisation, multi-database safety study, using a case-control design, to assess the risk of myotoxicity, hepatotoxicity, and acute pancreatitis in statin-exposed HF patients with or without concomitant use of sacubitril/valsartan (Entresto)

17.5.12. Sacubitril, valsartan - NEPARVIS (CAP) - EMEA/H/C/004343/MEA 002.6

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Anette Kirstine Stark

Scope: Submission of the final results for the validation sub study to assess the positive predictive value of the identification of specific primary safety events of interest (angioedema, acute pancreatitis, hepatotoxicity, and myotoxicity) for the post-authorisation multi-database safety LCZ696B2014: a non-interventional, post-authorisation, multi-database safety study to characterize the risk of angioedema and other specific safety events of interest in association with initiation of Entresto (sacubitril/valsartan) or use of an ACE inhibitor in adult patients with heart failure (HF)

17.5.13. Sacubitril, valsartan - NEPARVIS (CAP) - EMEA/H/C/004343/MEA 003.9

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Anette Kirstine Stark

Scope: Submission of the final results for the validation sub-study to assess the positive predictive value of the identification of specific primary safety events of interest (angioedema, acute pancreatitis, hepatotoxicity, and myotoxicity) for the post-authorisation multi-database safety study LCZ696B2015: a non-interventional, post-authorisation, multi-database safety study, using a case-control design, to assess the risk of myotoxicity, hepatotoxicity, and acute pancreatitis in statin-exposed HF patients with or without concomitant use of sacubitril/valsartan (Entresto)

17.5.14. Siponimod - MAYZENT (CAP) - EMEA/H/C/004712/MEA 002.3

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Submission of the first annual interim report for study CBAF312A2411 (listed as category 3 study in the RMP): evaluation of pregnancy and infant outcomes in Mayzent patients using pregnancy outcomes intensive monitoring (PRIM)

17.5.15. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/MEA 045.9

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: Third annual progress 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

17.6. Others

17.6.1. Acalabrutinib - CALQUENCE (CAP) - EMEA/H/C/005299/MEA 002.5

Applicant: AstraZeneca AB

PRAC Rapporteur: Željana Margan Koletić

Scope: MAH's response to MEA 002.3 [interim report for study D8220C00008 (ASSURE): a phase 3b, multicentre, open-label, single-arm study of acalabrutinib (ACP-196) in subjects with chronic lymphocytic leukaemia to address missing information around moderate to severe cardiac impaired patients] as per request for supplementary information (RSI) adopted in March 2022

17.6.2. Avapritinib - AYVAKYT (CAP) - EMEA/H/C/005208/SOB 008

Applicant: Blueprint Medicines (Netherlands) B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Submission of statistical analysis plan (SAP) for study NO BLU-285-1406: an

imposed non-interventional PASS aiming to collect long-term safety and efficacy data for avapritinib in first-line patients with PDGFRA D842V-mutated gastrointestinal stromal tumour (GIST) given as specific obligation 3 (SOB3) of the conditional marketing authorisation

17.6.3. Cabazitaxel - CABAZITAXEL ACCORD (CAP) - EMEA/H/C/005178/MEA 001.2

Applicant: Accord Healthcare S.L.U.

PRAC Rapporteur: Tiphaine Vaillant

Scope: Third six-monthly review of cases of 'medication error' for cabazitaxel reported during routine signal management activities

17.6.4. Coronavirus (COVID-19) vaccine (ChAdOx1-S [recombinant]) - VAXZEVRIA (CAP) - EMEA/H/C/005675/MEA 006.6

Applicant: AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

Scope: MAH's response to MEA 006.3 [statistical analysis plan (SAP) for study COVID-19 vaccines International Pregnancy Exposure Registry (C-VIPER) (listed as a category 3 study in the RMP): a pregnancy registry of women exposed to Vaxzevria (AZD1222 – COVID-19 vaccine) immediately before or during pregnancy (from initial opinion/marketing authorisation(s) (MA))] as per request for supplementary information (RSI) adopted in April 2022

