19 April 2023
EMA/PRAC/141718/2023
Human Medicines Division

Pharmacovigilance Risk Assessment Committee (PRAC)

Minutes of PRAC meeting on 09-12 January 2023

Chair: Sabine Straus – Vice-Chair: Martin Huber

Disclaimers

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

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

Note on access to documents

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

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Table of contents

1. Introduction

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

The Chairperson opened the 09-12 January 2023 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.

Finally, the Chairperson announced the start of the Swedish presidency of the Council of the European Union (EU).

1.2. Agenda of the meeting on 09-12 January 2023

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

1.3. Minutes of the previous meeting on 28 November – 01 December 2022

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

Post-meeting note: the PRAC minutes of the meeting held on 28 November – 01 December 2022 were published on the EMA website on 03 April 2023 (EMA/PRAC/135553/2023).

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

2.1. Newly triggered procedures

None

2.2. Ongoing procedures

None

2.3. Procedures for finalisation

None

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

3.1. Newly triggered procedures

None

3.2. Ongoing procedures

3.2.1. 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

A referral procedure under Article 31 of Directive 2001/83/EC is ongoing for topiramate- and topiramate/phentermine-containing medicines following the publication by *Bjørk et al.*[1] in which the authors concluded on a statistically significant increase of neurodevelopmental disorders, in particular autism spectrum disorders and intellectual disability, in children with prenatal exposure to topiramate. Given the potential increased risk of neurodevelopmental disorders highlighted in this study with in utero exposure to topiramate and the known risk of congenital malformations, the matter was referred to PRAC for further evaluation. For further background, see PRAC minutes September 2022[2] and PRAC minutes December 2022[3].

Summary of recommendation(s)/conclusions

- PRAC agreed on the need to convene the Scientific Advisory Group on Neurology (SAG-N). PRAC adopted a list of questions (LoQ) for a SAG-N meeting.

3.3. Procedures for finalisation

None

[1] 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
[2] Held on 29 August – 01 September 2022
[3] Held on 28 November – 01 December 2022

3.4. Re-examination procedures[4]

None

3.5. Others

3.5.1. 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

At the November 2022 meeting, PRAC adopted by majority a recommendation to vary the terms of the marketing authorisation(s) for Janus kinase inhibitors (JAKi) used to treat several chronic inflammatory disorders, namely Xeljanz (tofacitinib), Cibinqo (abrocitinib), Olumiant (baricitinib), Jyseleca (filgotinib) and Rinvoq (upadacitinib). For further background, see PRAC minutes November 2022[6].

At the current meeting, PRAC further reviewed measures to minimise the risks of serious side effects with JAKi and recommended alignment of dose recommendations in patients with certain risk factors.

Summary of recommendation(s)/conclusions

- PRAC adopted a revised recommendation, by majority, to recommend the use of a lower dose of Olumiant (baricitinib) for patients at higher risk for venous thromboembolism (VTE), major cardiovascular events (MACE) and malignancy in line with the dosing recommendations for other JAKi subject to the review, namely Rinvoq (upadacitinib), Cibinqo (abrocitinib) and Jyseleca (filgotinib).
- The direct healthcare professional communication (DHPC) adopted in November 2022 along with the communication plan for its distribution remain unchanged.

Twenty-seven members voted in favour of the revised recommendation, whilst six members[7] had divergent views. The Icelandic and Norwegian PRAC members agreed with the recommendation.

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

[4] Re-examination of PRAC recommendation under Article 32 of Directive 2001/83/EC
[5] Indicated for the treatment of inflammatory disorders
[6] Held on 24-27 October 2022
[7] Annalisa Capuano, Amelia Cupelli, Eva Jirsová, Nikica Mirošević Skvrce, Tiphaine Vaillant, Menno van der Elst

Post-meeting note 2: the PRAC assessment report (EMA/586384/2022) for the procedure was published on 22 March 2023.

4. Signals assessment and prioritisation[8]

4.1. New signals detected from EU spontaneous reporting systems

See also Annex I **Error! Reference source not found.**

4.1.1. Coronavirus (COVID-19) vaccine (ChAdOx1-S [recombinant]) - VAXZEVRIA (CAP)

Applicant: AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

Scope: Signal of myositis

EPITT 19882 – New signal

Lead Member State(s): BE

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 myositis was identified by EMA, based on 209 cases retrieved from EudraVigilance together with 21 cases from literature. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by PRAC.

Discussion

Having considered the available evidence from EudraVigilance and the literature, PRAC agreed that further evaluation on the signal of myositis is warranted.

Summary of recommendation(s)

- In the next PSUR, the MAH for Vaxzevria (Coronavirus (COVID-19) vaccine (ChAdOx1-S [recombinant])) should include a cumulative review of cases of myositis, including an analysis of all cases of idiopathic inflammatory myopathies (IIM)/myositis and related terms from clinical trials, scientific literature and post marketing data. Based on the review, the MAH should propose relevant risk minimisation measures as warranted, including an update of the product information and/or the RMP as applicable.

4.1.2. Elasomeran – SPIKEVAX (CAP)

Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur : Marie Louise Schougaard Christiansen

Scope : Signal of myositis

[8] 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

EPITT 19884 – New signal

Lead Member State(s): DK

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 myositis was identified by EMA, based on 227 cases from EudraVigilance alongside with 14 cases from literature. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by PRAC.

Discussion

Having considered the available evidence from EudraVigilance and the literature, PRAC agreed that further evaluation on the signal of myositis is warranted.

Summary of recommendation(s)

- The MAH for Spikevax (elasomeran) should submit to EMA, within 60 days, a cumulative review of cases of idiopathic inflammatory myopathies (IIM)/myositis, including an analysis of all case reports of IIM/myositis and related terms, data from clinical trials, scientific literature and post marketing exposure. Based on the review, the MAH should propose relevant risk minimisation measures as warranted, including an update of the product information and/or the RMP as applicable.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.1.3. Progesterone (NAP)

Applicant(s): various

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of meningioma

EPITT 19871 – New signal

Lead Member State(s): SE

Background

Progesterone is an endogenous sex hormone indicated in various gynaecological indications such as cycle disorders, hormone replacement therapy, premenstrual syndrome, mastopathy, as well as in obstetrical indications such as medically assisted reproduction, abortion, subject to certain conditions.

During routine signal detection activities, a signal of meningioma was identified by France based on 45 cases of meningioma reported in the French pharmacovigilance database. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by PRAC.

Discussion

Having considered the available evidence from the individual case study reports and the literature, PRAC agreed that further investigation on the signal on meningioma is warranted.

PRAC appointed Ulla Wändel Liminga as Rapporteur for the signal.

Summary of recommendation(s)

- The MAHs Besins Healthcare S.A., Laboratoires Besins International, Besins Healthcare Germany GmbH and Merck A/S should submit to EMA, within 60 days, a cumulative review of the signal from all available sources, i.e. clinical trials, post-marketing and literature, for progesterone-containing products authorised for long-term use, including combination products containing progesterone, administered specifically via oral and vaginal route. The MAHs should also discuss the need for amending the product information as well as the need to for any further risk minimisation measures, e.g. direct healthcare professional communication (DHPC).
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.1.4. Tozinameran – COMIRNATY (CAP)

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Signal of myositis

EPITT 19883 – New signal

Lead Member State(s): NL

Background

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

During routine signal detection activities, a signal of idiopathic inflammatory myopathies (IIM)/myositis was identified by EMA, based on 26 literature cases from 17 articles and 772 cases retrieved from EudraVigilance. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by PRAC.

Discussion

Having considered the available evidence from EudraVigilance and the literature, PRAC agreed that further evaluation on the signal of IIM/myositis 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, including an analysis of all case reports of IIM/myositis and related terms, from all available data from clinical trials, scientific literature and post marketing exposure. The MAH should discuss the need to update the product information and/or the RMP, including relevant risk minimisation measures and submit proposals as appropriate.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.2. New signals detected from other sources

4.2.1. Glucagon-like peptide-1 (GLP-1) receptor agonists: dulaglutide – TRULICITY (CAP); exenatide – BYDUREON (CAP), BYETTA (CAP); insulin degludec, liraglutide – XULTOPHY (CAP); liraglutide – SAXENDA (CAP), VICTOZA (CAP); lixisenatide – LYXUMIA (CAP); semaglutide – OZEMPIC (CAP), RYBELSUS (CAP), WEGOVY (CAP)

Applicant: AstraZeneca AB (Bydureon, Byetta), Eli Lilly Nederland B.V. (Trulicity), Novo Nordisk A/S (Ozempic, Rybelsus, Saxenda, Victoza, Wegovy, Xultophy), sanofi-aventis groupe (Lyxumia)

PRAC Rapporteur: Mari Thorn

Scope: Signal of thyroid cancer

EPITT 18292 – New signal

Lead Member State(s): IT, NL, SE

Background

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

Following the publication by *Bezin et al.*[9], a signal of thyroid cancer was identified by France, suggesting that there might be an increased risk of thyroid cancers with the use of glucagon-like peptide-1 (GLP-1) receptor agonists in patients with type 2 diabetes mellitus. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by PRAC.

PRAC appointed Mari Thorn as Rapporteur for the signal.

Discussion

Having considered the evidence from the literature, PRAC agreed that further evaluation of the signal is warranted.

Summary of recommendation(s)

- The PRAC Rapporteur will perform an assessment of the publication by *Bezin et al.* and propose amendments to the product information as warranted, for further consideration.
- A 90-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

Post-meeting note: On 06 February 2023, PRAC adopted a listed of question to the study authors by written procedure, leading to a revised recommendation.

4.3. Signals follow-up and prioritisation

4.3.1. 3-hydroxy 3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins): atorvastatin (NAP); fluvastatin (NAP); lovastatin (NAP); pitavastatin (NAP); pravastatin (NAP); rosuvastatin (NAP); simvastatin (NAP) and statin fixed dose

[9] Bezin et al. GLP-1 Receptor Agonists and the Risk of Thyroid Cancer. Bezin et al. 2022 Diabetes Care. 2022 Nov 10; dc221148. doi: 10.2337/dc22-1148. (Online ahead of print)

combinations; pravastatin, fenofibrate – PRAVAFENIX (CAP); simvastatin, fenofibrate – CHOLIB (CAP)

Applicant(s): Laboratoires SMB s.a. (Pravafenix), Mylan IRE Healthcare Limited (Cholib); various

PRAC Rapporteur: Nathalie Gault

Scope: Signal of myasthenia gravis

EPITT 19822 – Follow-up to July 2022

Background

For background information, see PRAC minutes July 2022[10].

The MAHs of originator single-ingredient statin-containing products (atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin and simvastatin) replied to the request for information on the signal of myasthenia gravis and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence, including EudraVigilance and literature data, as well as the MAHs' responses and the Rapporteur's assessment, PRAC concluded that a causal association between myasthenia gravis and use of 3-hydroxy 3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) is a reasonable possibility.

Summary of recommendation(s)

- The MAHs for atorvastatin-, fluvastatin-, lovastatin-, pitavastatin-, pravastatin-, rosuvastatin- and simvastatin-containing products, including any fixed-dose combination products, should submit to EMA, within 60 days, a variation to amend[11] the product information in order to add myasthenia gravis and ocular myasthenia as warnings and as undesirable effects with a frequency 'not known'.

For the full PRAC recommendation, see EMA/PRAC/4770/2023 published on 06 February 2023 on the EMA website.

4.3.2. Dabrafenib - TAFINLAR (CAP) - EMEA/H/C/002604/SDA/020; trametinib - MEKINIST (CAP) - EMEA/H/C/002643/SDA/015

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of haemophagocytic lymphohistiocytosis

EPITT 19824 – Follow-up to September 2022

Lead Member State(s): SE

Background

For background information, see PRAC minutes September 2022[12].

[10] Held on 04-07 July 2022
[11] Update of SmPC sections 4.4 and 4.8. The package leaflet is to be updated accordingly
[12] Held on 29 August – 01 September 2022

The MAH replied to the request for information on the signal of haemophagocytic lymphohistiocytosis (HLH) and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence and the data submitted by the MAH together with the Rapporteur's assessment, PRAC considered that there is a reasonable possibility for a causal relationship between combination of dabrafenib and trametinib and the risk for hemophagocytic lymphohistiocytosis (HLH).

Summary of recommendation(s)

- The MAH for Tafinlar (dabrafenib) and Mekinist (trametinib) should submit to EMA, within 60 days, a variation to amend the product information of both medicinal products in order to add a warning on HLH when dabrafenib is used in combination with tafinlar and to also add HLH as an undesirable effect with a frequency 'rare'.

For the full PRAC recommendation, see EMA/PRAC/4770/2023 published on 06 February 2023 on the EMA website.

4.3.3. Regorafenib - STIVARGA (CAP) - EMEA/H/C/002573/SDA/013

Applicant: Bayer AG

PRAC Rapporteur: Menno van der Elst

Scope: Signal of thrombotic microangiopathy

EPITT 19832 – Follow-up to September 2022

Background

For background information, see PRAC minutes September 2022[13].

The MAH replied to the request for information on the signal of thrombotic microangiopathy (TMA) and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence in EudraVigilance and in the literature, the plausibility of the interference on the vascular endothelial growth factor (VEGF) signalling pathway in the development of TMA, and the already known association of TMA with other medicinal products targeting the VEGF pathway, PRAC considered that there is a reasonable possibility for a causal relationship between regorafenib and thrombotic microangiopathy. Therefore, PRAC agreed that an update of the product information is warranted to add TMA as a warning and as an undesirable effect with frequency 'rare'.

Summary of recommendation(s)

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

For the full PRAC recommendation, see EMA/PRAC/4770/2023 published on 06 February 2023 on the EMA website.

[13] Held on 29 August – 01 September 2022
[14] Update of SmPC section 4.4 and 4.8. The package leaflet is updated accordingly.

4.3.4. Tozinameran - COMIRNATY (CAP) - EMEA/H/C/005735/SDA/056

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Signal of vulval ulceration

EPITT 19840 – Follow-up to September 2022

Background

For background information, see PRAC minutes September 2022[15].

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

Discussion

Having considered the available evidence from EudraVigilance, the literature and the data submitted by the MAH, PRAC agreed that there is insufficient evidence to establish a causal association between Comirnaty (tozinameran) and vulval ulceration at present.

Summary of recommendation(s)

- In the next PSUR, the MAH for Comirnaty (tozinameran) should submit to EMA an updated analysis of all cases of vulval ulceration following vaccination with the vaccine including post-marketing, clinical trials, literature data, as well as a causality assessment.

4.4. Variation procedure(s) resulting from signal evaluation

None

5. Risk management plans (RMPs)

5.1. Medicines in the pre-authorisation phase

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

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

See also Annex I 15.1.

5.1.1. Coronavirus (COVID-19) vaccine (recombinant protein receptor binding domain fusion heterodimer) – EMEA/H/C/006058

Scope: Active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 16 years of

[15] Held on 29 August – 01 September 2022

age and older

5.1.2. Leniolisib – EMEA/H/C/005927, Orphan

Applicant : Pharming Technologies B.V.

Scope (accelerated assessment): Treatment of activated phosphoinositide 3-kinase delta syndrome (APDS)

5.1.3. Mirikizumab - EMEA/H/C/005122

Scope: Treatment of moderately to severely active ulcerative colitis

5.1.4. Recombinant respiratory syncytial virus pre-fusion F protein, adjuvanted with AS01E – EMEA/H/C/006054

Scope (accelerated assessment): Active immunisation or the prevention of lower respiratory tract disease (LRTD)

5.1.5. Ublituximab – EMEA/H/C/005914

Scope: Treatment of relapsing forms of multiple sclerosis (RMS)

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

See also Annex I 15.2.

5.2.1. Glycopyrronium – SIALANAR (CAP) – EMEA/H/C/003883/II/0026

Applicant: Proveca Pharma Limited

PRAC Rapporteur: Zane Neikena

Scope: Submission of an updated RMP version 3.1 in order to remove study PRO/GLY/004: a drug utilisation study (DUS) to assess the efficacy of risk minimisation measures for Sialanar

Background

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

PRAC is evaluating a type II variation procedure for Sialanar, a centrally authorised medicine containing glycopyrronium, to update the RMP in order to remove study PRO/GLY/004, a drug utilisation study to assess the efficacy of risk minimisation measures. PRAC is responsible for adopting an outcome based on the assessment report from the PRAC Rapporteur, to be further considered at the level of CHMP, responsible for adopting an opinion on this variation.

Summary of advice

- The RMP for Sialanar (glycopirronium) in the context of the variation procedure under evaluation by CHMP could be considered acceptable provided that an update to RMP

version 3.1 and satisfactory responses to the request for supplementary information (RSI) are submitted.

- Regarding the list of safety concerns, PRAC considered that the important identified risks of all anticholinergic side effects should be re-fined to 'anticholinergic side effects due to dosing errors'. In addition, the following safety concerns listed as important identified risks should be removed from the RMP: overdose including unintentional overdose due to 8 ml syringe, off label treatment of children with mild to moderate sialorrhoea and off label use in patients below the age of 3 years due to the higher susceptibility to adverse effects, as well as safety in long-term use beyond 24 weeks listed as missing information. Regarding the additional risk minimisation measures, PRAC considered the reference to the drug utilisation study conducted to monitor and assess effectiveness of additional risk minimisation measures for anticholinergic side effects that may be dose dependent and the importance of contributing to such a study should be removed from the key elements of the physician educational material. Annex II-D on 'conditions or restrictions with regard to the safe and effective use of the medicinal product' and the educational material for healthcare professionals should be revised accordingly.

5.2.2. 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 (in fulfilment of MEA 091). In addition, the MAH is also taking this opportunity to introduce editorial changes

Background

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

PRAC is evaluating a type II worksharing variation procedure for Vfend, a centrally authorised medicine containing voriconazole and nationally authorised medicine(s) containing voriconazole, to update Annex II and the RMP to reflect the final study results of study A1501103, an active safety surveillance programme to monitor selected events in patients with long-term voriconazole use. PRAC is responsible for adopting an outcome based on the assessment report from the PRAC Rapporteur, to be further considered at the level of CHMP, responsible for adopting an opinion on this variation. For further background, see PRAC minutes September 2022[16].

