EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

31 March 2023
EMA/PRAC/145325/2023
Human Medicines Division

Pharmacovigilance Risk Assessment Committee (PRAC)

Minutes of the meeting on 04-07 July 2022

Chair: Sabine Straus – Vice-Chair: Martin Huber

Health and safety information

In accordance with the Agency's health and safety policy, delegates were briefed on health, safety and emergency information and procedures prior to the start of the meeting.

Disclaimers

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

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

Note on access to documents

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

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1. Introduction

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

The Chairperson opened the meeting by welcoming all participants. Due to the current coronavirus (COVID-19) pandemic, and the associated EMA Business Continuity Plan (BCP), the meeting was held in-person with some members connected remotely (hybrid setting).

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

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

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

The Chair announced the start of the Czech Republic presidency of the Council of the European Union (EU).

1.2. Agenda of the meeting on 04-07 July 2022

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

1.3. Minutes of the previous meeting on 07-10 June 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 07-10 June 2022 will be published on EMA website.

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. Terlipressin (NAP) - EMEA/H/A-31/1514

Applicant(s): various

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

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

Background

A referral procedure under Article 31 of Directive 2001/83/EC is ongoing for the review of terlipressin-containing products indicated in the treatment of hepatorenal syndrome (HRS). This procedure was initiated following the assessment of the results from a large clinical trial CONFIRM[1] involving patients with type 1 HRS within the PSUR single assessment (PSUSA) procedure on terlipressin (PSUSA/00002905/202104) concluded in December 2021[2] that raised serious safety concerns due to an increased risk of respiratory failure in patients treated with terlipressin, sometimes with fatal outcome, within 90 days after the first dose compared to those who were given a placebo. For further background, see PRAC minutes January 2022, PRAC minutes April 2022 and PRAC minutes June 2022.

Summary of recommendation(s)/conclusions

- PRAC received feedback from the ad-hoc expert group (AHEG) meeting held on 13 June 2022.
- PRAC adopted a second list of outstanding issues (LoOI) to be addressed by the MAHs of terlipressin-containing products indicated in the treatment of HRS in accordance with a revised timetable (EMA/PRAC/2205/2022 rev3).

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

3.3. Procedures for finalisation

3.3.1. Chlormadinone (NAP); chlormadinone, ethinylestradiol (NAP); nomegestrol (NAP); nomegestrol, estradiol – ZOELY (CAP); NAP - EMEA/H/A-31/1510

Applicant(s): Theramex Ireland Limited (Zoely), various

PRAC Rapporteur: Martin Huber; PRAC Co-rapporteur: Željana Margan Koletić

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 for the review of chlormadinone acetate- and nomegestrol acetate-containing products is to be concluded. The review was initiated following new data from two epidemiological studies conducted in France in women taking these medicines showing an increase of reported cases of meningioma depending on the dose and duration of treatment and suggesting that the risk may be greater in women taking chlormadinone or nomegestrol for several years. The studies also showed that after women had stopped taking chlormadinone or nomegestrol for one year or more, the risk of developing these tumours was reduced and comparable to the risk in people who never used these medicines. A final assessment of the data submitted was produced by the Rapporteurs according to the agreed timetable. For further background, see PRAC minutes October 2021[3], PRAC minutes February 2022 and PRAC minutes May 2022.

Discussion

PRAC discussed the conclusion reached by the Rapporteurs.

PRAC reviewed the available data on the risk of meningioma during or following the use of medicinal products containing chlormadinone acetate or nomegestrol acetate, either alone or in combination, in particular the epidemiological studies including the French Health Insurance (CNAM) studies, as well as post-marketing case reports and data submitted by the MAHs.

PRAC concluded from the data that the absolute risk of meningioma caused by treatment with medicinal products containing chlormadinone acetate or nomegestrol acetate use remains low. However, the risk increases with increasing cumulative doses and treatment duration of chlormadinone or nomegestrol acetate. PRAC also noted that the risk of meningioma may decrease after treatment discontinuation.

PRAC also discussed further risk minimisation proposals that would ensure effective minimisation of the risks to an acceptable level.