17.6.5. Elasomeran - SPIKEVAX (CAP) - EMEA/H/C/005791/MEA 004.7

Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: MAH's response to MEA 004.5 [submission of a statistical analysis plan (SAP) for study mRNA-1273-P904 (study 1) (listed as a category 3 study in the RMP): a post-authorisation active surveillance safety study using secondary data to monitor real-world safety of Spikevax (COVID-19 mRNA-1273 vaccine) in Europe - an enhanced pharmacovigilance study to provide additional evaluation of adverse events of special interest (AESI) and emerging validated safety signals in European populations and electronic database assessment of use in pregnant women [final clinical study report (CSR) expected in December 2023]] as per request for supplementary information adopted in April 2022

17.6.6. Icatibant - FIRAZYR (CAP) - EMEA/H/C/000899/MEA 034.1

Applicant: Takeda Pharmaceuticals International AG

PRAC Rapporteur: Mari Thörn

Scope: MAH's response to MEA 034 [proposal for discontinuation of icatibant outcome survey (IOS): a prospective, international, observational open-ended disease registry designed to document over time the routine clinical outcomes of adult and paediatric patients with hereditary angioedema (HAE; HAE types I and II and HAE with normal C1-

esterase inhibitor), angiotensin converting enzyme inhibitor (ACE-I)-induced angioedema, non-histaminergic idiopathic angioedema, and acquired angioedema; and notification of change to the legal entity sponsoring the study] as per request for supplementary information (RSI) adopted in April 2022

17.6.7. Melatonin - SLENYTO (CAP) - EMEA/H/C/004425/REC 002.2

Applicant: RAD Neurim Pharmaceuticals EEC SARL

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Third annual French 'recommendation temporaire d'utilisation (RTU)' report on special temporary recommendation of use for Circadin (melatonin) 2-6 mg in the autism spectrum disorder (ASD) and neurogenetic 6-18 year old population for the period from October 2015 to July 2019

17.6.8. Zanubrutinib - BRUKINSA (CAP) - EMEA/H/C/004978/MEA 002.1

Applicant: BeiGene Ireland Ltd

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to MEA 002 [protocol for study LTE1 (listed as a category 3 study in the RMP): a phase 3, open-label study to evaluate the long-term safety and efficacy of zanubrutinib, as monotherapy or in combination, in patients with B-cell malignancies who are or were previously enrolled in a BeiGene parent study and who are still benefiting or may benefit from treatment with zanubrutinib, or who are willing to have long-term survival follow-up] as adopted in May 2022

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

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

18.1. Annual reassessments of the marketing authorisation

18.1.1. Evinacumab - EVKEEZA (CAP) - EMEA/H/C/005449/S/0005 (without RMP)

Applicant: Ultragenyx Germany GmbH

PRAC Rapporteur: Mari Thörn

Scope: Annual reassessment of the marketing authorisation

18.1.2. Idursulfase - ELAPRASE (CAP) - EMEA/H/C/000700/S/0099 (without RMP)

Applicant: Takeda Pharmaceuticals International AG Ireland Branch

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Annual reassessment of the marketing authorisation

18.2. Conditional renewals of the marketing authorisation

18.2.1. Brexucabtagene autoleucel - TECARTUS (CAP) - EMEA/H/C/005102/R/0025 (without RMP)

Applicant: Kite Pharma EU B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Conditional renewal of the marketing authorisation

18.2.2. Coronavirus (COVID-19) vaccine (recombinant, adjuvanted) - NUVAXOVID (CAP) - EMEA/H/C/005808/R/0020 (without RMP)

Applicant: Novavax CZ, a.s.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Conditional renewal of the marketing authorisation

18.2.3. Elasomeran - SPIKEVAX (CAP) - EMEA/H/C/005791/R/0074 (without RMP)

Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Conditional renewal of the marketing authorisation

18.2.4. Sotorasib - LUMYKRAS (CAP) - EMEA/H/C/005522/R/0002 (without RMP)

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Conditional renewal of the marketing authorisation

18.2.5. Tozinameran - COMIRNATY (CAP) - EMEA/H/C/005735/R/0137 (without RMP)

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Conditional renewal of the marketing authorisation

18.2.6. Trastuzumab deruxtecan - ENHERTU (CAP) - EMEA/H/C/005124/R/0023 (without RMP)

Applicant: Daiichi Sankyo Europe GmbH

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Conditional renewal of the marketing authorisation