Summary of advice

- The RMP for Vfend (voriconazole) in the context of the worksharing variation procedure under evaluation by CHMP could be considered acceptable provided that an update to RMP version 6.1 and satisfactory responses to the request for supplementary information (RSI) are submitted.

[16] Held on 29 August – 01 September 2022

- PRAC considered that the following risks should be removed from the list of safety concerns in the RMP: hepatic toxicity, QTc prolongation, visual events, skin cancer (non-squamous cell carcinoma (SCC)), suicide-related events, effects in pregnancy, effects in paediatrics and off-label use, and that the only risks to be maintained in the list of safety concerns as important identified risks are phototoxicity and SCC. Regarding the additional risk minimisation measures, PRAC supported the removal of the educational materials for healthcare professionals. However, PRAC did not agree with the removal of the patient alert card intended to address the risks of phototoxicity and SCC. Therefore, the MAH should provide key elements for this additional risk minimisation measure (aRMM).

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

See also Annex I 15.3.

5.3.1. Givosiran - GIVLAARI (CAP) - EMEA/H/C/004775/II/0011/G, Orphan

Applicant: Alnylam Netherlands B.V.

PRAC Rapporteur: Martin Huber

Scope: Grouped application consisting of: 1) update of section 5.3 of the SmPC based on final results from study AS1-GLP18-007 listed as a category 3 study in the RMP: a 104-week subcutaneous injection carcinogenicity study in Sprague Dawley rats; 2) update of section 5.3 of the SmPC based on final results from study AS1-GLP18-004: a 26-week subcutaneous injection carcinogenicity study in TgRasH2 mice. The RMP version 2.1 has also been submitted. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet.

Background

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

CHMP is evaluating a type II variation for Givlaari, a centrally authorised product containing givosiran, to update the product information based on the final results from AS1-GLP18-007 and AS1-GLP18-004 studies. PRAC is responsible for providing advice to CHMP on the necessary updates to the RMP to support this type II variation. For further background, see PRAC minutes October 2022[17].

Summary of advice

- The RMP for Givlaari (givosiran) in the context of the variation procedure under evaluation by CHMP could be considered acceptable provided that an update to RMP version 2.1 and satisfactory responses to the request for supplementary information (RSI) are submitted.
- PRAC considered that hepatic neoplasia should be included as an important potential risk in the list of safety concerns. The MAH should provide a discussion on how to evaluate this risk further.

[17] Held on 26-29 September 2022

5.3.2. 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

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 Mysimba, a centrally authorised product containing naltrexone hydrochloride/bupropion hydrochloride, to evaluate an updated study design and a protocol synopsis for study CVOT-2: a phase 4 study to assess the effect of naltrexone ER/bupropion ER on the occurrence of MACE in overweight and obese subjects with cardiovascular disease. PRAC is responsible for providing advice to CHMP on the necessary updates to the RMP to support this variation. For further background, see PRAC minutes March 2022.

Summary of advice

- The RMP for Mysimba (naltrexone hydrochloride/bupropion hydrochloride) in the context of the variation procedure under evaluation by CHMP could be considered acceptable provided that an update to RMP version 13.2 and satisfactory responses to the request for supplementary information (RSI) are submitted.
- PRAC supported the CHMP Rapporteur's assessment conclusion that the alternative methodological approach proposed by the MAH is not suitable for evaluating the long-term cardiovascular safety of Mysimba (naltrexone hydrochloride/bupropion hydrochloride). PRAC also discussed the concerns regarding the long-term cardiovascular risk and the long-term efficacy of the medicine in the 'real life' setting and supported a re-evaluation of the benefit/risk balance of the medicine in the current context. PRAC advised CHMP that a thorough analysis of the reasons for the high rates of early treatment discontinuation should be further considered, as well as recent information regarding the effectiveness of restricting the treatment duration for obesity medication as a risk minimisation measure.

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

Applicant: Novartis Europharm Limited, ATMP[18]

[18] Advanced therapy medicinal product

PRAC Rapporteur: Ulla Wändel Liminga

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

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.

CAT and CHMP are evaluating a grouped type II variation for Zolgensma, a centrally authorised product containing onasemnogene abeparvovec, to update the product information in order to introduce additional guidance on liver function laboratory tests and monitoring before and after infusion and update information based on new safety information on the topic of ALF, to provide additional guidance relevant to patient's overall health status prior to dosing and to strengthen the existing description and guidance on systemic immune response, as well as to indicate prompt attention to TMA and to reflect the risk of life-threatening or fatal outcomes. PRAC is responsible for providing advice to CAT on the necessary updates to the RMP to support this type II variation. For further background, see PRAC minutes November 2022[19].

Summary of advice

- The RMP for Zolgensma (onasemnogene abeparvovec) in the context of the variation procedure under evaluation by CAT/CHMP could be considered acceptable provided that an update to RMP version 2.0 and satisfactory responses to the request for supplementary information (RSI) are submitted.
- Regarding additional risk minimisation measures (aRMM), PRAC considered that an aRMM addressed to healthcare professionals (HCPs) is warranted in order to minimise the risks of ALF and TMA. This should take the form of an HCP guide and address equally the key risk minimisation actions before treatment, at the time of and after infusion. While recognising that the medicinal product is used in specialised centres, the short HCP guide will provide key information, which should help prescribers summarise the key risk minimisation activities for the product; details included in the product information will further describe how monitoring and risk minimisation recommendations can be adapted based on the clinical evolution post treatment with Zolgensma (onasemnogene abeparvovec). PRAC considered that a checklist for caregivers is not needed, as there is sufficient information in the current caregiver information guide. PRAC also gave advice regarding the content of a direct healthcare professional communication (DHPC), with the aim to increase awareness on acute liver failure.

[19] Held on 24-27 October 2022

5.3.4. Ozanimod - ZEPOSIA (CAP) - EMEA/H/C/004835/II/0016

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Update of sections 4.2 and 5.2 of the SmPC in order to add a dose adjustment after completion of the dose escalation regimen in patients with mild or moderate chronic hepatic impairment (Child-Pugh class A or B) based on the final results from study RPC-1063-CP-004. This is a Phase 1, multicentre, open-label study to evaluate the effect of mild or moderate hepatic impairment on the multiple-dose pharmacokinetics of ozanimod. The package leaflet is updated accordingly. The updated 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.

CHMP is evaluating a type II variation for Zeposia, a centrally authorised product containing ozanimod, to update the product information in order to add a dose adjustment after completion of the dose escalation regimen in patients with mild or moderate chronic hepatic impairment (Child-Pugh class A or B) based on the final results from study RPC-1063-CP-004: a phase 1, multicentre, open-label study to evaluate the effect of mild or moderate hepatic impairment on the multiple-dose pharmacokinetics of ozanimod. 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 Zeposia (ozanimod) in the context of the variation procedure under evaluation by CHMP could be considered acceptable provided that an update to RMP version 5.0 and satisfactory responses to the request for supplementary information (RSI) are submitted.
- Regarding the pharmacovigilance plan, PRAC highlighted that the milestones of the ORION study should be reverted to the ones adopted in the last agreed RMP version. Regarding the additional risk minimisation measures, PRAC considered that the key elements for the educational material for healthcare professionals should be updated to reflect the newly introduced recommendations for dose reduction after completion of the dose escalation regimen in patients with mild or moderate chronic hepatic impairment (Child-Pugh class A or B). PRAC also discussed the need for a direct healthcare professional communication (DHPC) and concluded that an active redistribution of the educational material will be sufficient to inform prescribers about the new posology recommendation for patients with mild or moderate hepatic impairment, together with a cover letter highlighting the change in the posology in this subpopulation.

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

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Extension of indication to include treatment of moderately to severely active Crohn's

disease in adult patients based on final results from three Phase III studies, two confirmatory placebo-controlled induction studies (Study M14 431/U-EXCEED/CD-1 and Study M14 433/U-EXCEL/CD-2) and a placebo-controlled maintenance/long-term extension study (Study M14-430/U-ENDURE/CD-3). M14-431 study is a phase III, multicentre, randomised, double-blind, placebo-controlled induction study of the efficacy and safety of upadacitinib (ABT-494) in subjects with moderately to severely active Crohn's disease who have inadequately responded to or are intolerant to biologic therapy. M14-433 study is a phase III, multicentre, randomised, double-blind, placebo controlled induction study of the efficacy and safety of upadacitinib (ABT-494) in subjects with moderately to severely active Crohn's disease who have inadequately responded to or are intolerant to conventional and/or biologic therapies. M14-430 study is an ongoing phase III, multicentre, randomised, double-blind, placebo-controlled maintenance and long-term extension study of the efficacy and safety of upadacitinib (ABT-494) in subjects with Crohn's disease who completed studies M14-431 or M14-433. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The package leaflet is updated in accordance. Version 11 of the RMP has also been submitted

Background

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

CHMP is evaluating an extension of indication for Rinvoq, a centrally authorised product containing upadacitinib, to include treatment of moderately to severely active Crohn's disease in adult patients based on final results from three phase III studies. PRAC is responsible for providing advice to CHMP on the necessary updates to the RMP to support this type II variation. For further background, see PRAC minutes November 2022[20].

Summary of advice

- The RMP for Rinvoq (upadacitinib) in the context of the variation procedure under evaluation by CHMP could be considered acceptable provided that an update to RMP version 13.0 and satisfactory responses to the request for supplementary information (RSI) are submitted.
- PRAC considered that a further characterisation of the safety of Rinvoq (upadacitinib) in Crohn's disease is warranted, and that the MAH should discuss the possibility to perform a PASS using the same databases and protocol used to address the long-term safety of upadacitinib for the treatment of ulcerative colitis (EMEA/H/C/004760/MEA 017) but adjusted to the Crohn's disease population.

6. Periodic safety update reports (PSURs)

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

See also Annex I 16.1.

[20] Held on 24-27 October 2022

6.1.1. Anakinra - KINERET (CAP) - PSUSA/00000209/202205 (with RMP)

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

Background

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

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Kineret, a centrally authorised medicine containing anakinra 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 Kineret (anakinra) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to remove the existing warning regarding the risk of macrophage activation syndrome (MAS) in patients with Still's disease. Therefore, the current terms of the marketing authorisation(s) should be varied[21].
- In the next PSUR, the MAH should include the results from the randomised placebo-controlled trial[22] of subcutaneous anakinra in the management of hospitalised paediatric and adult patients with MAS.

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

6.1.2. Coronavirus (COVID-19) vaccine (ChAdOx1-S [recombinant]) - VAXZEVRIA (CAP) - PSUSA/00010912/202206

Applicant: AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

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.

[21] Update of SmPC sections 4.4 and 5.1. The package leaflet and Annex II D are updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion.
[22] A randomised placebo controlled trial of subcutaneous anakinra in the management of hospitalised paediatric and adult patients with macrophage activation syndrome (clinicalTrials.gov: NCT02780583)

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Vaxzevria, a centrally authorised medicine containing COVID-19 vaccine (ChAdOx1-S [recombinant]) 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 Vaxzevria COVID-19 vaccine (ChAdOx1-S [recombinant]) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add cutaneous vasculitis as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[23].
- In the next PSUR, the MAH should provide detailed reviews of cases of acute disseminated encephalomyelitis (ADEM) and severe cutaneous adverse reactions (SCAR), of new daily persistent headache and of myositis. The MAH should also provide updated literature reviews and discussions on cases of menstrual disorders, glomerulonephritis and nephrotic syndrome, venous thromboembolism (VTE), hearing loss cases with a recovered with sequelae or not recovered outcome. In addition, the MAH should provide a summary of the fatal cases reporting a thrombotic event after dose 3 (or dose 4) of the vaccine. Finally, the MAH should discuss the need for further updates to the product information and include a proposal to update the product information and/or RMP as warranted.

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

6.1.3. Human papillomavirus 9-valent vaccine (recombinant, adsorbed) - GARDASIL 9 (CAP) - PSUSA/00010389/202206

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Jean-Michel Dogné

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 Gardasil 9, a centrally authorised medicine containing human papillomavirus 9-valent vaccine (recombinant, adsorbed) and issued a recommendation on its marketing authorisation(s).

Summary of recommendation(s) and conclusions

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

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Gardasil 9 (human papillomavirus 9-valent vaccine (recombinant, adsorbed)) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to remove the statement referring to the possibility of observing the same undesirable effects for Gardasil (human papillomavirus vaccine [types 6, 11, 16, 18] (recombinant, adsorbed)) and Gardasil 9 (human papillomavirus 9-valent vaccine (recombinant, adsorbed)). Therefore, the current terms of the marketing authorisation(s) should be varied[24].

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

6.1.4. Levofloxacin[25] - QUINSAIR (CAP) - PSUSA/00010429/202205

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

Background

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

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Quinsair, a centrally authorised medicine containing levofloxacin 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 Quinsair (levofloxacin) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAH should provide cumulative reviews of cases of hallucinations and other psychotic adverse drug reactions, seizures/convulsions, paraesthesia, bronchopulmonary aspergillosis and cases of acute renal failure. The MAH should propose to update the product information as warranted. In addition, the MAH should discuss the final results of two completed non-interventional studies. The MAH should also provide information on confounding factors related to cases of haemoptysis as well as a detailed discussion on 'decreased *Pseudomonas aeruginosa* susceptibility to levofloxacin' as an important potential risk, together with a review of cases of susceptibility decrease related to the medicine.

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

- As a result of the referral procedure (EMEA/H/A-31/1452) concluded in 2019, the MAH should submit to EMA, by 21 December 2023, a 5-year cumulative review of cases of long-lasting, disabling and potentially irreversible adverse drug reactions.

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. Pegvaliase - PALYNZIQ (CAP) - PSUSA/00010761/202205

Applicant: BioMarin International Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

Background

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

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Palynziq (pegvaliase) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add diarrhoea and fatigue as undesirable effects with a frequency 'very common'. Therefore, the current terms of the marketing authorisation(s) should be varied[26].
- In the next PSUR, the MAH should continue to closely monitor all data sources for hypersensitivity reactions to other concurrent polyethylene glycol (PEG)-containing product(s) in patients taking Palynziq (pegvaliase) and present any evidence suggesting that the medicine may sensitise patients to other PEG-containing product(s).

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

6.1.6. Relugolix, estradiol, norethisterone acetate - RYEQO (CAP) - PSUSA/00010942/202205

Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

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

Background

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

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Ryeqo, a centrally authorised medicine containing relugolix/estradiol/norethisterone acetate 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 Ryeqo (relugolix/estradiol/norethisterone acetate) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add urticaria and angioedema as undesirable effects with a frequency 'uncommon'. Therefore, the current terms of the marketing authorisation(s) should be varied[27].
- In the next PSUR, the MAH should continue to closely monitor cases of depression/suicidal ideation (mood disorders), embolic and thrombotic events, hepatic transaminase elevations, tumours (breast, liver), gallbladder disease and uterine fibroid prolapse or expulsion. In addition, the MAH should discuss whether there is sufficient evidence to include other hypersensitivity-related adverse drug reactions in the product information of Ryeqo.

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

6.1.7. Semaglutide - OZEMPIC (CAP); RYBELSUS (CAP); WEGOVY (CAP) - PSUSA/00010671/202205

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Mari Thorn

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 Ozempic, Rybelsus and Wegovy, centrally authorised medicines containing semaglutide and issued a recommendation on their marketing authorisation(s).

Summary of recommendation(s) and conclusions

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

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Ozempic, Rybelsus and Wegovy (semaglutide) in the approved indication(s) remains unchanged.
- Nevertheless, the product information for Rybelsus (semaglutide) should be updated to add dysgeusia as undesirable effect with a frequency 'uncommon'. In addition, delayed gastric emptying should be added to the product information of Rybelsus, Ozempic and Wegovy (all containing semaglutide) as an undesirable effect with a frequency 'uncommon'. Therefore, the current terms of the marketing authorisation(s) should be varied[28].
- In the next PSUR, the MAH should submit a cumulative review of cases of intestinal obstruction, of potential drug-drug interaction with semaglutide and warfarin/coumarin derivates including acenocoumarol, of severe cutaneous adverse reactions (SCARs), of altered skin sensation and of dizziness. The MAH should provide a proposal to update the product information as warranted. In addition, the MAH should provide a review of post-marketing cases of acute kidney injury and/or acute renal failure without confounders, and without co-reported gastrointestinal events and/or dehydration or other co-reported events affecting renal perfusion.

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

6.1.8. Tozinameran - COMIRNATY (CAP) - PSUSA/00010898/202206

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

Background

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

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Comirnaty, a centrally authorised medicine containing tozinameran 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 Comirnaty (tozinameran) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAH should provide cumulative analyses of cases of dyspnoea, palpitations and tachycardia/heart rate increase, with a special focus on the duration of the events not considered stress/anxiety-related reactions. In addition, the MAH should

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

discuss the publication by *Kwan, A.C., Ebinger, J.E., Wei, J. et al.*[29] and provide a cumulative review of cases of post orthostatic tachycardia syndrome in association with the vaccine as warranted. The MAH should also discuss the need for an update of the product information and/or RMP as warranted. Furthermore, the MAH should closely monitor cases of multisystem inflammatory syndrome in children (MIS-C) and multisystem inflammatory syndrome in adults (MIS-A) as outlined in the final PRAC recommendation for the signal of MIS (EPITT 19732) finalised in November 2021[30] as well as any new cases of MIS-C/-A. The MAH should also ensure a clear presentation of cases reported from the newly approved variant vaccines including a continuous comparison of the safety issues identified with the evidence available for the original vaccine.

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 Annex 16.2.

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

See also Annex I 16.3.

6.3.1. Amikacin[31] (NAP) - PSUSA/00000143/202206

Applicant(s): various

PRAC Lead: Maia Uusküla

Scope: Evaluation of a PSUSA procedure

Background

Amikacin is a semisynthetic aminoglycoside derived from kanamycin indicated for use in all age groups intravenously for the treatment of nosocomial lower respiratory tract infections including severe pneumonia, intra-abdominal infections including peritonitis, complicated and recurrent urinary tract infections, skin and soft tissue infections including burn-wound infections, bacterial endocarditis, post-operative intra-abdominal infections, as well as bacteraemia associated to afore-mentioned indications.