Therefore, PRAC recommended that treatment with medicinal products containing high doses of chlormadinone acetate (5-10 mg) or nomegestrol acetate (3.75-5 mg) is restricted to situations where alternative treatments or interventions are considered inappropriate. Treatment should be limited to the lowest effective dose and shortest duration. Moreover, the Committee recommended that these high dose products are contraindicated in patients with meningioma or history of meningioma.

[3] Held on 27-30 September 2021

PRAC also concluded that while no increased risk of meningioma was specifically identified following the use of low dose chlormadinone acetate- or nomegestrol acetate-containing products, either alone or in combination, it is noted that there are situations where patients may be exposed to low dose products for a long period of time. Given that the risk increases with increasing cumulative doses of chlormadinone acetate or nomegestrol acetate, the Committee recommended that low dose chlormadinone acetate (1-2 mg) - or nomegestrol acetate (2.5 mg)- containing products should also be contraindicated in patients with meningioma or history of meningioma.

The Committee recommended further updates to the product information of chlormadinone acetate-containing products and nomegestrol acetate-containing products to reflect the current knowledge on the risk of meningioma.

The Committee also recommended that all MAHs should evaluate the effectiveness of the newly introduced risk minimisation measures (RMMs) in future PSURs for the respective active substances and fixed dose combinations (FDC).

PRAC concluded that the benefit-risk balance of chlormadinone acetate-containing products and nomegestrol acetate-containing products remains favourable subject to changes to the product information described above.

Summary of recommendation(s)/conclusions

- PRAC adopted a recommendation, by majority, to vary[4] the terms of the marketing authorisation(s) for chlormadinone acetate- and nomegestrol acetate-containing products and adopted a recommendation to be considered by CHMP for an opinion – see EMA Press release (EMA/621250/2022) entitled 'Medicines containing nomegestrol or chlormadinone: PRAC recommends new measures to minimise risk of meningioma' published on 08 July 2022.
- PRAC agreed on the content of a direct healthcare professional communication (DHPC) along with a communication plan for its distribution.

Twenty-nine members voted in favour of the recommendation whilst four members[5] had divergent views. The Icelandic and Norwegian PRAC members agreed with the recommendation.

Post-meeting note 1: the press release entitled 'New measures to minimise risk of meningioma with medicines containing nomegestrol or chlormadinone' (EMA/874908/2022) representing the opinion adopted by CHMP was published on the EMA website on 02 September 2022.

Post-meeting note 2: the PRAC assessment report (EMA/773938/2022) for the procedure was published on 14 December 2022.

3.4. Re-examination procedures[6]

None

[4] Update of SmPC sections 4.1, 4.2, 4.3, 4.4, 4.8 and 5.1 for high doses of chlormadinone acetate (5-10 mg) or nomegestrol acetate (3.75-5 mg) containing products and for high doses of nomegestrol acetate (3.75 mg) in combination with estradiol containing products. Update of SmPC sections 4.3 and 4.4 for low dose chlormadinone acetate (1-2 mg) and nomegestrol acetate (2.5 mg)-containing products. The package leaflets are updated accordingly.
[5] Patricia McGettigan, Julia Pallos, Nadine Petitpain, Tiphaine Vaillant
[6] Re-examination of PRAC recommendation under Article 32 of Directive 2001/83/EC

3.5. Others

None

4. Signals assessment and prioritisation[7]

4.1. New signals detected from EU spontaneous reporting systems

See also Annex I 14.1.

4.1.1. 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 other relevant fixed dose combinations; pravastatin, fenofibrate – PRAVAFENIX (CAP); simvastatin, fenofibrate – CHOLIB (CAP)

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

PRAC Rapporteur: Nathalie Gault

Scope: Signal of myasthenia gravis

EPITT 19822 – New signal

Lead Member State(s): AT, CZ, DE, EE, ES, FI, FR, HR, HU, IT, NL, SI

Background

Atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin and simvastatin, also known as statins, are inhibitors of 3-hydroxy 3-methylglutaryl coenzyme A (HMG-CoA) reductase. They are indicated for the reduction of elevated level of total and low density lipoprotein (LDL)-cholesterol as an adjunct to diet and for the prevention of cardiovascular events in adult patients estimated to have a high risk for a first cardiovascular event subject to certain conditions.

During routine signal detection activities, a signal of myasthenia gravis was identified by France, based on cases retrieved from the French pharmacovigilance database as well as published cases. Spain, Germany, France, The Netherlands and Finland confirmed that the signal needed initial analysis and prioritisation by PRAC.