18.3. Renewals of the marketing authorisation

18.3.1. Anagrelide - ANAGRELIDE MYLAN (CAP) - EMEA/H/C/004585/R/0010 (without RMP)

Applicant: Mylan Pharmaceuticals Limited

PRAC Rapporteur: Tiphaine Vaillant

Scope: 5-year renewal of the marketing authorisation

18.3.2. Darunavir - DARUNAVIR KRKA (CAP) - EMEA/H/C/004273/R/0013 (without RMP)

Applicant: KRKA, d.d., Novo mesto

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: 5-year renewal of the marketing authorisation

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

Applicant: Takeda Pharma A/S, ATMP[68]

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: 5-year renewal of the marketing authorisation

18.3.4. Efavirenz, emtricitabine, tenofovir disoproxil – EFAVIRENZ, EMTRICITABINE, TENOFOVIR DISOPROXIL KRKA (CAP) - EMEA/H/C/004274/R/0015 (without RMP)

Applicant: KRKA, d.d., Novo mesto

PRAC Rapporteur: Martin Huber

Scope: 5-year renewal of the marketing authorisation

18.3.5. Ertugliflozin - STEGLATRO (CAP) - EMEA/H/C/004315/R/0015 (without RMP)

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: 5-year renewal of the marketing authorisation

18.3.6. Ertugliflozin, metformin hydrochloride - SEGLUROMET (CAP) - EMEA/H/C/004314/R/0015 (without RMP)

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: 5-year renewal of the marketing authorisation

[68] Advanced therapy medicinal product

18.3.7. Ertugliflozin, sitagliptin - STEGLUJAN (CAP) - EMEA/H/C/004313/R/0018 (without RMP)

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: 5-year renewal of the marketing authorisation

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

Applicant: Mylan Pharmaceuticals Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: 5-year renewal of the marketing authorisation

18.3.9. Hydrocortisone - ALKINDI (CAP) - EMEA/H/C/004416/R/0014 (without RMP)

Applicant: Diurnal Europe BV

PRAC Rapporteur: Mari Thorn

Scope: 5-year renewal of the marketing authorisation

18.3.10. Gemtuzumab ozogamicin - MYLOTARG (CAP) - EMEA/H/C/004204/R/0025 (without RMP)

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: 5-year renewal of the marketing authorisation

18.3.11. Obeticholic acid - OCALIVA (CAP) - EMEA/H/C/004093/R/0034 (without RMP)

Applicant: Intercept Pharma International Limited

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: 5-year renewal of the marketing authorisation

18.3.12. Rurioctocog alfa pegol - ADYNOVI (CAP) - EMEA/H/C/004195/R/0033 (with RMP)

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Menno van der Elst

Scope: 5-year renewal of the marketing authorisation

18.3.13. Trastuzumab - HERZUMA (CAP) - EMEA/H/C/002575/R/0050 (with RMP)

Applicant: Celltrion Healthcare Hungary Kft.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: 5-year renewal of the marketing authorisation

18.3.14. Vandetanib - CAPRELSA (CAP) - EMEA/H/C/002315/R/0055 (without RMP)

Applicant: Genzyme Europe BV

PRAC Rapporteur: Tiphaine Vaillant

Scope: Conditional 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 29 August – 01 September 2022 meeting (marked as "a"), the Extraordinary PRAC Meeting - Comirnaty - Omicron BA.4 - BA.5 adapted vaccine on 08 September 2022 (marked as "b") and the September 2022 ORGAM TC (marked as "c").