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

Summary of recommendation(s) and conclusions

[29] Kwan, A.C., Ebinger, J.E., Wei, J. et al. Apparent risks of postural orthostatic tachycardia syndrome diagnoses after COVID-19 vaccination and SARS-Cov-2 infection. Nat Cardiovasc Res (2022). https://doi.org/10.1038/s44161-022-00177-8
[30] Held on 25-28 October 2021.
[31] Except for centrally authorised products

- Based on the review of the data on safety and efficacy, the benefit-risk balance of amikacin-containing product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add a warning on the increased risk of aminoglycoside-associated ototoxicity in patients with mitochondrial mutations. Therefore, the current terms of the marketing authorisation(s) should be varied[32].
- In the next PSUR, the MAH(s) should provide a cumulative review of severe cutaneous adverse reactions (SCARs).

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

6.3.2. Bemiparin (NAP) - PSUSA/00000312/202204

Applicant(s): various

PRAC Lead: Monica Martinez Redondo

Scope: Evaluation of a PSUSA procedure

Background

Bemiparin is an antithrombotic agent indicated for the prevention of thromboembolic disease in patients subjected to general surgery, the prevention of thromboembolic disease in patients subjected to orthopedic surgery, the prevention of thromboembolic disease in non-surgical patients with high or moderate risk, the secondary prevention of venous thromboembolism recurrences in patients with deep vein thrombosis and transient risk factors, the prevention of clotting in the extracorporeal circuit during haemodialysis, as well as for the treatment of established deep vein thrombosis (DVT), with or without pulmonary embolism, during the acute phase.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing bemiparin 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 bemiparin-containing product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the existing contraindication regarding hypersensitivity. Therefore, the current terms of the marketing authorisation(s) should be varied[33].
- In the next PSUR, the MAH(s) should provide a review of cases of cerebral haemorrhages and severe cutaneous adverse reactions (including dermatitis bullous). In addition, the MAH(s) should maintain liver disorders as an important identified risk in the list of PSUR safety concerns.

[32] 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
[33] Update of SmPC section 4.3. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position.

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

6.3.3. Diltiazem (NAP) - PSUSA/00001084/202205

Applicant(s): various

PRAC Lead: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

Background

Diltiazem is a benzothiazepine derivative calcium channel blocker indicated for the treatment and prevention of angina pectoris, and the treatment of hypertension, subject to certain conditions.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing diltiazem 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 diltiazem-containing product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add lupus-like syndrome as an undesirable effect with a frequency 'not known', as well as a warning regarding acute renal failure secondary to decreased renal perfusion in patients with reduced left ventricular function, severe bradycardia or severe hypotension, if similar or stricter information is not already included. Also, the product information should be updated to add acute kidney injury secondary to hypotension as overdose symptom, as well as to add a drug-drug interaction between diltiazem and lomitapide. Therefore, the current terms of the marketing authorisation(s) should be varied[34].

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

6.3.4. Esomeprazole, naproxen (NAP) - PSUSA/00001270/202204

Applicant(s): various

PRAC Lead: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

Background

Esomeprazole is a proton pump inhibitor (PPI) and naproxen is a non-steroidal anti-inflammatory non-selective (NSAID) cyclooxygenase (COX)-1-2 inhibitor drug. In

[34] Update of SmPC sections 4.3, 4.4, 4.5, 4.8 and 4.9. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position

combination, esomeprazole/naproxen is indicated in adults for the symptomatic treatment of osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, subject to certain conditions.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing esomeprazole/naproxen 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 esomeprazole/naproxen-containing product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to acute tubulointerstitial nephritis as a warning. Therefore, the current terms of the marketing authorisation(s) should be varied[35].
- In the next PSUR, the MAH(s) should provide a cumulative review on the risk of drug-drug interaction between esomeprazole (esomeprazole/naproxen) and immune checkpoint inhibitors using the term 'tubulointerstitial nephritis' to identify data from spontaneous reporting, clinical trials and the literature. The MAH(s) should 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.

6.3.5. Ibuprofen, pseudoephedrine (NAP) – PSUSA/00001711/202207

Applicant(s): various

PRAC Lead: Nathalie Gault

Scope: Evaluation of a PSUSA procedure

Background

Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID) with anti-pyretic, analgesic, and anti-inflammatory properties, while pseudoephedrine is an alpha agonist acting as a nasal decongestant. In combination, ibuprofen/pseudoephedrine is indicated for the symptomatic relief of nasal/sinus congestion with headache, fever and pain associated with the common cold and flu in adults and adolescents over 12 or 15 years old, subject to certain conditions.

PRAC is currently reviewing the benefit-risk balance of nationally authorised medicines containing ibuprofen/pseudoephedrine, in the framework of the assessment of a PSUR single assessment (PSUSA) procedure due for PRAC recommendation at the February 2023 PRAC meeting.

Summary of recommendation(s) and conclusions

- The PRAC Rapporteur presented the preliminary assessment of the currently ongoing PSUSA procedure, which is due to complete at the February 2023 PRAC meeting, where further discussion and adoption of a recommendation is planned.

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

6.3.6. Levomethadone (NAP) - PSUSA/00001855/202205

Applicant(s): various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

Background

Levomethadone is a synthetic opioid analgesic indicated for the treatment of severe pain and substitution in opioid-dependent adults.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing levomethadone 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 levomethadone-containing product(s) in the approved indication(s) remains unchanged.
- Nevertheless, in view of available data on drug abuse and dependence (opioid use disorder) from the literature and recent assessments of PSUSA procedures for other opioids, the existing warning on drug dependence and potential for abuse should be further strengthened. Moreover, dependence should be included as an undesirable effect with a frequency 'not known'. In addition, due to available data on accidental ingestion in the paediatric population, amendments to the package leaflet are warranted to highlight the potential serious consequences of accidental ingestion and the importance of appropriate storage. The product information should be also updated to add central sleep apnoea as a warning and as an undesirable effect with a frequency 'not known'. Based on post-marketing case reports and literature, the product information should be updated to reflect interactions with gabapentinoids and cannabinoids. Furthermore, based on available data on toxic leukoencephalopathy, the product information should be updated to include toxic leukoencephalopathy as a symptom of acute methadone overdose. Therefore, the current terms of the marketing authorisation(s) the current terms of the marketing authorisation(s) should be varied[36].
- In the next PSUR, the MAH(s) should provide a cumulative review of cases of neurodevelopmental impairment and on the risk of malformations in children exposed to levomethadone in utero. The MAHs Sanofi, Novartis, dne pharma As and Aristo Pharma should also provide a review regarding the abusive intravenous use of levomethadone-containing product(s) for oral use.

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. Methadone (NAP) - PSUSA/00002004/202205

Applicant(s): various

[36] Update of SmPC sections 4.2, 4.4, 4.5, 4.8 and 4.9. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position

PRAC Lead: Ronan Grimes

Scope: Evaluation of a PSUSA procedure

Background

Methadone is a synthetic opioid analgesic indicated for the treatment of moderate to severe pain and opioid addiction.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing methadone 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 methadone-containing product(s) in the approved indication(s) remains unchanged.
- Nevertheless, in view of available data on drug abuse and dependence (opioid use disorder) from the literature and recent assessments of PSUSA procedures for other opioids, the existing warning on drug dependence and potential for abuse should be further strengthened. Moreover, dependence should be included as an undesirable effect with a frequency 'not known'. In addition, given available data on accidental ingestion in the paediatric population, amendments to the package leaflet are warranted, to highlight the potential serious consequences of accidental ingestion, and the importance of appropriate storage. The product information should be also updated to add central sleep apnoea as a warning and as an undesirable effect with a frequency 'not known'. Based on post-marketing case reports and literature, the product information should be updated to reflect interactions with gabapentinoids and cannabinoids. Furthermore, based on available data on toxic leukoencephalopathy, the product information should be updated to include toxic leukoencephalopathy as a symptom of acute methadone overdose. Therefore, the current terms of the marketing authorisation(s) the current terms of the marketing authorisation(s) should be varied[37].
- In the next PSUR, the MAH(s) should continue to provide cumulative reviews of cases of drug abuse, dependence and withdrawal, as well as comparable cumulative reviews for overdose including accidental overdose, deaths related to overdose and cases of accidental exposure in the paediatric population. The MAH(s) should also discuss the need for further risk minimisation measures as warranted. In addition, the MAH(s) should closely monitor and provide updated critical analyses on cases of neurodevelopmental impairment in children born to opioid-dependent mothers, cases of stress cardiomyopathy and cases of optic nerve hypoplasia. The MAH(s) of solid pharmaceutical forms of methadone are also requested to closely monitor and provide critical analysis of any cases suggestive of a new risk related to critical excipients of this pharmaceutical form.

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.

[37] Update of SmPC sections 4.2, 4.4, 4.5, 4.8 and 4.9. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position

6.3.8. Tolperisone (NAP) - PSUSA/00002991/202206

Applicant(s): various

PRAC Lead: Melinda Palfi

Scope: Evaluation of a PSUSA procedure

Background

Tolperisone is a centrally acting muscle relaxant indicated for the symptomatic treatment of post-stroke spasticity (PSS) in adults.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing tolperisone 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 tolperisone-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(s) should continue to provide cumulative analyses of cases of hypersensitivity reactions, focusing on serious reactions occurring in the EU in order to identify any changing patterns of hypersensitivity reactions following the conclusion of the referral procedure (EMEA/H/A-31/1311) finalised in 2012. Retrieval of cases should be done using the SMQs[38] 'severe cutaneous adverse reactions', 'anaphylactic reaction', 'angioedema' and 'hypersensitivity', with the indications (in or off label) in such cases to be captured and further analysed. The MAH(s) should also further comment on the expected effectiveness and feasibility of restricting the prescription of tolperisone to specialists experienced in the rehabilitation of stroke to mitigate the extent of use in the indications that were removed following the referral procedure (EMEA/H/A-31/1311). Finally, the MAH Gedeon Richter should perform a further drug utilisation study to estimate the extent of in and off label use in a representative sample of Member States using a suitable database.

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

6.3.9. Venlafaxine (NAP) - PSUSA/00003104/202205

Applicant(s): various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

Background

[38] Standardised Medical Dictionary for Regulatory Activities (MedDRA) queries

Venlafaxine is a dual-acting serotonin (5-HT) and norepinephrine reuptake inhibitor (SNRI), indicated for the treatment of depression, anxiety or generalised anxiety disorder (GAD), social anxiety disorder (SAD) and panic disorder (PD), as well as for the prevention of relapse and prevention of recurrence of depression.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing venlafaxine 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 venlafaxine-containing product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated regarding the warning on the risk of overdose following concomitant use with alcohol, as well as to amend the information regarding the interaction between venlafaxine and ethanol. In addition, the product information should be updated to amend the overdose wording regarding severe poisoning symptoms in adults. Therefore, the current terms of the marketing authorisation(s) should be varied[39].
- In the next PSUR, the MAHs should provide a cumulative review of cases of non-fatal and fatal cases of poisoning, where information on amount of venlafaxine taken is available. Moreover, the MAHs should provide a discussion on the benefits and risks of the highest strengths, as well as of pack sizes, particularly for the highest strengths, and on the need for further risk minimisation, such as restricting their availability on the market, and/or reducing pack sizes.

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

6.4. Follow-up to PSUR/PSUSA procedures

See also Annex I 16.4.

6.4.1. Dupilumab - DUPIXENT (CAP) - EMEA/H/C/004390/LEG 008

Applicant: Sanofi Winthrop Industrie

PRAC Rapporteur: Kimmo Jaakkola

Scope: Submission of an update of the safety evaluation report (SER), addressing cutaneous T-cell lymphoma (CTCL) and dupilumab presented in the PSUR process 2021 and a discussion on the reasons for the higher than anticipated number of CTCL cases reported and whether conclusions of the SER are still valid (following PSUSA/00010645/202203 concluded in November 2022)

Background

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

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

Following the evaluation of the most recently submitted PSUR(s) for the above-mentioned medicine(s), PRAC requested the MAH to submit further data on CTCL and to discuss the reasons for the higher than anticipated number of cases of CTCL among dupilumab users, and whether the conclusions of the safety evaluation report (SER) are still valid. For background, see PRAC minutes November 2022[40]. The responses were assessed by the Rapporteur for further PRAC advice.

Summary of advice/conclusion(s)

- Based on the available data and the Rapporteur's assessment, PRAC agreed that no update of the product information is needed, as no causal association between dupilumab treatment and CTCL can be established.
- In the next PSUR, the MAH should continue to closely monitor post-marketing data concerning CTCL in dupilumab-treated patients with a special emphasis on information regarding previous treatments used for atopic dermatitis in patients who are diagnosed with CTCL during treatment with dupilumab.

6.5. Variation procedure(s) resulting from PSUSA evaluation

See also Annex I 16.5.

6.5.1. Tozinameran - COMIRNATY (CAP) - EMEA/H/C/005735/II/0152

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Update of section 4.8 of the SmPC, upon request by PRAC following the assessment of EMEA/H/C/PSUSA/00010898/202112, to add dizziness to the list of adverse drug reactions (ADRs) with a frequency 'uncommon'. The package leaflet is updated accordingly

Background

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

Following the evaluation of the most recently submitted PSUR(s) for the above-mentioned medicine(s), PRAC requested the MAH to submit a variation to add dizziness as an undesirable effect with a frequency 'uncommon'. For background information, see PRAC minutes July 2022[41]. PRAC is responsible for adopting an outcome based on the assessment report from the PRAC Rapporteur, to be further considered at the level of CHMP, responsible for adopting an opinion on this variation.

Summary of recommendation(s)

[40] Held on 24-27 October 2022
[41] Held on 04-07 July 2022

- Based on the available data and the Rapporteur's assessment, PRAC agreed that the product information should be amended[42] to add dizziness as an undesirable effect with a frequency 'uncommon'.

6.6. Expedited summary safety reviews[43]

See Annex 16.6.

7. Post-authorisation safety studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)[44]

See also Annex I **Error! Reference source not found.**

7.1.1. Valproate[45] (NAP) - EMEA/H/N/PSP/J/0075.9

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

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Fourth interim report and statistical analysis plan (SAP) version 6.0 for a drug utilisation study (DUS) extension (DUS ext.) to assess the effectiveness of the new risk minimisation measures and to further characterise the prescribing patterns for valproate and related substances

Background

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

In line with the conclusions reached in 2018 of the referral procedure under Article 31 of Directive 2001/83/EC (EMEA/H/A-31/1454) conducted by PRAC for valproate-containing medicines, MAHs were required as a condition to the marketing authorisation(s) (Annex IV) to conduct a non-interventional imposed PASS study in accordance with Article 107o of Directive 2001/83/EC as a DUS aiming to assess the effectiveness of the updated risk minimisation measures including the pregnancy prevention programme (PPP) conditions and to further characterise the prescribing patterns for valproate with a pre- and post-implementation analysis.

The MAH Sanofi-Aventis Recherche & Développement on behalf of a consortium submitted to EMA the fourth interim report of the DUS ext) for review by PRAC. For further background, see PRAC minutes October 2022[46].

Endorsement/Refusal of the interim report

[42] Update of SmPC section 4.8
[43] 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
[44] In accordance with Article 107n of Directive 2001/83/EC
[45] Valproic acid, sodium valproate, valproate pivoxil, valproate semisodium, valpriomide, valproate bismuth, calcium valproate, valproate magnesium
[46] Held on 26-29 September 2022

- PRAC considered that the fourth interim report could be endorsed provided that satisfactory responses are provided to a request of supplementary information RSI endorsed by the Committee.
- The MAH should provide additional information on valproate exposed pregnancies, as well as a discussion on the differences in age of pregnant women exposed to valproate in the pre-implementation period and post-implementation period. In addition, the MAH should provide available data on the pre- and post-implementation period for Germany and Sweden using descriptive statistics.
- The MAH should submit a response to RSI within 60 days to EMA. A 60-day assessment timetable will be followed.

7.1.2. Valproate[47] (NAP) - EMEA/H/N/PSP/J/0075.10

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

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Submission of an amended protocol (version 10) together with responses to the request for supplementary information (RSI) to the third interim report for a drug utilisation study (DUS) extension (DUS ext.) to assess the effectiveness of the new risk minimisation measures and to further characterise the prescribing patterns for valproate and related substances

Background

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

In line with the conclusions reached in 2018 of the referral procedure under Article 31 of Directive 2001/83/EC (EMEA/H/A-31/1454) conducted by PRAC for valproate-containing medicines, MAHs were required as a condition to the marketing authorisation(s) (Annex IV) to conduct a non-interventional imposed PASS study in accordance with Article 107o of Directive 2001/83/EC as a DUS aiming to assess the effectiveness of the updated risk minimisation measures including the pregnancy prevention programme (PPP) conditions and to further characterise the prescribing patterns for valproate.

The MAH Sanofi-Aventis Recherche & Développement on behalf of a consortium submitted to EMA protocol version 10 of the DUS ext. and responses to the the RSI of the third interim report for review by PRAC. For further background, see PRAC minutes October 2022[48].

Endorsement/Refusal of the protocol

- Having considered the protocol version 10 in accordance with Article 107o of Directive 2001/83/EC, PRAC considered that the amendments to the protocol are not acceptable based on the currently provided information.
- The MAH should clarify whether the data can be provided for the initial planned post-implementation period of 36 months and should further elaborate on the amount of

[47] Valproic acid, sodium valproate, valproate pivoxil, valproate semisodium, valpriomide, valproate bismuth, calcium valproate, valproate magnesium
[48] Held on 26-29 September 2022

additional time needed to collect the data for this planned period in all involved countries. Of note, the post-implementation period of 36 months was decided to ensure sufficient time for the PPP implementation in clinical practice, ultimately to observe meaningful changes in the prescribing behaviour and consequently on exposed pregnancies.

- The MAH should submit a revised PASS protocol within 60 days to EMA. A 60-day assessment timetable will be followed.

7.2. Protocols of PASS non-imposed in the marketing authorisation(s)[49]

See also Annex I **Error! Reference source not found.**

7.2.1. Abrocitinib - CIBINQO (CAP) - EMEA/H/C/005452/MEA 002.1

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: MAH's response to MEA 002 [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] as per the request to supplementary information (RSI) as adopted in September 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 for Cibinqo (abrocitinib), the MAH was required to conduct a drug utilisation study (DUS) to monitor the real-world safety of abrocitinib among patients with AD in the EU. The MAH submitted a protocol for evaluation which was assessed by the Rapporteur. PRAC was requested to provide advice to CHMP on the protocol submitted by the MAH.