Discussion

PRAC discussed the available evidence from EudraVigilance and the literature regarding the risk of myasthenia gravis in patients treated with statins and agreed that the signal required further investigation.

PRAC appointed Nathalie Gault as Rapporteur for the signal.

Summary of recommendation(s)

[7] 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

- The MAHs of originator single-ingredient statin-containing products (atorvastatin, pravastatin, lovastatin, fluvastatin, simvastatin, rosuvastatin or pitavastatin) should submit to EMA, within 60 days, any addition relevant data on the association between statins and myasthenia, including data from clinical trials and a discussion on possible pathological mechanisms, as well as to comment on the amendments to the product information proposed by PRAC.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.2. New signals detected from other sources

See also Annex I 14.2.

4.2.1. Topiramate (NAP)

Applicant(s): various

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of neurodevelopmental disorders due to in utero exposure

EPITT 19825 – New signal

Lead Member State(s): SE

Background

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

Following the publication by *Bjørk et al*[8], a signal of neurodevelopmental disorders due to in utero exposure was identified by France. This study investigated the risk of neurodevelopmental disorders, including autism spectrum disorder (ASD) and intellectual disability (ID) associated with several anti-epileptic drugs. The publication suggests a possible increase in the risks of ASD, ID and child neurodevelopmental disorders associated with the exposure to topiramate during pregnancy.

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

Discussion

PRAC discussed the new data available in the publication from *Bjørk et al.* and agreed that it raises further concerns in addition to the well-established risks of congenital malformations, following exposure to topiramate during pregnancy. PRAC agreed that further assessment is warranted to determine the scope and the most suitable regulatory procedure to assess the potential risk for neurodevelopmental disorders due to in utero exposure to topiramate.

PRAC appointed Ulla Wändel Liminga as Rapporteur for the signal.

Summary of recommendation(s)

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

- PRAC will conduct a detailed assessment of the publication and consider its regulatory implication(s).
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.3. Signals follow-up and prioritisation

4.3.1. Tocilizumab – ROACTEMRA (CAP) - EMEA/H/C/000955/SDA/061

Applicant: Roche Registration GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

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

EPITT 19360 – Follow-up to February 2022

Background

For background information, see PRAC minutes February 2022.

The MAH replied to the request for information on the signal of drug reaction with eosinophilia and systemic symptoms (DRESS) and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence from EudraVigilance, the literature, the review provided by the MAH and the Rapporteur's assessment, PRAC agreed that there is insufficient evidence at present to establish a causal relationship between DRESS and treatment with tocilizumab.

Summary of recommendation(s)

- The MAH should monitor cases of encephalopathy including DRESS as part of routine safety surveillance.

4.3.2. Tocilizumab – ROACTEMRA (CAP) - EMEA/H/C/000955/SDA/060.1

Applicant: Roche Registration GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Signal of encephalopathy including posterior reversible encephalopathy syndrome (PRES)

EPITT 19731 – Follow-up to April 2022

Background

For background information, see PRAC minutes April 2022.

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

Discussion

Having considered the available evidence from EudraVigilance, the literature, the review provided by the MAH and the Rapporteur's assessment, PRAC agreed that there is insufficient evidence at present to establish a causal relationship between PRES and treatment with tocilizumab.

Summary of recommendation(s)

- The MAH should monitor cases of encephalopathy including PRES as part of routine safety surveillance.

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 age and older

5.1.2. Deucravacitinib - EMEA/H/C/005755

Scope: Treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy

5.1.3. Efbemalenograstim alfa - EMEA/H/C/005828

Scope: Treatment to reduce the duration of neutropenia and the incidence of febrile neutropenia

5.1.4. Etranacogene dezaparvovec - EMEA/H/C/004827, PRIME, Orphan

Applicant: CSL Behring GmbH, ATMP[9]

Scope accelerated assessment: Treatment of adults with haemophilia B

[9] Advanced therapy medicinal product

5.1.5. Gozetotide - EMEA/H/C/005488

Scope: Identification of prostate-specific membrane antigen (PSMA)-positive lesions after radiolabelling with gallium-68