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Sabine Straus [a, b, c]	Chair	The Netherlands	No interests declared	Full involvement
Jan Neuhauser [a, b]	Member	Austria	No interests declared	Full involvement
Sonja Hrabcik [a]	Alternate	Austria	No interests declared	Full involvement
Jean-Michel Dogné [a, b, c]	Member	Belgium	No interests declared	Full involvement
Jo Robays [a, c]	Alternate (new mandate as Alternate for Belgium started on 26/07/2022)	Belgium	No interests declared	Full involvement
Maria Popova-Kiradjieva [a, c]	Member	Bulgaria	No interests declared	Full involvement
Nikica Mirošević Skvrce [a, b, c]	Member	Croatia	No interests declared	Full involvement
Željana Margan Koletić [a]	Alternate	Croatia	No interests declared	Full involvement
Elena Kaisis [a, b, c]	Member	Cyprus	No interests declared	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Panagiotis Psaras [a, b]	Alternate	Cyprus	No interests declared	Full involvement
Eva Jirsová [a, b, c]	Member	Czechia	No interests declared	Full involvement
Jana Lukacisinova [a, c]	Alternate	Czechia	No interests declared	Full involvement
Anette Kirstine Stark [a, b]	Member	Denmark	No interests declared	Full involvement
Marie Louise Schougaard Christiansen [a, b, c]	Alternate	Denmark	No interests declared	Full involvement
Maia Uusküla [a]	Member	Estonia	No interests declared	Full involvement
Krõõt Aab [a]	Alternate	Estonia	No interests declared	Full involvement
Kirsti Villikka [a, b, c]	Member	Finland	No interests declared	Full involvement
Kimmo Jaakkola [a, b]	Alternate	Finland	No interests declared	Full involvement
Tiphaine Vaillant [a, b, c]	Member	France	No interests declared	Full involvement
Nathalie Gault [a, b, c]	Alternate	France	No interests declared	Full involvement
Martin Huber [a, b, c]	Member (Vice-Chair)	Germany	No interests declared	Full involvement
Brigitte Keller-Stanislawski [a, b]	Alternate	Germany	No interests declared	Full involvement
Sofia Trantza [a, b]	Member	Greece	No interest declared	Full involvement
Georgia Gkegka [a]	Alternate	Greece	No interest declared	Full involvement
Julia Pallos [a, b, c]	Member	Hungary	No participation in final deliberations and voting on	15.3.23. Ipilimumab - YERVOY (CAP) - EMEA/H/C/002213/WS2187/0098; nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/WS2187/0121 15.3.24. Lisocabtagene maraleucel -

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				BREYANZI (CAP) - EMEA/H/C/004731/II/0005 16.1.25. Paclitaxel albumin - ABRAXANE (CAP) - PSUSA/00010123/202201 16.2.3. Paclitaxel - APEALEA (CAP); NAP - PSUSA/00002264/202112 17.2.9. Lenalidomide - REVLIMID (CAP) - EMEA/H/C/000717/MEA 046.5 17.2.12. Ozanimod - ZEPOSIA (CAP) - EMEA/H/C/004835/MEA 005 17.5.7. Ipilimumab - YERVOY (CAP) - EMEA/H/C/002213/MEA 036.4
Melinda Palfi [a]	Alternate	Hungary	No interest declared	Full involvement
Guðrún Stefánsdóttir [a, b, c]	Member	Iceland	No participation in final deliberations and voting on:	17.1.3. Blinatumomab - BLINCYTO (CAP) - EMEA/H/C/PSA/S/0084 17.4.4. Romiplostim - NPLATE (CAP) - EMEA/H/C/000942/II/0083 17.4.6.

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				Talimogene laherparepvec - IMLYGIC (CAP) - EMEA/H/C/002771/II/0056 17.5.3. Apremilast - OTEZLA (CAP) - EMEA/H/C/003746/MEA 008.2 18.2.4. Sotorasib - LUMYKRAS (CAP) - EMEA/H/C/005522/R/0002 (without RMP)
Gudrun Thengilsdottir [b]	Alternate	Iceland	No interests declared	Full involvement
Rhea Fitzgerald [a, c]	Member	Ireland	No interests declared	Full involvement
Ronan Grimes [a, b]	Alternate	Ireland	No interests declared	Full involvement
Amelia Cupelli [a, b, c]	Member	Italy	No interests declared	Full involvement
Valentina Di Giovanni [a, b, c]	Alternate	Italy	No interests declared	Full involvement
Zane Neikena [a, b, c]	Member	Latvia	No interests declared	Full involvement
Rugile Pilviniene [a]	Member	Lithuania	No interests declared	Full involvement
Lina Seibokiene [a, b]	Alternate	Lithuania	No participation in discussion, final deliberations and voting on:	7.3.1. Rivaroxaban - XARELTO (CAP) - EMEA/H/C/PSR/S/0027
Nadine Petitpain [a, b]	Member	Luxembourg	No participation in final deliberations and voting on:	2.1.1. Pholcodine (NAP); pholcodine, biclotymol, chlorphenamine (NAP); pholcodine, chlorphenamine