Summary of advice

- The study protocol for Cibinqo (abrocitinib) could be acceptable provided an updated protocol and satisfactory responses to a request for supplementary information (RSI) are submitted to EMA before finalisation of the procedure.
- The MAH should submit a revised protocol to EMA by 28 March 2023. A 60-day assessment timetable will be followed.

7.2.2. Abrocitinib - CIBINQO (CAP) - EMEA/H/C/005452/MEA 003.1

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Nikica Mirošević Skvrce

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

Scope: MAH's responses to MEA 003 [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] as per the request to supplementary information (RSI) adopted in September 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 for Cibinqo (abrocitinib), the MAH was required to conduct a drug utilisation study to evaluate the effectiveness of RMMs for abrocitinib in the EU using electronic healthcare data. The MAH submitted a protocol for evaluation which was assessed by the Rapporteur. PRAC was requested to provide advice to CHMP on the protocol submitted by the MAH.

Summary of advice

- The study protocol for Cibinqo (abrocitinib) could be acceptable provided an updated protocol and satisfactory responses to a request for supplementary information (RSI) are submitted to EMA before finalisation of the procedure.
- The MAH should submit a revised protocol to EMA by 28 March 2023. A 60-day assessment timetable will be followed.

7.2.3. Abrocitinib - CIBINQO (CAP) - EMEA/H/C/005452/MEA 004.1

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: MAH's response to MEA 004 [Protocol for study B7451015: an adolescent imaging substudy to evaluate if abrocitinib has any clinically meaningful effects on bone growth and development] as per the request to supplementary information (RSI) as adopted in September 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 for Cibinqo (abrocitinib), the MAH was required to conduct a drug utilisation study to evaluate whether abrocitinib has any clinically meaningful effects on bone growth and development. The MAH submitted a protocol for evaluation which was assessed by the Rapporteur. PRAC was requested to provide advice to CHMP on the protocol submitted by the MAH.

Summary of advice

- The study protocol for Cibinqo (abrocitinib) could be acceptable provided an updated protocol and satisfactory responses to a request for supplementary information (RSI) are submitted to EMA before finalisation of the procedure.

- The MAH should submit a revised protocol to EMA by 28 February 2023. A 60-day assessment timetable will be followed.

7.2.4. Upadacitinib - RINVOQ (CAP) - EMEA/H/C/004760/MEA 003.2

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Amendment to a previously agreed protocol for study P19-150: a long-term post-authorisation safety study (PASS) of upadacitinib use in rheumatoid arthritis (RA) patients in Europe to evaluate the safety of upadacitinib among patients with RA receiving routine clinical care to include additional study outcomes of bone fractures and add further clarification that the malignancy outcomes will be stratified for malignancies excluding NMSC and NMSC, separately (RMP version 6.2)

Background

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

As part of the RMP for Rinvoq (upadacitinib), the MAH was required to conduct a PASS study to evaluate and characterise the important identified and potential risks of upadacitinib. The MAH submitted a protocol for evaluation which was assessed by the Rapporteur. PRAC was requested to provide advice to CHMP on the protocol submitted by the MAH.

Summary of advice

- The study protocol for Rinvoq (upadacitinib) could be acceptable provided an updated protocol and satisfactory responses to a request for supplementary information (RSI) is submitted to the EMA before finalisation of the procedure.
- The MAH should submit a revised protocol to EMA by 28 March 2023. A 60-day assessment timetable will be followed.

7.2.5. Upadacitinib - RINVOQ (CAP) - EMEA/H/C/004760/MEA 004.2

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Amendment to a previously agreed protocol for study P19-141: a long-term post-authorisation safety study (PASS) of upadacitinib use in rheumatoid arthritis (RA) patients in the US in order to: 1) compare the incidence of malignancy, non-melanoma skin cancer (NMSC), major adverse cardiovascular events (MACE), venous thromboembolism (VTE) and serious infection events in adults with RA who receive upadacitinib in the course of routine clinical care relative to those who receive biologic therapy for the treatment of RA; 2) describe the incidence rates of herpes zoster, opportunistic infections and evidence of drug-induced liver injury (DILI); 3) describe the incidence of the above outcomes in very elderly patients (aged $\geqslant$ 75 years); 4) characterise VTE clinical risk factors and baseline biomarkers in a sub-study of new initiators of upadacitinib and comparator biologic therapies

Background

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

As part of the RMP for Rinvoq (upadacitinib), the MAH was required to conduct a PASS to characterise the safety of Rinvoq (upadacitinib) in patients with rheumatoid arthritis in the post-approval setting. The MAH submitted a protocol for evaluation which was assessed by the Rapporteur. PRAC was requested to provide advice to CHMP on the protocol submitted by the MAH.

Summary of advice

- The study protocol for Rinvoq (upadacitinib) could be acceptable provided an updated protocol and satisfactory responses to a request for supplementary information (RSI) is submitted to EMA before finalisation of the procedure.
- The MAH should submit a revised protocol to EMA by 28 March 2023. A 60-day assessment timetable will be followed.

7.2.6. Upadacitinib - RINVOQ (CAP) - EMEA/H/C/004760/MEA 012.2

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: MAH's response to MEA 012.1 [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 the request for supplementary information (RSI) adopted in September 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 for Rinvoq (upadacitinib), the MAH was required to conduct a PASS study to evaluate the effectiveness of additional risk minimisation measures for upadacitinib in the treatment of atopic dermatitis. The MAH submitted a protocol for evaluation which was assessed by the Rapporteur. PRAC was requested to provide advice to CHMP on the protocol submitted by the MAH.

Summary of advice

- The study protocol for Rinvoq (upadacitinib) could be acceptable provided an updated protocol and satisfactory responses to a request for supplementary information (RSI) is submitted to the EMA before finalisation of the procedure.
- The MAH should submit a revised protocol to EMA by 28 March 2023. A 60-day assessment timetable will be followed.

7.2.7. Upadacitinib - RINVOQ (CAP) - EMEA/H/C/004760/MEA 014.2

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: MAH's response to MEA 014.1 [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 September 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 for Rinvoq (upadacitinib), the MAH was required to conduct a PASS study to evaluate the effectiveness of additional risk minimisation measures for upadacitinib in the treatment of atopic dermatitis. The MAH submitted a protocol for evaluation which was assessed by the Rapporteur. PRAC was requested to provide advice to CHMP on the protocol submitted by the MAH.

Summary of advice

- The study protocol for Rinvoq (upadacitinib) could be acceptable provided an updated protocol and satisfactory responses to a request for supplementary information (RSI) is submitted to the EMA before finalisation of the procedure.
- The MAH should submit a revised protocol to EMA by 25 April 2023. A 60-day assessment timetable will be followed.

7.2.8. Upadacitinib - RINVOQ (CAP) - EMEA/H/C/004760/MEA 016

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Protocol for study P23-479: a drug utilisation study for evaluation of the effectiveness of additional risk minimisation measures for upadacitinib in the treatment of ulcerative colitis in Sweden and Denmark

Background

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

As part of the RMP for Rinvoq (upadacitinib), the MAH was required to conduct a PASS study to evaluate the effectiveness of additional risk minimisation measures for upadacitinib in the treatment of ulcerative colitis in Sweden and Denmark. The MAH submitted a protocol for evaluation which was assessed by the Rapporteur. PRAC was requested to provide advice to CHMP on the protocol submitted by the MAH.

Summary of advice

- The study protocol for Rinvoq (upadacitinib) could be acceptable provided an updated protocol and satisfactory responses to a request for supplementary information (RSI) is submitted to the EMA before finalisation of the procedure.
- The MAH should submit a revised protocol to EMA by 28 March 2023. A 60-day assessment timetable will be followed.

7.2.9. Upadacitinib - RINVOQ (CAP) - EMEA/H/C/004760/MEA 017

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Protocol for study P23-480: comparative cohort study of long-term safety of upadacitinib for the treatment of ulcerative colitis (UC) in a real-world setting in Sweden and Denmark

Background

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

As part of the RMP for Rinvoq (upadacitinib), the MAH was required to conduct a PASS study to evaluate the long-term safety of upadacitinib in routine clinical care for the treatment of UC in adults ark. The MAH submitted a protocol for evaluation which was assessed by the Rapporteur. PRAC was requested to provide advice to CHMP on the protocol submitted by the MAH.

Summary of advice

- The study protocol for Rinvoq (upadacitinib) could be acceptable provided an updated protocol and satisfactory responses to a request for supplementary information (RSI) is submitted to the EMA before finalisation of the procedure.
- The MAH should submit a revised protocol to EMA by 28 March 2023. A 60-day assessment timetable will be followed.

7.3. Results of PASS imposed in the marketing authorisation(s)[50]

See also Annex I **Error! Reference source not found.**

7.3.1. Valproate[51] (NAP) - EMEA/H/N/PSR/J/0036

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

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Results for a joint survey among healthcare professionals (HCP) to assess knowledge of HCP and behaviour with regards to pregnancy prevention programme (PPP) as well as receipt/use of a direct healthcare professional communication (DHPC) and educational materials and survey among patients to assess knowledge of the patients with regards to PPP as well as receipt/use of educational materials, as required in the outcome of the referral procedure under Article 31 of Directive 2001/83/EC on valproate-containing products completed in February 2018 (EMEA/H/A-31/1454)]

Background

[50] In accordance with Article 107p-q of Directive 2001/83/EC
[51] Valproic acid, sodium valproate, valproate pivoxil, valproate semisodium, valpriomide, valproate bismuth, calcium valproate, valproate magnesium

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

The MAH Sanofi-Aventis Recherche & Développement, on behalf of a consortium, submitted to EMA the final results version 1.0 of the 'surveys among HCP and patients to assess their knowledge and behaviour with respect to the new risk minimisation measures (RMM) for valproate use in Europe'. For further background, see PRAC minutes November 2021[52], PRAC minutes June 2022[53] and PRAC minutes November 2022[54].

Summary of recommendation(s) and conclusions

- PRAC adopted a list of questions (LoQ) for a stakeholder meeting.

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

See also Annex I **Error! Reference source not found.**

7.4.1. Regorafenib - STIVARGA (CAP) - EMEA/H/C/002573/II/0039

Applicant: Bayer AG

PRAC Rapporteur: Menno van der Elst

Scope: Update of section 4.4 of the SmPC in order to remove the disease specific precaution for hepatocellular carcinoma based on final results from study REFINE (study number 19244) listed as a category 3 study in the RMP; this is an international, prospective, open-label, multi-center, observational study to describe the safety and effectiveness of treatment with regorafenib in real-world settings. The RMP version 6.1 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 Stivarga (regorafenib), the MAH conducted a prospective observational study to describe the safety and effectiveness of treatment with regorafenib in real-world settings. The Rapporteur assessed the MAH's final study report.

Summary of advice

- Based on the available data and the assessment of the Rapporteur, PRAC considered that the ongoing variation assessing the final study report can be recommended for approval.
- PRAC supported the update of the product information[56] in order to remove the disease specific precaution for hepatocellular carcinoma in light of the study results. In addition, PRAC agreed with the removal of the REFINE study as an additional pharmacovigilance

[52] Held on 25-28 October 2021
[53] Held on 07-10 June 2022
[54] Held on 24-27 October 2022
[55] In accordance with Article 61a (6) of Regulation (EC) No 726/2004, in line with the revised variations regulation for any submission as of 4 August 2013
[56] SmPC section 4.4.

activity from the RMP and supported the removal of 'safety in hepatocellular carcinoma patients who discontinued prior sorafenib therapy due to sorafenib-related toxicity' from the list of safety concerns.

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

See Annex **Error! Reference source not found.**

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

None

9.3. Others

None

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

10.1. Safety related variations of the marketing authorisation

None

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

None

10.3. Other requests

None

10.4. Scientific Advice

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

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

11.1. Safety related variations of the marketing authorisation

11.1.1. Montelukast (NAP) - FI/H/xxxx/WS/112

Applicant: Organon

PRAC Lead: Kimmo Jaakkola

Scope: PRAC consultation on a worksharing variation (WS) procedure evaluating the risk of severe and prolonged neuropsychiatric events/harms as well as the existing risk minimisation measures and the need for any further ones and/or labelling updates as per conclusions of the PSUSA procedure (PSUSA/00002087/202107) concluded in March 2022, on request of Finland

Background

Montelukast is a selective leukotriene receptor antagonist indicated for the treatment of asthma as add-on therapy in patients with mild to moderate persistent asthma, for the prophylaxis of asthma in which the predominant component is exercise-induced bronchoconstriction as well as for the prophylaxis of asthma to provide symptomatic relief of

seasonal allergic rhinitis. In some Member States, montelukast is also indicated for the relief of daytime and night-time symptoms of allergic rhinitis.

Based on the assessment of the recent PSUR single assessment (PSUSA) procedure for montelukast (PSUSA/00002087/202107) concluded in March 2022, PRAC considered that the risk of severe and prolonged neuropsychiatric events/harms should be further assessed and that the MAH for the originator montelukast-containing product(s) should provide a discussion on the effectiveness of the current risk minimisation measures (RMMs) and the need for further RMMs that will aim to increase the awareness of the neuropsychiatric events to prevent severe and prolonged neuropsychiatric events/harms which could be avoided with timely treatment withdrawal, as warranted. For further background, see PRAC minutes March 2022[57].

On request of CMDh, MAH for the originator montelukast-containing product(s) submitted the requested safety reviews for evaluation within a worksharing variation procedure. In the context of the ongoing evaluation of this procedure (FI/H/xxxx/WS/112), Finland, as lead Member State (LMS), requested PRAC advice on its assessment.

Summary of advice

- Based on the review of the available information and evidence, PRAC supported that the product information of montelukast-containing product(s) should be updated in order to increase awareness on the risk of neuropsychiatric events. In addition, PRAC discussed whether there is a need for increasing the visibility of this warning in the product information by highlighting this text in bold type font within a black box. However, no recommendation was made in this regard.

11.2. Other requests

None

12. Organisational, regulatory and methodological matters

12.1. Mandate and organisation of PRAC

12.1.1. PRAC membership

None

12.1.2. Vote by proxy

None

12.2. Coordination with EMA Scientific Committees or CMDh-v

None

[57] Held on 07-10 March 2022

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

12.3.1. Methodology Working Party (MWP) – overview of scope and activities

The EMA Secretariat, together with the Methodology Working Party (MWP) Vice-Chair, presented to PRAC the scope and activities of the newly constituted MWP, as well as an overview of the 3-year work plan. The EMA Secretariat announced that an open call was launched for the Methodology European Specialised Expert Community (ESEC). PRAC members were invited to send nominations in the area of e.g. statistics, clinical trial methodology, modelling & simulation, physiological based pharmacokinetic (PBPK) modelling and simulation, pharmacokinetics, pharmacogenomics, epidemiology, real world evidence (RWE), or artificial intelligence that are part of the European Regulatory Network (e.g. assessors working for a NCA, members of the different WPs or members from academia in institutions/universities with relevant expertise for the Methodology ESEC). Nominations along with a brief summary their expertise should be sent to EMA.

12.3.2. Scientific advice working party (SAWP) – re-nomination of PRAC representative(s)

The EMA Secretariat presented to PRAC the mandate and composition of the Scientific advice working party (SAWP) and announced that an open call was launched for the renomination of all SAWP members for a mandate of three years. PRAC members were invited to express their interest as a PRAC-SAWP member and send their nominations to EMA by 15 February 2023. The full SAWP composition will be further adopted by CHMP.

Post-meeting note: Marie Louise Schougaard Christiansen was appointed as PRAC-SAWP member.

12.4. Cooperation within the EU regulatory network

12.4.1. Coronavirus (COVID-19) pandemic - update

The EMA Secretariat presented to PRAC an overview of the evolution of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) including current circulating variants. PRAC was also updated on the activities of the COVID-19 EMA pandemic Task Force (ETF), including an overview of ongoing clinical trials and epidemiological studies, and including study results on the effectiveness of the COVID-19 vaccines against various SARS-CoV 2 variants. The EMA Secretariat also provided an update on the status of the monkeypox disease outbreak.

12.5. Cooperation with International Regulators

None

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

None

12.7. PRAC work plan

12.7.1. PRAC work plan 2023

PRAC lead: Sabine Straus, Martin Huber

At the organisational, regulatory and methodological matters (ORGAM) meeting on 23 January 2023, the EMA Secretariat presented to PRAC the final draft PRAC work plan 2023, further to previous discussion and comments received. For further background, see PRAC minutes November 2022[58]. No further comments were raised and PRAC adopted the work plan 2023.

Post-meeting note: the PRAC work plan 2023 was published on the EMA website (EMA/PRAC/45172/2023) on 27 January 2023.

12.8. Planning and reporting

12.8.1. Marketing authorisation applications (MAA) forecast for 2023 – planning update dated Q4 2022

At the organisational, regulatory and methodological matters (ORGAM) meeting on 23 January 2023, the EMA Secretariat presented a quarterly updated report on marketing authorisation applications planned for submission (the business 'pipeline') in 2023 for information to PRAC. For previous update, see PRAC minutes October 2022[59].

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

[58] Held on 24-27 October 2022
[59] Held on 26-29 September 2022

12.10.2. Granularity and Periodicity Advisory Group (GPAG)

None

12.10.3. PSURs repository

None

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

PRAC endorsed the draft revised EURD list, version January 2023, reflecting PRAC's comments impacting on the data lock point (DLP) and PSUR submission frequencies of the substances/combinations. PRAC endorsed the newly allocated Rapporteurs for upcoming PSUSAs in accordance with the principles previously endorsed by PRAC (see PRAC minutes April 2013).

Post-meeting note: following the PRAC meeting of January 2023, the updated EURD list was adopted by CHMP and CMDh and published on the EMA website, see: Home> Human Regulatory>Pharmacovigilance>Post-authorisation>Periodic safety update reports>List of Union reference dates and frequency of submission of periodic safety update reports (PSURs)

12.11. Signal management

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

PRAC lead: Menno van der Elst

PRAC was updated on the progress from the signal management review technical (SMART) working group (WG) meeting on Methods held on 07 December 2022, including the announcement on the new SMART WG members, the implementation of the EU Substance Registration System (EU-SRS) and its use in signal detection, as well as the masking effect of COVID-19 vaccine case reports in EudraVigilance, together with some proposals to mitigate the impact of masking during screening activities.