5.1.6. Loncastuximab tesirine - EMEA/H/C/005685, Orphan

Applicant: FGK Representative Service GmbH

Scope: Treatment of adult patients with relapsed or refractory large B-cell lymphoma

5.1.7. Lutetium (^{177}Lu) vipivotide tetraxetan - EMEA/H/C/005483

Scope: Treatment of prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC)

5.1.8. Mavacamten - EMEA/H/C/005457

Scope: Treatment of symptomatic obstructive hypertrophic cardiomyopathy

5.1.9. Spesolimab - EMEA/H/C/005874

Scope: Treatment of flares in adult patients with generalised pustular psoriasis

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

See also Annex I 15.2.

5.2.1. Mepolizumab - NUCALA (CAP) - EMEA/H/C/003860/II/0048

Applicant: GlaxoSmithKline Trading Services Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Submission of an updated RMP (version 9) to reflect the proposal to stop the enrolment and to close the pregnancy registry known as mepolizumab pregnancy exposure study 200870 (listed as category 3 study in the RMP): a phase 4, prospective, observational, exposure cohort study of pregnancy outcomes in women. The application also includes details of the proposed enhanced data collection for all pregnancies reported as an alternative

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 Nucala, a centrally authorised medicine containing mepolizumab, to update the RMP to reflect the proposal to stop the enrolment and to close the pregnancy registry known as mepolizumab pregnancy exposure study 200870 (listed as category 3 study in the RMP). PRAC is responsible for adopting an outcome based on the assessment report from the PRAC Rapporteur, to be further considered at the level of

CHMP, responsible for adopting an opinion on this variation. For further background, see PRAC minutes April 2022.

Summary of advice

- The RMP version 9.1 for Nucala (mepolizumab) in the context of the variation under evaluation by PRAC and CHMP was considered acceptable.

5.2.2. Naloxegol - MOVENTIG (CAP) - EMEA/H/C/002810/II/0038

Applicant: Kyowa Kirin Holdings B.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: Submission of an updated RMP (version 7.2) to remove study D3820R00009 (listed as a category 3 study in the RMP): an observational drug utilisation PASS of Moventig (naloxegol) in selected European populations, following the completion of procedure MEA 006.11 in November 2021

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 Moventig, a centrally authorised medicine containing naloxegol, to update the RMP to reflect the removal of D3820R00009 study (listed as a category 3 study in the RMP): an observational drug utilisation PASS of Moventig (naloxegol) in selected European populations, following the completion of procedure MEA 006.11 in November 2021. 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 March 2022.

Summary of advice

- The RMP version 7.2 for Moventig (naloxegol) in the context of the variation under evaluation by PRAC and CHMP was considered acceptable.

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

See also Annex I 15.3.

5.3.1. Ibrutinib - IMBRUVICA (CAP) - EMEA/H/C/003791/II/0069

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Update of section 4.4 of the SmPC to include information on fatal and serious cardiac arrythmias and cardiac failure, relevant warnings and periodical monitoring of patients following a safety assessment for increased risk of sudden death/cardiac death with the use of ibrutinib. The MAH took the opportunity to correct typographical errors throughout the product information. The package leaflet and the RMP (version 11.0) 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 Imbruvica, a centrally authorised product containing ibrutinib, to update the section 4.4 of the SmPC to include information on fatal and serious cardiac arrythmias and cardiac failure, relevant warnings and periodical monitoring of patients following a safety assessment for increased risk of sudden death/cardiac death with the use of ibrutinib. PRAC is responsible for providing advice to CHMP on the necessary updates to the RMP to support this procedure. For background, see PRAC minutes January 2022 and PRAC minutes May 2022.

Summary of advice

- The RMP for Imbruvica (ibrutinib) in the context of the variation procedure under evaluation by CHMP could be considered acceptable provided that an update to RMP version 18.3 and satisfactory responses to the request for supplementary information (RSI) are submitted.
- PRAC considered that the MAH should include 'cardiac arrest' in the PSUR list of safety concerns to be followed as an important identified risk. Also, the MAH should add 'ischemic heart disease' including myocardial infarction as an important potential risk in the PSUR list of safety concerns.