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				(NAP); pholcodine, diphenhydramine (NAP); pholcodine, diphenhydramine, paracetamol, pseudoephedrine (NAP); pholcodine, guaiacol (NAP); pholcodine, paracetamol, pseudoephedrine (NAP) - EMEA/H/A-107i/1521
Anne-Cécile Vuillemin [b]	Alternate	Luxembourg	No interests declared	Full involvement
John Joseph Borg [a]	Member	Malta	No interests declared	Full involvement
Benjamin Micallef [b]	Alternate	Malta	No interests declared	Full involvement
Menno van der Elst [a, b]	Member	The Netherlands	No interests declared	Full involvement
Liana Gross-Martirosyan [a, c]	Alternate	The Netherlands	No interests declared	Full involvement
David Olsen [a, b, c]	Member	Norway	No participation in final deliberations and voting on:	6.3.8. Testosterone (NAP) - PSUSA/00010631/202112 7.3.1. Rivaroxaban – XARELTO (CAP) - EMEA/H/C/PSR/S/0027 14.2.1. Regorafenib - STIVARGA (CAP) 5.3.10. Darolutamide - NUBEQA (CAP) - EMEA/H/C/004790/II/0009 15.3.11. Darolutamide - NUBEQA (CAP) -

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				EMEA/H/C/004790/II/0012 16.1.10. Darolutamide - NUBEQA (CAP) - PSUSA/00010843/202201 16.1.38. Vericiguat - VERQUVO (CAP) - PSUSA/00010950/202201 17.5.9. Octocog alfa - KOVALTRY (CAP) - EMEA/H/C/003825/MEA 005.4
Karen Pernille Harg [a, c]	Alternate	Norway	No interests declared	Full involvement
Adam Przybylkowski [a]	Member	Poland	No interests declared	Full involvement
Katarzyna Ziolkowska [b, c]	Alternate	Poland	No interests declared	Full involvement
Ana Diniz Martins [a, c]	Member	Portugal	No interests declared	Full involvement
Marcia Sofia Sanches de Castro Lopes Silva [b]	Alternate	Portugal	No interests declared	Full involvement
Roxana Dondera [a, b, c]	Member	Romania	No interests declared	Full involvement
Alexandra - Maria Spurni [a, b, c]	Alternate	Romania	No interests declared	Full involvement
Anna Mareková [a, b, c]	Member	Slovakia	No interests declared	Full involvement
Lucia Kuráková [b, c]	Alternate	Slovakia	No interests declared	Full involvement
Polona Golmajer [a, b, c]	Member	Slovenia	No interests declared	Full involvement
Eva Segovia [a]	Member	Spain	No interests declared	Full involvement
Maria del Pilar Rayon [a, b, c]	Alternate	Spain	No interests declared	Full involvement
Ulla Wändel Liminga [a, b, c]	Member	Sweden	No interests declared	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Mari Thorn [a, c]	Alternate (New mandate as Alternate for Sweden started on 15/07/2022)	Sweden	No restrictions applicable to this meeting	Full involvement
Annalisa Capuano [a, b]	Member	Independent scientific expert	No interests declared	Full involvement
Milou Daniel Drici [a, b]	Member	Independent scientific expert	No interests declared	Full involvement
Maria Teresa Herdeiro [a, b, c]	Member	Independent scientific expert	No interests declared	Full involvement
Patricia McGettigan [a, b]	Member	Independent scientific expert	No interests declared	Full involvement
Daniel Morales [a]	Member	Independent scientific expert	No interests declared	Full involvement
Roberto Frontini [a, b, c]	Member	Healthcare Professionals' Representative	No restrictions applicable to the meeting	Full involvement
Salvatore Antonio Giuseppe Messana [a, b]	Alternate	Healthcare Professionals' Representative	No interests declared	Full involvement
Declan Noone [a]	Member	Patients' Organisation Representative	No interests declared	Full involvement
Marko Korenjak [a, b]	Alternate	Patients' Organisation Representative	No participation in discussion, final deliberations and voting on:	5.1.4. Palovarotene - SOHONOS (CAP MAA) - EMEA/H/C/004867, Orphan