12.12. Adverse drug reactions reporting and additional monitoring

12.12.1. Management and reporting of adverse reactions to medicinal products

None

12.12.2. Additional monitoring

None

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

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

Post-meeting note: The updated additional monitoring list was published on the EMA

website, see: Home>Human Regulatory>Post-authorisation>Pharmacovigilance>Medicines under additional monitoring>List of medicines under additional monitoring

12.12.4. Specific adverse drug reaction (ADR) follow-up questionnaire (FUQ) drafting group – update on the activities – next steps on Specific ADR FUQ repository

PRAC lead: Tiphaine Vaillant

The EMA Secretariat presented to PRAC an update on the activities performed so far by the specific adverse drug reaction (ADR) follow-up questionnaire (FUQ) drafting group, as part of the PRAC work plan 2023. The main objectives of the future guidance on specific ADR FUQ were presented to PRAC together with a proposal for collecting ADR FUQs. PRAC input was requested on the proposal to establish a specific ADR FUQ repository for CAPs (and subsequently for NAPs in collaboration with CMDh) to be published on the EMA website. PRAC agreed, in principle, with the creation of the repository. However, the Committee advised that the focus should be made on the finalisation of the guidance and the criteria to be fulfilled for the FUQ to be listed in the repository first and that the specific ADR FUQs should be collected prospectively. The drafting group representatives will come back and ask for further PRAC input once a first draft of the specific ADR FUQ guideline will be ready.

12.12.5. Activities related to the confirmation of full functionality

None

12.13. EudraVigilance database

12.13.1. Activities related to the confirmation of full functionality

None

12.14. Risk management plans and effectiveness of risk minimisations

12.14.1. Risk management systems

None

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

None

12.15. Post-authorisation safety studies (PASS)

12.15.1. Post-authorisation Safety Studies – imposed PASS

None

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

None

12.16. Community procedures

12.16.1. Referral procedures for safety reasons

None

12.17. Renewals, conditional renewals, annual reassessments

None

12.18. Risk communication and transparency

12.18.1. Public hearings – procedural and best practice guidance for PRAC members

At the organisational, regulatory and methodological matters (ORGAM) meeting held on 23 January 2023, following an EMA initiative to improve the process of preparing EMA analyses on the appropriateness of holding public hearing, the EMA Secretariat presented to PRAC the proposed changes to the public hearing process, rules of procedures, procedural and best practice guidance, as well as the template used for the EMA analysis on this matter. PRAC endorsed the revised rules of procedures for the organisation and conduct of public hearings at PRAC, and agreed with the changes presented.

12.18.2. Safety communication

None

12.19. Continuous pharmacovigilance

12.19.1. Incident management

None

12.20. Impact of pharmacovigilance activities

12.20.1. Impact of EU label changes for fluoroquinolone-containing medicinal products for systemic and inhalation use: post-referral prescribing trends – study report

PRAC lead: Martin Huber, Eva Jirsová

PRAC discussed the results of a study entitled 'Impact of European Union label changes for fluoroquinolone containing medicinal products for systemic and inhalation use' (EUPAS37856) commissioned under the remit of the PRAC Strategy on measuring the impact of pharmacovigilance activities following the referral procedure (EMEA/H/A-31/1452) concluded in 2019 where risk minimisation measures including restrictions of the use of fluoroquinolones and updates to the prescribing information for healthcare professionals and patients were introduced regarding the risk of disabling, long-lasting and potentially irreversible adverse reactions. The study concluded that fluoroquinolone-containing products prescribing decreased over time in the six countries studied, although it seems that the risk minimisation measures may have had only a modest impact in the primary care setting. The study suggested that fluoroquinolones may still be used outside the revised indications as recommended following the referral procedure. PRAC also discussed

the input from patients who experienced adverse events after being prescribed a fluoroquinolone. PRAC agreed that a refined communication strategy involving a wide range of different stakeholders is warranted to ensure the prescribing information is adhered to. A follow-up discussion will take place in due course to agree on the details of an appropriate communication strategy.

12.20.2. Strategy on measuring the impact of pharmacovigilance – PRAC interest group (IG) Impact – revision of the process for prioritisation and follow-up of impact research

PRAC discussed the proposed revised process for prioritisation and regulatory follow-up of impact research commissioned under the remit of the PRAC Strategy on measuring the impact of pharmacovigilance activities with further clarification on the roles and responsibilities of PRAC (Co-)Rapporteurs and PRAC Sponsors of impact research and focus on regulatory oversight and follow-up on impact study results. The revised process considers the appropriate regulatory framework for assessment and need for stakeholder communication at the time study results become publicly available. PRAC members were invited to provide written comments to facilitate implementation, including comments on respective templates.

12.21. Others

12.21.1. EMA-funded safety studies: analysis on Coronavirus (COVID-19) vaccines and myocarditis – updated study results

An updated analysis on COVID-19 vaccines and myocarditis conducted as part of the EMA-funded study led by the EU Pharmacoepidemiology and Pharmacovigilance (PE&PV) Research Network led by Utrecht University was presented to PRAC. The analysis was further updated to include an additional hospital data source, more recent data including exposure to the third dose, and additional information on sequence of vaccinations and distance between doses.

13. Any other business

None

14. Annex I – Signals assessment and prioritisation[60]

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[61].

[60] 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

[61] 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

14.1.1. Lenvatinib – LENVIMA (CAP); KISPLYX (CAP)

Applicant: Eisai GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of adrenal insufficiency

EPITT 19870 – New signal

Lead Member State(s): SE

15. Annex I – Risk management plans

15.1. Medicines in the pre-authorisation phase

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

15.1.1. Aripiprazole - EMEA/H/C/005929

Scope: Indicated for the maintenance treatment of schizophrenia

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

Applicant: Marinus Pharmaceuticals Emerald Limited

Scope: Treatment of epileptic seizures associated with cyclindependent kinase-like 5 deficiency disorder (CDD)

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. Alectinib - ALECENSA (CAP) - EMEA/H/C/004164/II/0044

Applicant: Roche Registration GmbH

PRAC Rapporteur: Jana Lukacisinova

Scope: Submission of an updated RMP version 3.2 in order to remove the important identified risks of Interstitial Lung Disease (ILD)/Pneumonitis, Hepatotoxicity, Photosensitivity, Bradycardia, Severe myalgia and Creatine Phosphokinase (CPK) elevations as safety concerns. Furthermore, template updates in line with the GVP Product or Population-Specific Considerations III: Pregnant and breastfeeding women are made

15.2.2. Efavirenz - STOCRIN (CAP) - EMEA/H/C/000250/II/0130

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Submission of an updated RMP version 9.0 including removal of all safety concerns in line with revision 2 of GVP module V on 'Risk management

15.2.3. Elasomeran - SPIKEVAX (CAP) - EMEA/H/C/005791/II/0085/G

Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Grouped application comprising of : 1) submission of RMP version 6.0 to add Spikevax bivalent Original / Omicron BA.4-5 vaccine (mRNA-1273.222), to update studies mRNA-1273-P904, mRNA-1273-P905 and mRNA-1273-P910 in the Pharmacovigilance Plan to include exposure to Spikevax bivalent vaccines, to update the INN to elasomeran/davesomeran, and to reclassify studies mRNA-1273-P205 from category 2 to category 3 studies in the Pharmacovigilance Plan; 2) submission of the final clinical study report (CSR) from study mRNA-1273-P201, a Phase 2a, Randomized, Observer-Blind, Placebo-Controlled, Dose-Confirmation Study to Evaluate the Safety, Reactogenicity, and Immunogenicity of mRNA-1273 SARS-CoV-2 Vaccine in Adults ≥= 18 Years listed as a category 3 study including addition of clinical trial exposure data for part C of the study mRNA-1273-P201

15.2.4. Elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil - STRIBILD (CAP) - EMEA/H/C/002574/WS2320/0120; emtricitabine, tenofovir disoproxil - TRUVADA (CAP) - EMEA/H/C/000594/WS2320/0177

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Update of Annex II and the RMP for Truvada and Stribild to version 18.1 and 14.1 to remove of the paediatric additional Risk Minimisation Measures (aRMMs) for HIV indication. In addition, the MAH took the opportunity to introduce changes to the PI

15.2.5. Fenfluramine - FINTEPLA (CAP) - EMEA/H/C/003933/II/0017, Orphan

Applicant: Zogenix ROI Limited

PRAC Rapporteur: Martin Huber

Scope: Submission of an updated RMP version 2.10 in order to implement a targeted follow-up questionnaire (FUQ) to further improve the collection of follow-up information on cases of vascular heart disease (VHD) and pulmonary arterial hypertension (PAH) suggested by PRAC following PSUSA/00010907/2021122

15.2.6. Filgrastim - FILGRASTIM HEXAL (CAP) - EMEA/H/C/000918/WS2369/0066; ZARZIO (CAP) - EMEA/H/C/000917/WS2369/0067

Applicant(s): Sandoz GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Submission of an updated RMP version 13.0 to reduce the list of safety concerns and remove risks which are well characterised and already included in the product information, following PSUR single assessment (PSUSA) procedure (PSUSA/00001391/202109) concluded in May 2022. Additionally, the due date of the final study report EP06-501 (MEA007) has been updated from Q3 2025 to Q1 2025

15.2.7. Rivastigmine - EXELON (CAP) - EMEA/H/C/000169/WS2378/0140; PROMETAX (CAP) - EMEA/H/C/000255/WS2378/0141

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Tiphaine Vaillant

Scope: Submission of an updated RMP version 11.0 for Exelon/Prometax to remove the standalone multiple patch use annual report as an additional pharmacovigilance activity, which was endorsed by PRAC (EMA/CHMP/PRAC/342229/2021) on 22-Jul-2021 and to include the initial risks reviewed at the time of initial marketing authorisation that were agreed to within RMP Version 1.1 (final: 16-July-2007), as well as submission of the rationale for the removal of some safety concerns from the currently approved RMP Version 10.0, following the PRAC Assessment Report from the currently approved RMP (version 10.0) (EMEA/H/C/XXX/WS/1773). Furthermore, the MAH took the opportunity to introduce editorial changes in the RMP

15.2.8. Smallpox vaccine (live modified vaccinia virus Ankara) - IMVANEX (CAP) - EMEA/H/C/002596/II/0081

Applicant: Bavarian Nordic A/S

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Submission of an updated RMP version 9.1 in order to update the safety specifications in line with extension of the indication to "active immunisation against smallpox, monkeypox and disease caused by vaccinia virus in adults", update the missing information from the list of safety concerns, differentiate routine pharmacovigilance activities and additional pharmacovigilance activities, addition of non-BN (Bavarian Nordic) sponsored clinical study SEMVAc to additional pharmacovigilance activities and deletion of paediatric study POX-MVA-035 upon request by PRAC following the assessment of procedure EMEA/H/C/002596/II/0076 concluded at PRAC in July 2022

15.2.9. Sofosbuvir - SOVALDI (CAP) - EMEA/H/C/002798/WS2356/0081; sofosbuvir, ledipasvir - HARVONI (CAP) - EMEA/H/C/003850/WS2356/0107; sofosbuvir, velpatasvir - EPCLUSA (CAP) - EMEA/H/C/004210/WS2356/0068; sofosbuvir, velpatasvir, voxilaprevir - VOSEVI (CAP)-EMEA/H/C/004350/WS2356/0057

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Submission of updated RMPs (version 8.1 – Epclusa, version 8.1 – Harvoni, version 6.1 – Vosevi, version 11.1- Sovaldi) following finalisation of procedure EMEA/H/C/WS2222 providing the final CSR for the non-imposed joint PASS study to evaluate the risk of de novo hepatocellular carcinoma in patients with compensated cirrhosis treated with direct-

acting antivirals (DAA) for chronic hepatitis C (Study B20-146). In particular, the list of safety concerns has been updated to remove the important potential risks "recurrence of hepatocellular carcinoma (HCC)" and "emergence of HCC", and to remove "safety in patients with previous HCC" as an area of missing information. In addition, the completed PASS studies: DAA PASS and De Novo DAA PASS have been removed from the pharmacovigilance plan

15.2.10. Somatropin - NUTROPINAQ (CAP) - EMEA/H/C/000315/II/0077

Applicant: Ipsen Pharma

PRAC Rapporteur: Anette Kirstine Stark

Scope: Submission of an updated RMP version 4.0 in order to remove some of the safety concerns in compliance with GVP Module V Revision 2. In addition, the MAH took the opportunity to add data from final clinical study report of International Cooperative Growth Study (iNCGS) registry (non-interventional study) and exposure and safety information

15.2.11. Talimogene laherparepvec - IMLYGIC (CAP) - EMEA/H/C/002771/II/0059

Applicant: Amgen Europe B.V., ATMP[62]

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Submission of an updated RMP version 10 in order to update and reclassify identified risk of 'disseminated herpetic infection' based on the cumulative assessment of literature review and MAH Global Safety Database and to remove studies 20180062 and 20180099 from Planned and Ongoing Studies from the list of Pharmacovigilance Plan studies in the Annex II

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. Agomelatine - VALDOXAN (CAP) - EMEA/H/C/000915/II/0051

Applicant: Les Laboratoires Servier

PRAC Rapporteur: Pernille Harg

Scope: Extension of indication to include new therapeutic indication in adolescents aged 12 to 17 years for the treatment of moderate to severe major depressive episodes, if depression is unresponsive to psychological therapy alone, for Valdoxan, further to the results of the phase 2 (CL2-20098-075) and phase 3 (CL3-20098-076) paediatric clinical studies included in the Paediatric Investigation Plan number EMEA-001181-PIP-11; As a consequence the sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated.
The package leaflet is updated accordingly. The updated RMP version 25.1 has also been submitted

[62] Advanced therapy medicinal product

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

Applicant: CSL Behring GmbH

PRAC Rapporteur: Menno van der Elst

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

15.3.3. Andexanet alfa - ONDEXXYA (CAP) - EMEA/H/C/004108/II/0033

Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: Update of section 5.1 of the SmPC based on interim results from pharmacokinetic (PK)/pharmacodynamic (PD) study (listed as a specific obligation in the Annex II in order to fulfil SOB 1 and SOB 3): a PK and PK/PD analysis of intravenously administered andexanet after dosing to steady state with a factor Xa inhibitor, rivaroxaban or Apixaban, in healthy subjects and patients who have acute major bleeding. In addition, the MAH took the opportunity implement editorial changes in Annex II of the SmPC. The RMP version 3.0 has also been submitted

15.3.4. Ataluren - TRANSLARNA (CAP) - EMEA/H/C/002720/II/0069, Orphan

Applicant: PTC Therapeutics International Limited

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Update of sections 4.8 and 5.1 of the SmPC in order to update efficacy and safety information following results from study PTC124-GD-041-DMD, listed as a specific obligation in the Annex II; This is a Phase 3 multicentre, randomised, double-blind, 18-month, placebo-controlled study, followed by a 18-month open label extension to confirm the efficacy and safety of ataluren in the treatment of ambulant patients with mnDMD aged 5 years or older. Annex II, and Annex IIB are updated to delete the SOB and to reflect the switch from conditional to full marketing authorisation. The package leaflet is updated accordingly. The RMP version 11.0 has also been submitted. Minor corrections were done to align the PI with the latest QRD templates

15.3.5. Atezolizumab - TECENTRIQ (CAP) - EMEA/H/C/004143/II/0075

Applicant: Roche Registration GmbH

PRAC Rapporteur: Inês Ribeiro-Vaz

Scope: Update of sections 4.2, 4.4 and 4.8 of the SmPC in order to add ‘pericardial disorders’ to the list of adverse drug reactions (ADRs) with frequency common in

monotherapy and uncommon in combination therapy/based on final results from Drug Safety Report (DSR 1115896) including review of available clinical trial data, post-marketing data, and literature. In addition, the MAH took the opportunity to update Annex II section D of the SmPC and to implement editorial changes in the SmPC. The package leaflet was updated accordingly. The RMP version 23.1 has also been submitted

15.3.6. Baricitinib - OLUMIANT (CAP) - EMEA/H/C/004085/X/0035/G

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Extension application to introduce a new strength (1 mg film-coated tablet), grouped with a type II variation (C.I.6.a) in order to extend the indication to include treatment, as monotherapy or in combination with conventional synthetic disease modifying antirheumatic drugs (DMARDs), of active juvenile idiopathic arthritis (JIA) in patients 2 years of age and older who have had an inadequate response or intolerance to one or more prior conventional synthetic or biologic DMARDs, based on final results from the pivotal study JAHV (I4V-MC-JAHV); this is a multicentre, double-blind, randomised, placebo-controlled, medication-withdrawal Phase 3 study in children from 2 years to less than 18 years of age with JIA who have had an inadequate response or intolerance to treatment with at least 1 conventional DMARD (cDMARD) or biological (bDMARD). As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated. The package leaflet is updated in accordance. Version 15.1 of the RMP has also been submitted

15.3.7. Brolucizumab - BEOVU (CAP) - EMEA/H/C/004913/II/0021

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of sections 4.2, 4.8, 5.1 and 5.2 of the SmPC in order to change posology recommendation in including an additional dose regimen (q16w) for diabetic macular edema (DME) patients during the maintenance phase, update the frequency of adverse drug reactions, update pharmacokinetic, pharmacodynamic, efficacy and safety information, following the assessment of procedure II/10, based on final results from studies CRTH258B2301 (KESTREL) and CRTH258B2302 (KITE). The package leaflet is updated accordingly. The RMP version 10 has also been submitted

15.3.8. Caplacizumab - CABLIVI (CAP) - EMEA/H/C/004426/II/0040, Orphan

Applicant: Ablynx NV

PRAC Rapporteur: Jan Neuhauser

Scope: Update of sections 4.2, 4.4, 4.5, 4.8 and 5.1 of the SmPC in order to update information on long-term efficacy and safety based on final results from study ALX0681-C302/LTS16371 - Prospective Follow-up Study for Patients who Completed Study ALX0681-C301 (HERCULES) to Evaluate Long-term Safety and Efficacy of Caplacizumab (Post-HERCULES), listed as a category 3 study in the RMP. The Post-HERCULES study was a Phase III, 36-month follow-up study from HERCULES (parent study) to evaluate the long-term outcomes as well as the safety and efficacy of repeat use of caplacizumab in patients who experienced a recurrence of acquired thrombotic thrombocytopenic purpura (aTTP).