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

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Liana Gross-Martirosyan

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

Background

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

CHMP is evaluating an extension application (line extension) for Skyrizi, a centrally authorised product containing risankizumab, to introduce a new pharmaceutical form (concentrate for solution for infusion), a new strength (600 mg) and a new route of administration (intravenous use) and to add a new strength of 360 mg (150 mg/mL) for risankizumab solution for injection (in cartridge) for subcutaneous use. PRAC is responsible

for providing advice to CHMP on the necessary updates to the RMP to support this variation for a line extension.

Summary of advice

- The RMP for Skyrizi (rusankizumab) in the context of the extension application procedure under evaluation by CHMP could be considered acceptable provided that an update to RMP version 4.2 and satisfactory responses to the request for supplementary information (RSI) are submitted.
- PRAC agreed with the proposed list of safety concerns proposed by the MAH. Regarding the pharmacovigilance plan, PRAC endorsed the proposed PASS studies for the new Crohn's disease indication, namely one long-term safety PASS and one pregnancy PASS. PRAC agreed that there is no need for additional risk minimisations measures (aRMM) in light of the current knowledge.

5.3.3. Smallpox vaccine (live modified vaccinia virus Ankara) - IMVANEX (CAP) - EMEA/H/C/002596/II/0076

Applicant: Bavarian Nordic A/S

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include active immunisation against monkeypox and related orthopoxvirus infection and disease in adults 18 years of age and older for Imvanex; as a consequence, sections 1, 4.1, 4.2, 4.4, 4.6 and 5.1 of the SmPC are updated. The package leaflet and labelling are updated in accordance. Version 9.0 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 the therapeutic indication for Imvanex, a centrally authorised product containing smallpox vaccine (live modified vaccinia virus Ankara), to include active immunisation against monkeypox and related orthopoxvirus infection and disease in adults 18 years of age and older. PRAC is responsible for providing advice to CHMP on the necessary updates to the RMP to support this extension of indication.

Summary of advice

- The RMP for Imvanex (smallpox vaccine (live modified vaccinia virus Ankara) in the context of the variation procedure under evaluation by CHMP could be considered acceptable provided that an update to RMP version 9.0 and satisfactory responses to the request for supplementary information (RSI) are submitted.
- As there is currently no paediatric indication approved, PRAC considered that 'children and adolescents' should be removed as missing information from the list of safety concerns. In addition, the MAH should provide further justification for including the following safety concerns as missing information: elderly persons, individuals with organ impairment and interaction with other vaccines and concomitantly administered immunoglobulins. Also, the risk of 'safety experience in a mass vaccination due to a smallpox outbreak' should be removed from list of safety concerns. Regarding the

pharmacovigilance plan, the MAH should describe routine pharmacovigilance in the scenario of a mass vaccination campaign and should present how it will ensure the traceability, shipping and transport conditions of the vaccine. In addition, the MAH should either amend the current observational PASS/PAES to study safety and efficacy for the prophylactic vaccination following re-emergence of circulating smallpox infections in order to include the monkeypox indication or propose a new PASS in collaboration with the Member States where the vaccination is planned to be rolled out and provide detailed timelines and protocol/protocol synopsis for the study. PRAC agreed that routine risk minimisations measures are sufficient to minimise the risks of the medicinal product in the proposed indication(s) in light of the current knowledge.

- The MAH should submit to EMA, within 60 days, an updated RMP following the approval of the new indication.

6. Periodic safety update reports (PSURs)

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

See also Annex I 16.1.

6.1.1. Cabozantinib - CABOMETYX (CAP); COMETRIQ (CAP) - PSUSA/00010180/202111

Applicant: Ipsen Pharma

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 Cabometyx and Cometriq, centrally authorised medicines containing cabozantinib and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Cabometyx and Cometriq (cabozantinib) in the approved indication(s) remains unchanged.
- Nevertheless, the products information should be updated to add cutaneous vasculitis and pneumothorax as undesirable effects with a frequency 'not known' and 'uncommon' respectively. In addition, the product information of Cabometyx should be updated to amend the warning on hypertension. Therefore, the current terms of the marketing authorisations should be varied[10].

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

- In the next PSUR, the MAH should provide a review of cases of heart failure, tumour lysis syndrome and nephrotic syndrome.
- The MAH should submit to EMA, within 60 days, a detailed individual causality assessment of pneumonia cases already reported as confounded by the MAH in the current PSUR, as well as of any newly reported cases.