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Christelle Bizimungu [a]	Expert	Belgium	No restrictions applicable to this meeting	Full involvement
Laurence de Fays [a]	Expert	Belgium	No interests declared	Full involvement
Flora Musuamba Tshinanu [a]	Expert	Belgium	No restrictions applicable to this meeting	Full involvement
Martine Sabbe [a]	Expert	Belgium	No interests declared	Full involvement
Françoise Wuillaume [a]	Expert	Belgium	No interests declared	Full involvement
Michaela Dlouhá [a]	Expert	Czechia	No interests declared	Full involvement
Magdalena Senkyrova [a]	Expert	Czechia	No interests declared	Full involvement
Alexander Braathen [a]	Expert	Denmark	No interests declared	Full involvement
Helle Gerda Olsen [a]	Expert	Denmark	No interests declared	Full involvement
Karin Susanne Erneholm [a]	Expert	Denmark	No restrictions applicable to this meeting	Full involvement
Marianne Hald Clemmensen [a]	Expert	Denmark	No restrictions applicable to this meeting	Full involvement
Kristina Laursen [a]	Expert	Denmark	No interests declared	Full involvement
Pernille Lynge Gammelgaard [a]	Expert	Denmark	No interests declared	Full involvement
Moritz Sander [a, b]	Expert	Denmark	No interests declared	Full involvement
Aynur Sert [a, b]	Expert	Denmark	No interests declared	Full involvement
Josiane Uwera [a]	Expert	Denmark	No interests declared	Full involvement
Thomas Berbain [a]	Expert*	France	No interests declared	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Benjamin Burrus [a]	Expert	France	No interests declared	Full involvement
Samuel Crommelynck [a]	Expert	France	No interests declared	Full involvement
Vincent Gazin [a]	Expert	France	No interests declared	Full involvement
Camille de Kervasdoué [a]	Expert*	France	No interests declared	Full involvement
Marie-Caroline Pesquidous [a]	Expert	France	No restrictions applicable to this meeting	Full involvement
Martine Reidiboym [a]	Expert	France	No interests declared	Full involvement
Dennis Lex [a]	Expert	Germany	No restrictions applicable to this meeting	Full involvement
Wiebke Seemann [a]	Expert	Germany	No interests declared	Full involvement
Sheena Kennedy [a]	Expert	Ireland	No restrictions applicable to this meeting	Full involvement
Grainne Kirwan [a]	Expert	Ireland	No interests declared	Full involvement
Marcel Kwa [a]	Expert	The Netherlands	No interests declared	Full involvement
Maria Vanenburg [a, b]	Expert	The Netherlands	No interests declared	Full involvement
Carla Torre [a]	Expert	Portugal	No restrictions applicable to this meeting	Full involvement
María Martínez González [a]	Expert	Spain	No restrictions applicable to this meeting	Full involvement
Helena Back [a]	Expert	Sweden	No interests declared	Full involvement
Charlotte Backman [b, c]	Expert	Sweden	No interests declared	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Charlotta Bergquist [a]	Expert	Sweden	No interests declared	Full involvement
Filip Josephson [a, b]	Expert	Sweden	No interests declared	Full involvement
Karin Nylén [a]	Expert	Sweden	No interests declared	Full involvement
Kim Sherwood [a]	Expert	Sweden	No interests declared	Full involvement
A representative from the European Commission attended the meeting				
Meeting run with support from relevant EMA staff				

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

20. Annex III - List of acronyms and abbreviations

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

21. Explanatory notes

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

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

(Items 2 and 3 of the PRAC minutes)

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

Signals assessment and prioritisation

(Item 4 of the PRAC minutes)

A safety signal is information on a new or incompletely documented adverse event that is potentially caused by a medicine and that warrants further investigation. Signals are generated from several sources such as spontaneous reports, clinical studies and the scientific literature. The evaluation of safety signals is a routine part of pharmacovigilance and is essential to ensuring that regulatory authorities have a comprehensive knowledge of a medicine's benefits and risks.
The presence of a safety signal does not mean that a medicine has caused the reported adverse event. The adverse event could be a symptom of another illness or caused by another medicine taken by the patient. The evaluation of safety signals is required to establish whether or not there is a causal relationship between the medicine and the reported adverse event.

The evaluation of safety signals may not necessarily conclude that the medicine caused the adverse event in question. In cases where a causal relationship is confirmed or considered likely, regulatory action may be necessary and this usually takes the form of an update of the summary of product characteristics and the package leaflet.

Risk Management Plans (RMPs)

(Item 5 of the PRAC minutes)

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

Assessment of Periodic Safety Update Reports (PSURs)

(Item 6 of the PRAC minutes)

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

Post-authorisation Safety Studies (PASS)

(Item 7 of the PRAC minutes)

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

Product related pharmacovigilance inspections

(Item 9 of the PRAC minutes)

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

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