The RMP version 3.0 has also been submitted

15.3.9. 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

15.3.10. 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

15.3.11. Dulaglutide - TRULICITY (CAP) - EMEA/H/C/002825/II/0065

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Amelia Cupelli

Scope: Extension of indication to include treatment of type 2 diabetes mellitus (T2DM) in children and adolescents aged 10 to less than 18 years based on final results from study H9X-MC-GBGC; this is a phase 3, double-blind, randomised, multi-centre, placebo-controlled superiority trial to evaluate PK, PD, safety and efficacy of dulaglutide in children from 10 to less than 18 years of age, with an open label extension to evaluate safety. As a consequence, sections 4.1, 4.2, 4.8, 5.1, and 5.2 of the SmPC are updated. The package leaflet is updated in accordance. Version 7.1 of the RMP has also been submitted

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

Applicant: Sanofi Winthrop Industrie

PRAC Rapporteur: Kimmo Jaakkola

Scope: Extension of indication to include treatment of atopic dermatitis in paediatric patients from 6 months to <6 years of age based on final results from study R668-AD-1539: a phase 2/3 study investigating the pharmacokinetics, safety, and efficacy of dupilumab in patients aged ⩾6 months to <6 years with moderate-to-severe atopic

dermatitis. As a consequence, sections 4.1, 4.2, 4.8, 5.1, 5.2 of the SmPC are updated. The package leaflet and the RMP (version 7.0) are updated in accordance

15.3.13. Entrectinib - ROZLYTREK (CAP) - EMEA/H/C/004936/II/0014

Applicant: Roche Registration GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Update of sections 4.2 and 5.2 the SmPC in order to update pharmacokinetic information based on final results from study GP411174 listed as an additional pharmacovigilance activity in the RMP; this is a Phase I, non-randomised, single-dose, open-label study to investigate the effect of impaired hepatic function on the pharmacokinetics of entrectinib in volunteers with different levels of hepatic function. The RMP version 4.0 has also been submitted. In addition, the MAH took the opportunity to update in Annex II section C and to update the list of local representatives in the package leaflet

15.3.14. Fenfluramine - FINTEPLA (CAP) - EMEA/H/C/003933/II/0015, Orphan

Applicant: Zogenix ROI Limited

PRAC Rapporteur: Martin Huber

Scope: Update of sections 4.2 and 5.2 of the SmPC to update the safety information based on final results from study ZX008-1903 listed as a category 3 study in the RMP: a phase 1, open-label, single-dose study to evaluate the safety, tolerability, and pharmacokinetics of ZX008 (fenfluramine hydrochloride) in subjects with varying degrees of hepatic impairment. The primary objective of this study was to compare the pharmacokinetics (PK) of a single dose of ZX008 (fenfluramine hydrochloride) in subjects with varying degrees of hepatic impairment with that of healthy matched control subjects. The RMP (version 2.7) was updated accordingly

15.3.15. Human fibrinogen, human thrombin - EVICEL (CAP) - EMEA/H/C/000898/II/0099

Applicant: Omrix Biopharmaceuticals N. V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of sections 4.8 and 5.1 of the SmPC in order to update the frequency of adverse drug reactions (ADRs), add Pseudomeningocele to the list of ADRs with frequency uncommon and to update efficacy and safety information on paediatric population, following P46/0030 based on the final results from paediatric clinical study BIOS-13-006. This is a Prospective Randomised Controlled Study Evaluating the Safety and Efficacy of EVICEL used for Suture- Line Sealing in Dura-Mater Closure during Paediatric Neurosurgical Cranial Procedures. The package leaflet is updated accordingly. Editorial changes are proposed to sections of the product information. In addition, the MAH took the opportunity to bring the PI in line with the latest QRD template version 10.3. The RMP version 15 has also been submitted

15.3.16. 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

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

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Jo Robays

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

15.3.18. Nintedanib - OFEV (CAP) - EMEA/H/C/003821/X/0052/G

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Extension application to add a new strength of 25 mg soft capsule grouped with a type II variation C.I.6.a to add a new indication of treatment of fibrosing Interstitial Lung Diseases (ILDs) in children and adolescents from 6 to 17 years of age, based on results from study 1199 0337 (InPedILD); a randomised, placebo-controlled, double-blind, multicentre, multinational, phase III clinical trial undertaken to evaluate dose-exposure and safety of nintedanib on top of standard of care in children and adolescents (6 to 17 years old) with clinically significant fibrosing ILD. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The package leaflet is updated in accordance. In addition, the MAH took the opportunity to implement minor editorial changes to the list of local representatives in the package leaflet. The updated RMP version 12.0 is also submitted

15.3.19. 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

15.3.20. Pneumococcal polysaccharide conjugate vaccine (adsorbed) - VAXNEUVANCE (CAP) - EMEA/H/C/005477/II/0013/G

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Grouped application comprising two type II variations as follows: 1) update sections 4.2, 4.4, 4.8, 5.1 of the SmPC in order to add safety data on recipients of haematopoietic stem cell transplant (HSCT) based on final results from study V114-022, listed as a category 3 study in the RMP; This is a Clinical Study to Evaluate the Safety, Tolerability, and Immunogenicity of Vaxneuvance in Recipients of Allogeneic Hematopoietic Stem Cell Transplant; 2) update sections 4.2, 5.1 of the SmPC in order to update the information regarding a 3-dose regimen based on final results from study V114-026; a Clinical Study to Evaluate the Safety, Tolerability, and Immunogenicity of a 3-dose Regimen of Vaxneuvance in Healthy Infants. The package leaflet is updated accordingly. The RMP version 2.1 has also been submitted

15.3.21. Polatuzumab vedotin - POLIVY (CAP) - EMEA/H/C/004870/II/0018, Orphan

Applicant: Roche Registration GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of the final report from study GO29365 listed as a category 3 study in the RMP in order to address MEA/002. This is a phase Ib/II, multicenter, open-label study evaluating the safety, tolerability, and anti-tumor activity of polatuzumab vedotin in combination with rituximab or obinutuzumab plus bendamustine in patients with relapsed/refractory follicular lymphoma or relapsed/refractory diffuse large B-cell lymphoma. The RMP version 3.0 has also been submitted

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

Applicant: Paion Deutschland GmbH

PRAC Rapporteur: Rhea Fitzgerald

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

package leaflet solely for the 50 mg strength and the GA indication is provided. The RMP (version 1.1) is also updated accordingly.

15.3.23. 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

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

Applicant(s): 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

15.3.25. 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

15.3.26. Tezepelumab - TEZSPIRE (CAP) - EMEA/H/C/005588/II/0001

Applicant: AstraZeneca AB

PRAC Rapporteur: Eva Jirsová

Scope: Addition of a new autoinjector (AI) presentation as an alternative method of administration, with consequential update to the product information. RMP (version 1.1) has

been updated accordingly

15.3.27. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/II/0096

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: Update of section 5.1 of the SmPC in order to update information with the 4-year clinical data in patients with ulcerative colitis based on the final report from study CNTO1275UCO3001 listed as a category 3 study in the RMP; this is a phase 3, randomised, double blind, placebo-controlled, parallel-group, multicentre study to evaluate the safety and efficacy of ustekinumab induction and maintenance therapy in subjects with moderately to severely active ulcerative colitis. The RMP version 23.1 has also been submitted. In addition, the MAH took the opportunity to introduce a correction to the product information

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

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

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

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

16.1.1. Afamelanotide – SCENESSE (CAP) – PSUSA/00010314/202206

Applicant: Clinuvel Europe Limited

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.2. Alpelisib – PIQRAY (CAP) – PSUSA/00010871/202205

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.3. Amivantamab – RYBREVANT (CAP) – PSUSA/00010977/202205

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.4. Artesunate – ARTESUNATE AMIVAS (CAP) – PSUSA/00010958/202206

Applicant: Amivas Ireland Ltd

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.5. Atidarsagene autotemcel – LIBMELDY (CAP) – PSUSA/00010899/202206

Applicant: Orchard Therapeutics (Netherlands) B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.6. Avatrombopag – DOPTELET (CAP) – PSUSA/00010779/202205

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Monica Martinez Redondo

Scope: Evaluation of a PSUSA procedure

16.1.7. Berotralstat – ORLADEYO (CAP) – PSUSA/00010930/202206

Applicant: BioCryst Ireland Limited

PRAC Rapporteur: Julia Pallos

Scope: Evaluation of a PSUSA procedure

16.1.8. Binimetinib – MEKTOVI (CAP) – PSUSA/00010717/202206

Applicant: Pierre Fabre Medicament

PRAC Rapporteur: Inês Ribeiro-Vaz

Scope: Evaluation of a PSUSA procedure

16.1.9. Buprenorphine[63] - SIXMO (CAP) – PSUSA/00010778/202205

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

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.10. Cannabidiol[64] - EPIDYOLEX (CAP) – PSUSA/00010798/202206

Applicant: GW Pharma (International) B.V.

[63] Implant(s) only
[64] Centrally authorised product(s) only

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.1.11. Cholera vaccine, oral, live – VAXCHORA (CAP) – PSUSA/00010862/202206

Applicant: Emergent Netherlands B.V.

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

16.1.12. Coronavirus (COVID-19) vaccine (recombinant, adjuvanted) – NUVAXOVID (CAP) – PSUSA/00010972/202206

Applicant: Novavax CZ, a.s.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.13. Delafloxacin – QUOFENIX (CAP) – PSUSA/00010822/202206

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

PRAC Rapporteur: Željana Margan Koletić

Scope: Evaluation of a PSUSA procedure

16.1.14. Efmoroctocog alfa – ELOCTA (CAP) – PSUSA/00010451/202206

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Sonja Hrabcik

Scope: Evaluation of a PSUSA procedure

16.1.15. Elasomeran – SPIKEVAX (CAP) – PSUSA/00010897/202206

Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Evaluation of a PSUSA procedure

16.1.16. Encorafenib – BRAFTOVI (CAP) – PSUSA/00010719/202206

Applicant: Pierre Fabre Medicament

PRAC Rapporteur: Rugile Pilviniene

Scope: Evaluation of a PSUSA procedure

16.1.17. Enfortumab vedotin – PADCEV (CAP) – PSUSA/00010989/202206

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Eva Jirsová

Scope: Evaluation of a PSUSA procedure

16.1.18. Entrectinib – ROZLYTREK (CAP) – PSUSA/00010874/202206

Applicant: Roche Registration GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.19. Fenfluramine – FINTEPLA (CAP) – PSUSA/00010907/202206

Applicant: Zogenix ROI Limited

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.20. Formoterol fumarate dihydrate, glycopyrronium bromide, budesonide – RILTRAVA AEROSPHERE (CAP); TRIXEO AEROSPHERE (CAP) – PSUSA/00010908/202206

Applicant(s): AstraZeneca AB

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.1.21. Galsulfase – NAGLAZYME (CAP) – PSUSA/00001515/202205

Applicant: BioMarin International Limited

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.1.22. Glasdegib – DAURISMO (CAP) – PSUSA/00010859/202205

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.23. Glibenclamide[65] - AMGLIDIA (CAP) – PSUSA/00010690/202205

Applicant: Ammtek

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

[65] Centrally authorised product(s) only

16.1.24. Human papillomavirus vaccine (rDNA[66]) – 4-valent – GARDASIL (CAP) – PSUSA/00001634/202205

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.25. Hydroxycarbamide[67] - SIKLOS (CAP); XROMI (CAP) – PSUSA/00001692/202206

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

PRAC Rapporteur: Jo Robays

Scope: Evaluation of a PSUSA procedure

16.1.26. Imiglucerase – CEREZYME (CAP) – PSUSA/00001727/202205

Applicant: Genzyme Europe BV

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

16.1.27. Inclisiran – LEQVIO (CAP) – PSUSA/00010904/202206

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

16.1.28. Indacaterol, mometasone furoate – ATECTURA BREEZHALER (CAP); BEMRIST BREEZHALER (CAP) – PSUSA/00010850/202205

Applicant(s): Novartis Europharm Limited

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.1.29. Inebilizumab – UPLIZNA (CAP) – PSUSA/00010996/202206

Applicant: Horizon Therapeutics Ireland DAC

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.1.30. Larotrectinib – VITRAKVI (CAP) – PSUSA/00010799/202205

Applicant: Bayer AG

PRAC Rapporteur: Rugile Pilviniene

[66] Ribosomal deoxyribonucleic acid
[67] Centrally authorised product(s) only

Scope: Evaluation of a PSUSA procedure

16.1.31. Latanoprost, netarsudil – ROCLANDA (CAP) – PSUSA/00010905/202206

Applicant: Santen Oy

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.32. Levodopa – INBRIJA (CAP) – PSUSA/00107800/202206

Applicant: Acorda Therapeutics Ireland Limited

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Evaluation of a PSUSA procedure

16.1.33. Lidocaine, prilocaine[68] - FORTACIN (CAP) – PSUSA/00010110/202205

Applicant: Recordati Ireland Ltd

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

16.1.34. Luspatercept – REBLOZYL (CAP) – PSUSA/00010860/202206

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Jo Robays

Scope: Evaluation of a PSUSA procedure

16.1.35. Netarsudil – RHOKIINSA (CAP) – PSUSA/00107812/202206

Applicant: Santen Oy

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

16.1.36. Nirmatrelvir, ritonavir – PAXLOVID (CAP) – PSUSA/00010984/202206

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.37. Nonacog beta pegol – REFIXIA (CAP) – PSUSA/00010608/202205

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Brigitte Keller-Stanislawski

[68] Centrally authorised product(s) only

Scope: Evaluation of a PSUSA procedure

16.1.38. Nusinersen – SPINRAZA (CAP) – PSUSA/00010595/202205

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.39. Obeticholic acid – OCALIVA (CAP) – PSUSA/00010555/202205

Applicant: Advanz Pharma Limited

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

16.1.40. Onasemnogene abeparvovec – ZOLGENSMA (CAP) – PSUSA/00010848/202205

Applicant: Novartis Europharm Limited, ATMP[69]

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.41. Pandemic influenza vaccine (H5N1) (live attenuated, nasal) – PANDEMIC INFLUENZA VACCINE H5N1 ASTRAZENECA (CAP) – PSUSA/00010501/202205

Applicant: AstraZeneca AB

PRAC Rapporteur: Sonja Hrabcik

Scope: Evaluation of a PSUSA procedure

16.1.42. Pertuzumab, trastuzumab – PHESGO (CAP) – PSUSA/00010906/202206

Applicant: Roche Registration GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.43. Pixantrone – PIXUVRI (CAP) – PSUSA/00009261/202205

Applicant: Les Laboratoires Servier

PRAC Rapporteur: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

16.1.44. Pneumococcal polysaccharide conjugate vaccine (20-valent, adsorbed) – APEXXNAR (CAP) – PSUSA/00010981/202206

Applicant: Pfizer Europe MA EEIG

[69] Advanced therapy medicinal product

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

16.1.45. Polatuzumab vedotin – POLIVY (CAP) – PSUSA/00010817/202206

Applicant: Roche Registration GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.46. Roxadustat – EVRENZO (CAP) – PSUSA/00010955/202206

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Anna Mareková

Scope: Evaluation of a PSUSA procedure

16.1.47. Rucaparib – RUBRACA (CAP) – PSUSA/00010694/202206

Applicant: Clovis Oncology Ireland Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.48. Satralizumab – ENSPRYNG (CAP) – PSUSA/00010944/202205

Applicant: Roche Registration GmbH

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.1.49. Setmelanotide – IMCIVREE (CAP) – PSUSA/00010941/202205

Applicant: Rhythm Pharmaceuticals Netherlands B.V.,

PRAC Rapporteur: Anna Mareková

Scope: Evaluation of a PSUSA procedure

16.1.50. Shingles (herpes zoster) vaccine (live) – ZOSTAVAX (CAP) – PSUSA/00009289/202205

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.51. Sofosbuvir, velpatasvir – EPCLUSA (CAP) – PSUSA/00010524/202206

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.1.52. Sonidegib – ODOMZO (CAP) – PSUSA/00010408/202206

Applicant: Sun Pharmaceutical Industries Europe B.V.

PRAC Rapporteur: Željana Margan Koletić

Scope: Evaluation of a PSUSA procedure

16.1.53. Sotorasib – LUMYKRAS (CAP) – PSUSA/00010970/202205

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Evaluation of a PSUSA procedure

16.1.54. Tirbanibulin – KLISYRI (CAP) – PSUSA/00010943/202206

Applicant: Almirall, S.A.

PRAC Rapporteur: Anna Mareková

Scope: Evaluation of a PSUSA procedure

16.1.55. Tralokinumab – ADTRALZA (CAP) – PSUSA/00010937/202206

Applicant: LEO Pharma A/S

PRAC Rapporteur: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

16.1.56. Trametinib – MEKINIST (CAP) – PSUSA/00010262/202205

Applicant: Novartis Europharm Limited

PRAC Rapporteur: David Olsen

Scope: Evaluation of a PSUSA procedure

16.1.57. Trastuzumab deruxtecan – ENHERTU (CAP) – PSUSA/00010894/202206

Applicant: Daiichi Sankyo Europe GmbH

PRAC Rapporteur: Inês Ribeiro-Vaz

Scope: Evaluation of a PSUSA procedure

16.1.58. Treosulfan[70] - TRECONDI (CAP) – PSUSA/00010777/202206

Applicant: medac Gesellschaft fur klinische Spezialpraparate mbH

PRAC Rapporteur: Julia Pallos

[70] Centrally authorised product(s) only

Scope: Evaluation of a PSUSA procedure

16.1.59. Turoctocog alfa pegol – ESPEROCT (CAP) – PSUSA/00010782/202206

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

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

16.2.1. Dasatinib – SPRYCEL (CAP); NAP – PSUSA/00000935/202206

Applicants: Bristol-Myers Squibb Pharma EEIG (Sprycel), various

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Evaluation of a PSUSA procedure

16.2.2. Naloxone[71] - NYXOID (CAP); NAP – PSUSA/00010657/202205

Applicants: Mundipharma Corporation (Ireland) Limited (Nyxoid), various

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

16.2.3. Nepafenac – NEVANAC (CAP); NAP – PSUSA/00002143/202205

Applicants: Novartis Europharm Limited (Nevanac), various

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

16.2.4. Treprostinil – TREPULMIX (CAP); NAP – PSUSA/00003013/202205

Applicants: SciPharm Sarl (Trepulmix), various

PRAC Rapporteur: Zane Neikena

Scope: Evaluation of a PSUSA procedure

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

16.3.1. Alteplase (NAP) – PSUSA/00000112/202205

Applicant(s): various

PRAC Lead: Martin Huber

[71] For use in non-medical setting(s) only

Scope: Evaluation of a PSUSA procedure

16.3.2. Betaxolol (NAP) – PSUSA/00000401/202205

Applicant(s): various

PRAC Lead: Melinda Palfi

Scope: Evaluation of a PSUSA procedure

16.3.3. Calcifediol (NAP) – PSUSA/00000491/202206

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.3.4. Eprosartan (NAP) – PSUSA/00001243/202204

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.3.5. Eprosartan, hydrochlorothiazide (NAP) – PSUSA/00001244/202204

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.3.6. Fusidic acid[72] (NAP) – PSUSA/00010226/202205

Applicant(s): various

PRAC Lead: Melinda Palfi

Scope: Evaluation of a PSUSA procedure

16.3.7. Lanreotide (NAP) – PSUSA/00001826/202205

Applicant(s): various

PRAC Lead: Zane Neikena

Scope: Evaluation of a PSUSA procedure

16.3.8. Latanoprost, timolol (NAP) – PSUSA/00001833/202206

Applicant(s): various

PRAC Lead: Ulla Wändel Liminga

[72] Systemic use

Scope: Evaluation of a PSUSA procedure

16.3.9. Levonorgestrel[73] (NAP) – PSUSA/00010827/202205

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.3.10. Levofloxacin, dexamethasone[74] (NAP) – PSUSA/00010881/202206

Applicant(s): various

PRAC Lead: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.3.11. Macrogol 3350 (NAP) – PSUSA/00001924/202205

Applicant(s): various

PRAC Lead: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.3.12. Macrogol 4000, macrogol 4000 combinations[75] (NAP) – PSUSA/00010392/202205

Applicant(s): various

PRAC Lead: Nathalie Gault

Scope: Evaluation of a PSUSA procedure

16.3.13. Nicardipine (NAP) – PSUSA/00002149/202205

Applicant(s): various

PRAC Lead: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.3.14. Olsalazine (NAP) – PSUSA/00002213/202205

Applicant(s): various

PRAC Lead: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

16.3.15. Piracetam (NAP) – PSUSA/00002429/202204

Applicant(s): various

[73] For emergency contraception only
[74] Ocular use
[75] Oral use

PRAC Lead: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

16.3.16. Procyanidolic oligomers (NAP) – PSUSA/00002537/202205

Applicant(s): various

PRAC Lead: Melinda Palfi

Scope: Evaluation of a PSUSA procedure

16.3.17. Risperidone (NAP) – PSUSA/00002649/202205

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.3.18. Sodium tetradecyl sulphate (NAP) – PSUSA/00002767/202204

Applicant(s): various

PRAC Lead: Ronan Grimes

Scope: Evaluation of a PSUSA procedure

16.3.19. Tirofiban (NAP) – PSUSA/00002974/202205

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.3.20. Valsartan (NAP), hydrochlorothiazide, valsartan (NAP) – PSUSA/00010396/202204

Applicant(s): various

PRAC Lead: Mari Thorn

Scope: Evaluation of a PSUSA procedure

16.4. Follow-up to PSUR/PSUSA procedures

16.4.1. Fentanyl – INSTANYL (CAP) – EMEA/H/C/000959/LEG 028.6

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Tiphaine Vaillant

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

16.5. Variation procedure(s) resulting from PSUSA evaluation

16.5.1. Baricitinib – OLUMIANT (CAP) – EMEA/H/C/004085/II/0031

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Adam Przybylkowski

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

16.5.2. Erlotinib – TARCEVA (CAP) – EMEA/H/C/000618/II/0071

Applicant: Roche Registration GmbH

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Update of section 4.8 of the SmPC in order to provide a single table listing all ADRs following PSUSA/00001255/202111. The package leaflet is updated accordingly

16.5.3. Nirmatrelvir, ritonavir – PAXLOVID (CAP) – EMEA/H/C/005973/II/0032

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Martin Huber

Scope: Update of section 4.8 of the SmPC in order to add 'hypertension' to the list of adverse drug reactions (ADRs) with frequency 'uncommon', following procedure EMEA/H/C/005973/LEG 006 (LEG assessed by PRAC), based on review of aggregated post-marketing data. The package leaflet is updated accordingly

16.6. Expedited summary safety reviews[76]

16.6.1. Coronavirus (COVID-19) vaccine (inactivated, adjuvanted, adsorbed) – COVID-19 VACCINE (INACTIVATED, ADJUVANTED) VALNEVA (CAP) – EMEA/H/C/006019/MEA 009.4

Applicant: Valneva Austria GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

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

[76] 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

16.6.2. Coronavirus (COVID-19) vaccine (recombinant, adjuvanted) – NUVAXOVID (CAP) – EMEA/H/C/005808/MEA 014.7

Applicant: Novavax CZ, a.s.

PRAC Rapporteur: Brigitte Keller-Stanislawski

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

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

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

17.1. Protocols of PASS imposed in the marketing authorisation(s)[77]

17.1.1. Buprenorphine – SIXMO (CAP) – EMEA/H/C/PSA/S/0097

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

PRAC Rapporteur: Adam Przybylkowski

Scope: Substantial amendment to a protocol for a prospective, observational (non-interventional), post-authorisation safety cohort study to evaluate the incidence of the breakages and insertion/removal complications of buprenorphine implants (Sixmo) in routine clinical care

17.1.2. Blinatumomab – BLINCYTO (CAP) – EMEA/H/C/PSA/S/0101

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Eva Jirsová

Scope: Substantial amendment to a protocol for an observational study of blinatumomab safety and effectiveness, utilisation, and treatment practices

17.1.3. Ciltacabtagene autoleucel – CARVYKTI (CAP) – EMEA/H/C/PSP/S/0099.1

Applicant: Janssen-Cilag International NV, ATMP[78]

PRAC Rapporteur: Jo Robays

Scope: MAH's response to PSP/0099 [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 characterize and understand the long-term safety profile of cilta-cel] as per the request to supplementary information (RSI) adopted in September 2022

[77] In accordance with Article 107n of Directive 2001/83/EC
[78] Advanced therapy medicinal product

17.1.4. Evinacumab – EVKEEZA (CAP) – EMEA/H/C/PSA/S/0098

Applicant: Regeneron Ireland DAC

PRAC Rapporteur: Mari Thorn

Scope: Substantial amendment to a protocol for an evaluation of the long-term effects of evinacumab treatment in patients with homozygous familial hypercholesterolemia (HoFH): safety outcomes in patients with HoFH who are ⩾12 years old, frequency and outcomes of pregnancy in female patients with HoFH, atherosclerosis process over time in patients with HoFH who undergo cardiovascular imaging (as data allow), frequency of cardiovascular imaging of patients with HoFH

17.1.5. Methylphenidate hydrochloride (NAP) – EMEA/H/N/PSA/S/0074.2

Applicant: MEDICE Arzneimittel Pütter GmbH & Co. KG

PRAC Rapporteur: Martin Huber

Scope: MAH's response to PSA/S/0074.1 [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]

17.1.6. Tisagenlecleucel – KYMRIAH (CAP) – EMEA/H/C/PSA/S/0099

Applicant: Novartis Europharm Limited, ATMP[79]

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Substantial amendment #05 to a protocol for a registry study to assess the long-term safety of patients with B lymphocyte malignancies treated with tisagenlecleucel

17.1.7. Tisagenlecleucel – KYMRIAH (CAP) – EMEA/H/C/PSA/S/0100

Applicant: Novartis Europharm Limited, ATMP[80]

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Substantial amendment #06 to a protocol for a registry study to assess the long-term safety of patients with B lymphocyte malignancies treated with tisagenlecleucelProtocols of PASS non-imposed in the marketing authorisation(s)[81]

17.2. Protocols of PASS non-imposed in the marketing authorisation(s)[82]

17.2.1. Avalglucosidase alfa – NEXVIADYME (CAP) – EMEA/H/C/005501/MEA 007

Applicant: Genzyme Europe BV

[79] Advanced therapy medicinal product
[80] Advanced therapy medicinal product
[81] 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
[82] 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

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Protocol for study OBS17445 (listed as category 3 study in the RMP): a PASS to assess long term safety in patients with Pompe disease treated with avalglucosidase alfa in the commercial setting

17.2.2. Beclometasone, formoterol, glycopyrronium bromide – TRIMBOW (CAP) – EMEA/H/C/004257/MEA 002.3

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Jan Neuhauser

Scope: Amendment to a previously agreed protocol for study CLI-05993BA1-05 (TRIBE) (listed as category 3 study in the RMP): 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)

17.2.3. Coronavirus (COVID-19) vaccine (ChAdOx1-S [recombinant]) – VAXZEVRIA (CAP) – EMEA/H/C/005675/MEA 007.7

Applicant: AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

Scope: Amendment to a previously agreed protocol (version 4) for study D8111R00006 (listed as category 3 study in the RMP): A post-authorisation/post-marketing observational study using existing secondary health data sources to evaluate the association between exposure to AZD1222 and safety concerns

17.2.4. Coronavirus (COVID-19) vaccine (ChAdOx1-S [recombinant]) – VAXZEVRIA (CAP) – EMEA/H/C/005675/MEA 008.1

Applicant: AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

Scope: Protocol for a systematic literature review for studies evaluating adverse events of Vaxzevria (AZD1222) in patients taking immunosuppressant medications and/or with primary immunodeficiency

17.2.5. Coronavirus (COVID-19) vaccine (recombinant, adjuvanted) – NUVAXOVID (CAP) – EMEA/H/C/005808/MEA 004.2

Applicant: Novavax CZ, a.s.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: MAH's response to MEA 004.1 [protocol for study 2019nCoV-402: UK Post-Authorisation Safety Study Using the Clinical Practice Research Datalink (CPRD): A surveillance study to characterize the safety profile of Nuvaxovid in adults aged 18 years and older in the real-world setting using the UK CPRD] as per request for supplementary information (RSI) adopted in November 2022

17.2.6. Dulaglutide – TRULICITY (CAP) – EMEA/H/C/002825/MEA 006.5

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Amelia Cupelli

Scope: Amendment to a previously agreed protocol for study H9X-MC-B013 (listed as category 3 study in the RMP): a non-interventional retrospective study to estimate the incidence rates of events of interest among type 2 diabetes mellitus (T2DM) patients treated with dulaglutide compared to other glucagon-like peptide 1 (GLP-1) receptor agonists in order to better characterise the safety profile of dulaglutide in terms of acute pancreatitis, pancreatic and thyroid malignancies

17.2.7. Elasomeran – SPIKEVAX (CAP) – EMEA/H/C/005791/MEA 072

Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Protocol for study mRNA-1273-P919 (listed as category 3 study in the RMP): an observational study to assess maternal and infant outcomes following exposure to Spikevax during pregnancy and to assess whether the rate of pregnancy complications, adverse pregnancy outcomes, or adverse neonatal outcomes is associated with prenatal exposure to Spikevax

17.2.8. Elasomeran – SPIKEVAX (CAP) – EMEA/H/C/005791/MEA 034.5

Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: MAH's response to MEA 034.4 [protocol for study mRNA-1273-P905 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 September 2022 together with a revised protocol (v 1.2) and the second interim report

17.2.9. Fenfluramine – FINTEPLA (CAP) – EMEA/H/C/003933/MEA 005.4

Applicant: Zogenix ROI Limited

PRAC Rapporteur: Martin Huber

Scope: MAH's response to MEA 005.3 [Protocol for study ZX008-2102: a drug utilisation study (DUS) in Europe to describe fenfluramine use in routine clinical practice] as per the request for supplementary information (RSI) adopted in September 2022

17.2.10. Galcanezumab – EMGALITY (CAP) – EMEA/H/C/004648/MEA 004.1

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Kirsti Villikka

Scope: Amendment to a previously agreed protocol for study I5Q-MC-B001: galcanezumab US drug utilisation and safety outcomes study to describe, in real-world clinical practice, the

utilisation of galcanezumab in the US, and the incidence of important safety outcomes such as serious hypersensitivity and long-term safety including serious cardiovascular events, and malignancies

17.2.11. Risankizumab – SKYRIZI (CAP) – EMEA/H/C/004759/MEA 001.6

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Amendment to a previously agreed protocol (v.1.6) for study P19-633: a post-marketing registry-based prospective cohort study of long-term safety of risankizumab in real world setting in Denmark and Sweden

17.2.12. Tixagevimab, cilgavimab – EVUSHELD (CAP) – EMEA/H/C/005788/MEA 012

Applicant: AstraZeneca AB

PRAC Rapporteur: Kimmo Jaakkola

Scope: Protocol for study D8850R00006: a Non-interventional Multi-country Cohort Study to Assess the Safety of EVUSHELD (Tixagevimab/Cilgavimab) During Pregnancy

17.2.13. Ustekinumab – STELARA (CAP) – EMEA/H/C/000958/MEA 053.2

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: MAH's response to MEA 053.1 [protocol for study CNTO1275PSO4005: a Nordic database initiative for exposure to ustekinumab – a review and analysis of major adverse cardiovascular events (MACE) from the Swedish and Danish national registry systems] as per the request for supplementary information (RSI) adopted in October 2022

17.2.14. Ustekinumab – STELARA (CAP) – EMEA/H/C/000958/MEA 054.2

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: MAH's response to MEA 054.1 [protocol for study PCSIMM004697: An Observational Longitudinal PASS of STELARA in the Treatment of Psoriasis and Psoriatic Arthritis: Analysis of Major Adverse Cardiovascular Events (MACE) using Swedish National Health Registers] as per the request for supplementary information (RSI) adopted in October 2022

17.3. Results of PASS imposed in the marketing authorisation(s)[83]

None

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

17.4. Results of PASS non-imposed in the marketing authorisation(s)[84]

17.4.1. 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

17.4.2. Siltuximab – SYLVANT (CAP) – EMEA/H/C/003708/II/0038, Orphan

Applicant: EUSA Pharma (Netherlands) B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

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

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

17.5.1. Benralizumab – FASENRA (CAP) – EMEA/H/C/004433/MEA 004.6

Applicant: AstraZeneca AB

PRAC Rapporteur: David Olsen

Scope: Second interim report for study D3250R00042: a descriptive study of the incidence of malignancy in patients with severe asthma overall and among those receiving benralizumab and other therapies in real-world settings

17.5.2. Cabazitaxel – CABAZITAXEL ACCORD (CAP) – EMEA/H/C/005178/MEA 001.3

Applicant: Accord Healthcare S.L.U.

PRAC Rapporteur: Tiphaine Vaillant

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

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

17.5.3. Damoctocog alfa pegol – JIVI (CAP) – EMEA/H/C/004054/ANX 001.1

Applicant: Bayer AG

PRAC Rapporteur: Menno van der Elst

Scope: First interim report for study 20904 (HA-SAFE): an observational study evaluating long-term safety of real-world treatment with damoctocog alfa pegol in previously treated patients with hemophilia A' (HA-SAFE). The HA-SAFE study is a post-authorisation measure defined in Annex II.D of the Jivi EU product information. The study protocol was agreed with EMA/PRAC in Nov 2019 (outcome letter); the date of FPFV was 14 May 2021 (impacted by the Covid-19 pandemic). As Annex to the first interim report also the statistical analysis plan is submitted

17.5.4. Elasomeran – SPIKEVAX (CAP) – EMEA/H/C/005791/MEA 004.8

Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Third interim report 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 and submission of MAH's response to MEA 004.6 as per request for supplementary information (RSI) adopted in September 2022

17.5.5. Etanercept – NEPEXTO (CAP) – EMEA/H/C/004711/MEA 001.1

Applicant: Mylan IRE Healthcare Limited

PRAC Rapporteur: Monica Martinez Redondo

Scope: First interim report for a prospective, observational study using the German Biologics Register – Rheumatoid Arthritis (RABBIT): 1) to assess the long-term safety of etanercept in RA patients and 2) to describe the long-term effectiveness and response to treatment in patients using Nepexto in a real-life environment (listed as Category 3 study in the RMP)

17.5.6. Ketoconazole – KETOCONAZOLE HRA (CAP) – EMEA/H/C/003906/ANX 002.9

Applicant: HRA Pharma Rare Diseases

PRAC Rapporteur: Željana Margan Koletić

Scope: Fifth interim annual report for a prospective, multi-country, observational registry study to collect clinical information on patients with endogenous Cushing's syndrome exposed to ketoconazole using the existing European registry on Cushing's syndrome (ERCUSYN) to assess drug utilisation pattern and to document the safety (e.g. hepatotoxicity, QT prolongation) and effectiveness of ketoconazole

17.5.7. Natalizumab – TYSABRI (CAP) – EMEA/H/C/000603/MEA 064.3

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Sixth interim report for study 101MS411 (listed as a category 3 study in the RMP): an observational cohort study utilising the Tysabri outreach unified commitment to health (TOUCH) prescribing programme and certain EU multiple sclerosis (MS) registries to estimate the risk of progressive multifocal leukoencephalopathy (PML) and other serious opportunistic infections among patients who were exposed to an MS disease modifying therapies prior to treatment with Tysabri (natalizumab)

17.5.8. Natalizumab – TYSABRI (CAP) – EMEA/H/C/000603/MEA 066.4

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Annual report of a retrospective analysis of extended interval dosing (EID) versus standard interval dosing (SID) to further investigate the efficacy and safety in terms of progressive multifocal leukoencephalopathy (PML) risk reduction with EID relative to SID (TOUCH database)

17.5.9. Natalizumab – TYSABRI (CAP) – EMEA/H/C/000603/MEA 067.1

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Annual progress report for study: IMA-06-02: an open label, multinational, multi-center, prospective, observational study. Amendment is primarily to extend patient follow up from 10 to 15 years

17.5.10. Patisiran – ONPATTRO (CAP) – EMEA/H/C/004699/MEA 003.4

Applicant: Alnylam Netherlands B.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: Second interim report for study ALN-TTR02-010: patisiran- lipid nanoparticle (LNP) pregnancy surveillance programme (PSP) to collect primary data on pregnant women from the US, the United Kingdom (UK), France, Spain, Italy, Portugal and Germany, and other potential countries, who have been exposed to patisiran during the exposure window, defined as 12 weeks prior to their last menstrual period (LMP), or at any time during pregnancy as well as to collect and analyse information pertaining to pregnancy complications and birth outcomes in women exposed to patisiran during pregnancy

17.5.11. Semaglutide – OZEMPIC (CAP) – EMEA/H/C/004174/MEA 002.5

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Mari Thorn

Scope: Third study progress report for study NN9535-4447: an epidemiological database

study to estimate the risk of pancreatic cancer in patients with type 2 diabetes mellitus (T2DM) taking semaglutide – a cohort study based on Nordic registry data

17.5.12. Semaglutide – RYBELSUS (CAP) – EMEA/H/C/004953/MEA 002.3

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Mari Thorn

Scope: Third study progress report for study NN9535-4447: an epidemiological database study to estimate the risk of pancreatic cancer in patients with type 2 diabetes mellitus (T2DM) taking semaglutide – a cohort study based on Nordic registry data

17.5.13. Tozinameran – COMIRNATY (CAP) – EMEA/H/C/005735/MEA 017.5

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Second interim report for study C4591021 (former ACCESS/VAC4EU): an assessment of potential increased risk of adverse events of special interest (AESI), including myocarditis/pericarditis after being vaccinated with COVID-19 messenger ribonucleic acid (mRNA) vaccine estimating the time trend, in relation to DHPC letter dissemination, of the proportion of individuals who received real-world clinical assessments for myocarditis/pericarditis following Comirnaty (tozinameran) vaccination

17.5.14. Ustekinumab – STELARA (CAP) – EMEA/H/C/000958/MEA 045.10

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: MAH's response to MEA 045.9 [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] as per the request for supplementary information (RSI) adopted in September 2022

17.6. Others

17.6.1. Avapritinib – AYVAKYT (CAP) – EMEA/H/C/005208/SOB 008.1

Applicant: Blueprint Medicines (Netherlands) B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Submission of statistical analysis plan for study 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 for Ayvakyt (avapritinib)

17.6.2. Avatrombopag – DOPTELET (CAP) – EMEA/H/C/004722/MEA 002.5

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Monica Martinez Redondo

Scope: MAH's response to MEA 002.4 [feasibility assessment for study AVA-CLD-402: evaluation of the feasibility of conducting a PASS of Doptelet (avatrombopag) in patients with severe chronic liver disease (CLD) and of the use of potential European electronic health care databases] as per the request for supplementary information (RSI) adopted in May 2022

17.6.3. Dimethyl fumarate – TECFIDERA (CAP) – EMEA/H/C/002601/MEA 007.6

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Martin Huber

Scope: Submission of a clarification regarding the closure of the ESTEEM study 109MS401 (A Multicentre, Global, Observational Study to Collect Information on Safety and to Document the Drug Utilisation of BG00012 When Used in Routine Medical Practice in the Treatment of Relapsing Multiple Sclerosis). ESTEEM is a Category 3 PASS listed in the Risk Management Plan with a commitment to provide a yearly update. The MAH also submitted a clarification regarding the status of study 109MS401, together with a justification for proceeding with the closure of the study in October 2022, as previously agreed with the PRAC

17.6.4. Tozinameran – COMIRNATY (CAP) – EMEA/H/C/005735/MEA 011.7

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Response to Comirnaty BA.1 and BA.4.5 bivalent vaccine protocol amendments (following variation procedures II/0140 and II/0143): containing a combined justification not to amend the following post-authorisation safety studies (PASS): C4591010, C4591009, C4591021, and C4591022 regarding Omicron BA.1 and Omicron BA.4-5

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

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

18.1. Annual reassessments of the marketing authorisation

18.1.1. Metreleptin – MYALEPTA (CAP) – EMEA/H/C/004218/S/0030 (without RMP)

Applicant: Amryt Pharmaceuticals DAC

PRAC Rapporteur: Adam Przybylkowski

Scope: Annual reassessment of the marketing authorisation

18.2. Conditional renewals of the marketing authorisation

18.2.1. Andexanet alfa – ONDEXXYA (CAP) – EMEA/H/C/004108/R/0034 (without RMP)

Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: Conditional renewal of the marketing authorisation

18.2.2. Ciltacabtagene autoleucel – CARVYKTI (CAP) – EMEA/H/C/005095/R/0008 (with RMP)

Applicant: Janssen-Cilag International NV, ATMP[85]

PRAC Rapporteur: Jo Robays

Scope: Conditional renewal of the marketing authorisation

18.2.3. Delamanid – DELTYBA (CAP) – EMEA/H/C/002552/R/0062 (without RMP)

Applicant: Otsuka Novel Products GmbH

PRAC Rapporteur: Jo Robays

Scope: Conditional renewal of the marketing authorisation

18.2.4. Lorlatinib – LORVIQUA (CAP) – EMEA/H/C/004646/R/0025 (without RMP)

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Conditional renewal of the marketing authorisation

18.2.5. Pandemic influenza vaccine (h5n1) (live attenuated, nasal) – PANDEMIC INFLUENZA VACCINE H5N1 ASTRAZENECA (CAP) – EMEA/H/C/003963/R/0057 (without RMP)

Applicant: AstraZeneca AB

PRAC Rapporteur: Sonja Hrabcik

Scope: Conditional renewal of the marketing authorisation

18.2.6. Volanesorsen – WAYLIVRA (CAP) – EMEA/H/C/004538/R/0022 (without RMP)

Applicant: Akcea Therapeutics Ireland Limited

PRAC Rapporteur: Martin Huber

[85] Advanced therapy medicinal product

Scope: Conditional renewal of the marketing authorisation

18.3. Renewals of the marketing authorisation

18.3.1. Blinatumomab – BLINCYTO (CAP) – EMEA/H/C/003731/R/0048 (with RMP)

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Eva Jirsová

Scope: 5-year renewal of the marketing autorisation

18.3.2. Brexpiprazole - RXULTI (CAP) - EMEA/H/C/003841/R/0014 (with RMP)

Applicant: Otsuka Pharmaceutical Netherlands B.V.

PRAC Rapporteur: Lucia Kuráková

Scope: 5-year renewal of the marketing authorisation–

18.3.3. Carmustine - CARMUSTINE OBVIUS (CAP) - EMEA/H/C/004326/R/0009 (with RMP)

Applicant: Obvius Investment B.V

PRAC Rapporteur: Jan Neuhauser

Scope: 5-year renewal of the marketing authorisation

18.3.4. Ciclosporin - VERKAZIA (CAP) - EMEA/H/C/004411/R/0021 (with RMP)

Applicant: Santen Oy

PR AC Rapporteur: Jan Neuhauser

Scope: 5-year renewal of the marketing authorisation

18.3.5. Inotersen - T–GSEDI (CAP) - EMEA/H/C/004782/R/0035 (without RMP)

Applicant: Akcea Therapeutics Ireland Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: 5-year renewal of the marketing authorisation

18.3.6. Lipegfilgrastim - LONQUEX (CAP) - EMEA/H/C/002556/R/0077 (without RMP)

Applicant: Teva B.V.

PRAC Rapporteur: Kirsti Villikka

Scope: 5-year renewal of the marketing authorisation

18.3.7. Lomitapide - LOJUXTA (CAP) - EMEA/H/C/002578/R/0054 (without RMP)

Applicant: Amryt Pharmaceuticals DAC

PRAC Rapporteur: Menno van der Elst

18.3.8. Scope: 5-year renewal of the marketing authorisation Metreleptin - MYALEPTA (CAP) - EMEA/H/C/004218/R/0031 (without RMP)

Applicant: Amryt Pharmaceuticals DAC

PRAC Rapporteur: Adam Przybylkowski

Scope: 5-year renewal of the marketing authorisation

18.3.9. Neratinib - NERLYNX (CAP) - EMEA/H/C/004030/R/0031 (with RMP)

Applicant: Pierre Fabre Medicament

PRAC Rapporteur: Menno van der Elst

Scope: 5-year renewal of the marketing authorisation

18.3.10. Nitisinone - NITYR (CAP) - EMEA/H/C/004582/R/0015 (with RMP)

Applicant: Cycle Pharmaceuticals (Europe) Limited

PRAC Rapporteur: Amelia Cupelli

Scope: 5-year renewal of the marketing authorisation

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

Applicant: Mylan Pharmaceuticals Limited

PRAC Rapporteur: Anette Kirstine Stark

Scope: 5-year renewal of the marketing authorisation

18.3.12. Sufentanil - DZUVEO (CAP) - EMEA/H/C/004335/R/0009 (with RMP)

Applicant: Laboratoire Aguettant

PRAC Rapporteur: Adam Przybylkowski

Scope: 5-year renewal of the marketing authorisation

18.3.13. Trastuzumab - TRAZIMERA (CAP) - EMEA/H/C/004463/R/0020 (without RMP)

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: 5-year renewal of the marketing authorisation

19. Annex II – List of participants

including any restrictions with respect to involvement of members / alternates / experts following evaluation of declared interests for the 09-12 January 2023 meeting. Participants marked with "a" attended the plenary session while those marked with "b" attended ORGAM.

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

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
	(Vice-Chair)		declared	
Brigitte Keller-Stanislawski [a,b]	Alternate	Germany	No interests declared	
Sophia Trantza [a,b]	Member	Greece	No interests declared	
Georgia Gkegka [a,b]	Alternate	Greece	No interests declared	
Julia Pallos [a,b]	Member	Hungary	No participation in final deliberations and voting on:	5.3.4. Ozanimod - ZEPOSIA (CAP) - EMEA/H/C/004835/II/0016 15.3.17. Luspatercept - REBLOZYL (CAP) - EMEA/H/C/004444/II/0009, Orphan 16.1.34 Luspatercept - REBLOZYL (CAP) - PSUSA/00010860/202206 16.2.1. Dasatinib - SPRYCEL (CAP); NAP - PSUSA/00000935/202206
Melinda Palfi [a]	Alternate	Hungary	No interests declared	
Guðrún Stefánsdóttir [a,b]	Member	Iceland	No participation in final deliberations and voting on:	15.2.11. Talimogene laherparepvec - IMLYGIC (CAP) - EMEA/H/C/002771/II/0059 16.1.53. Sotorasib - LUMYKRAS (CAP) - PSUSA/00010970/202205 17.1.2. Blinatumomab -

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				BLINCYTO (CAP) - EMEA/H/C/PSA/S/0101 18.3.1. Blinatumomab - BLINCYTO (CAP) - EMEA/H/C/003731/R/0048 (with RMP)
Ronan Grimes [a,b]	Alternate	Ireland	No interests declared	
Amelia Cupelli [a]	Member	Italy	No interests declared	
Valentina Di Giovanni [a,b]	Alternate	Italy	No interests declared	
Zane Neikena [a,b]	Member	Latvia	No interests declared	
Lina Seibokiene [a]	Alternate	Lithuania	No restrictions applicable to this meeting	
Nadine Petitpain [a,b]	Member	Luxembourg	No restrictions applicable to this meeting	
John Joseph Borg [a]	Member (CHMP member)	Malta	No interests declared	
Menno van der Elst [a,b]	Member	Netherlands	No interests declared	
Liana Gross-Martirosya [a,b]	Alternate	Netherlands	No interests declared	
David Olsen [a,b]	Member	Norway	No participation in final deliberations and voting on:	4.3.3. Regorafenib - STIVARGA (CAP) - EMEA/H/C/002573/SDA/013 7.4.1. Regorafenib - STIVARGA (CAP) - EMEA/H/C/002573/II/0039

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				15.3.9. Darolutamide - NUBEQA (CAP) - EMEA/H/C/004790/II/0009 15.3.10. Darolutamide - NUBEQA (CAP) - EMEA/H/C/004790/II/0012 16.1.30. Larotrectinib - VITRAKVI (CAP) - PSUSA/00010799/202205 17.5.3. Damoctocog alfa pegol - JIVI (CAP) - EMEA/H/C/004054/ANX 001.1
Karen Pernille Harg [a,b]	Alternate	Norway	No interests declared	
Katarzyna Ziolkowska [a]	Alternate	Poland	No interests declared	
Ana Diniz Martins [a,b]	Member	Portugal	No interests declared	
Ines Ribeiro-Vaz [a]	Alternate	Portugal	No interests declared	
Roxana Dondera [a]	Member	Romania	No interests declared	
Alexandra - Maria Spurni [a]	Alternate	Romania	No interests declared	
Anna Mareková [a,b]	Member	Slovakia	No interests declared	
Lucia Kuráková [a,b]	Alternate	Slovakia	No interests declared	
Polona Golmajer [a,b]	Member	Slovenia	No interests declared	
Maria del Pilar Rayon [a,b]	Member	Spain	No interests declared	
Monica Martinez Redondo [a,b]	Alternate	Spain	No interests declared	
Ulla Wändel Liminga [a,b]	Member	Sweden	No interests	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			declared	
Mari Thorn [a,b]	Alternate	Sweden	No interests declared	
Annalisa Capuano [a]	Member	Independent scientific expert	No interests declared	
Milou Daniel Drici [a,b]	Member	Independent scientific expert	No interests declared	
Maria Teresa Herdeiro [a,b]	Member	Independent scientific expert	No interests declared	
Patricia McGettigan [a]	Member	Independent scientific expert	No interests declared	
Hedvig Nordeng [a]	Member	Independent scientific expert	No interests declared	
Roberto Frontini [a]	Member	Healthcare Professionals' Representative	No restrictions applicable to this meeting	
Salvatore Messana [a]	Alternate	Healthcare Professionals' Representative	No interests declared	
Declan Noone [a]	Member	Patients' Organisation Representative	No interests declared	
Marko Korenjak [a]	Alternate	Patients' Organisation Representative	No participation in discussion, final deliberations and voting on:	15.2.10. Somatropin - NUTROPINAQ (CAP) - EMEA/H/C/000315/II/0077 16.3.7. Lanreotide (NAP) - PSUSA/00001826/202205 16.3.12. Macrogol 4000, macrogol 4000 combinations (NAP) - PSUSA/00010392/202205
Christelle Bizimungu [a]	Expert	Belgium	No restrictions applicable to this meeting	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Martine Sabbe [a]	Expert	Belgium	No interests declared	
Françoise Wuillaume [a]	Expert	Belgium	No interests declared	
Melita Dumančić [a]	Expert	Croatia	No restrictions applicable to this meeting	
Ivana Ljubičić [a]	Expert	Croatia	No interests declared	
Petar Mas [a]	Expert	Croatia	No interests declared	
Anna Kroupová [a]	Expert	Czechia	No interests declared	
Petra Vackova [a]	Expert	Czechia	No interests declared	
Hanna Belcik Christensen [a]	Expert	Denmark	No restrictions applicable to this meeting	
Alexander Braathen [a]	Expert	Denmark	No interests declared	
Karin Erneholm [a]	Expert	Denmark	No restrictions applicable to this meeting	
Marianne Hald Clemmensen [a]	Expert	Denmark	No restrictions applicable to this meeting	
Marian Hjortlund Allon [a]	Expert	Denmark	No interests declared	
Line Michan [a]	Expert	Denmark	No interests declared	
Aynur Sert [a]	Expert	Denmark	No interests declared	
Emma Stadsbjerg [a]	Expert	Denmark	No interests declared	
Caroline Marie Voss [b]	Expert	Denmark	No interests declared	
Julia Maslovskaja [a]	Expert	Estonia	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Helve Vestman [a]	Expert	Estonia	No interests declared	
Samuel Crommelynck [a]	Expert	France	No interests declared	
Pauline Dayani [a]	Expert	France	No interests declared	
Vincent Gazin [a]	Expert	France	No interests declared	
Valérie Gras-Champel [a]	Expert	France	No interests declared	
Marie-Caroline Pesquidous [a]	Expert	France	No restrictions applicable to this meeting	
Jean-Michel Race [a]	Expert	France	No interests declared	
Laure Tiquet [a]	Expert	France	No interests declared	
Jelena Katic [a]	Expert	Germany	No interests declared	
Anne Kleinau [a]	Expert	Germany	No interests declared	
Dennis Lex [a,b]	Expert	Germany	No interests declared	
Tania Meier [a]	Expert	Germany	No interests declared	
Aine McKenna [a]	Expert	Ireland	No interests declared	
Eamon O'Murchu [a,b]	Expert	Ireland	No interests declared	
David O'Riordan [a]	Expert	Ireland	No interests declared	
Marcia Silva [a]	Expert	Portugal	No interests declared	
Carla Torre [a]	Expert	Portugal	No interests declared	
Eva Cantarero [a]	Expert	Spain	No interests declared	
Carmen Gallego [a]	Expert	Spain	No interests declared	
María Martínez [a]	Expert	Spain	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Consuelo Mejías [a]	Expert	Spain	No interests declared	
Charlotte Backman [a,b]	Expert	Sweden	No interests declared	
Kristin Karlsson [a]	Expert	Sweden	No restrictions applicable to this meeting	
Kristina Magnusson Lundqvist [a]	Expert	Sweden	No interests declared	
Sofia Persson [a]	Expert	Sweden	No interests declared	
Carla Herberts [a]	Expert	The Netherlands	No interests declared	
Jaap Fransen [a]	Expert	The Netherlands	No interests declared	
Gerlienke Geurts-Voerman [a]	Expert	The Netherlands	No interests declared	
Marianne Klanker [a]	Expert	The Netherlands	No interests declared	
Paul ten Berg [a]	Expert	The Netherlands	No interests declared	
Meeting run with support from relevant EMA staff				

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

20. Annex III - List of acronyms and abbreviations

For a list of acronyms and abbreviations used in the PRAC minutes, see:
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/enhttps://www.ema.europa.eu/en