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/00010912/202112

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.

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Vaxzevria, a centrally authorised medicine containing coronavirus (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 (coronavirus (COVID-19) Vaccine (ChAdOx1-S [recombinant])) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add tinnitus, paraesthesia and hypoaesthesia as undesirable effects with a frequency 'uncommon'. Therefore, the current terms of the marketing authorisation(s) should be varied[11].
- In the next PSUR, the MAH should submit cumulative reviews of cases of 'glomerulonephritis and nephrotic syndrome' and 'myocarditis', together with a causality assessment. The MAH should also submit cumulative reviews of cases of cutaneous vasculitis, hearing loss, sarcoidosis, menstrual disorders and tinnitus, together with a discussion on possible biological mechanisms. In addition, the MAH should provide a literature review on subacute thyroiditis. The MAH should also provide any data available on booster dose. Finally, the MAH should propose to update the product information as warranted.

6.1.3. Elasomeran - SPIKEVAX (CAP) - PSUSA/00010897/202112

Applicant: Moderna Biotech Spain, S.L.

[11] 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.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

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 Spikevax, a centrally authorised medicine containing elasomeran 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 Spikevax (elasomeran) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add extensive swelling of vaccinated limb as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[12].
- In the next PSUR, the MAH should provide cumulative reviews of cases of chronic urticaria/chronic spontaneous urticaria and polymyalgia rheumatica, including a re-evaluation of causality assessment. The MAH should also submit a detailed review of cases of solid organ cutaneous vasculitis from all sources observed versus expected (O/E) analysis, disproportionality analysis, as well as a justification on the causality assessment. In addition, the MAH should provide cumulative reviews of cases of neuralgic amyotrophy, delayed onset urticaria, and myasthenia gravis flares. The MAH should also discuss the need for improvement of the follow-up questionnaires for myocarditis, pericarditis and vaccine-associated enhanced disease including vaccine-associated enhanced respiratory disease, as warranted. Moreover, the MAH should provide data from all sources regarding the use of the vaccine during pregnancy. Furthermore, the MAH should provide a cumulative review of cases of acquired haemophilia including a disproportionality analysis and a discussion on plausible biological mechanisms. Finally, the MAH should propose to update the product information as warranted.

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

6.1.4. Fenfluramine - FINTEPLA (CAP) - PSUSA/00010907/202112

Applicant: Zogenix ROI Limited

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

[12] 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.

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 Fintepla, a centrally authorised medicine containing fenfluramine 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 Fintepla (fenfluramine) 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 add medication error, status epilepticus and prolonged seizures, as well as sleep disturbances in the summary of safety concerns.
- The MAH should submit to EMA, within 90 days, a variation including a revised RMP, together with a targeted follow-up questionnaire (FUQ) aiming to improve the follow-up on cases of valvular heart disease (VHD) and pulmonary arterial hypertension (PAH).

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. Lutetium (^{177}Lu) oxodotreotide - LUTATHERA (CAP) - PSUSA/00010643/202112

Applicant: Advanced Accelerator Applications

PRAC Rapporteur: Adam Przybylkowski

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 Lutathera, a centrally authorised medicine containing lutetium (^{177}Lu) oxodotreotide 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 Lutathera (lutetium (^{177}Lu) oxodotreotide) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add hypersensitivity as a warning, as well as to add angioedema as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[13].

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

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

6.1.6. Mexiletine[14] - NAMUSCLA (CAP) - PSUSA/00010738/202112

Applicant: Lupin Europe GmbH

PRAC Rapporteur: Eva Jirsová

Scope: Evaluation of a PSUSA procedure

Background

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

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

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

6.1.7. Osimertinib - TAGRISSO (CAP) - PSUSA/00010472/202111

Applicant: AstraZeneca AB

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

[14] Centrally authorised product(s) only

- Nevertheless, the product information should be updated to add aplastic anaemia as a warning and as an undesirable effect with a frequency 'rare' and to add left ventricular ejection fraction decreased and cardiac failure as undesirable effects with a frequency 'common' and 'uncommon' respectively. In addition, the product information should be updated to amend the table regarding dose modifications to recommend permanently discontinuation in case of occurrence of Stevens-Johnson syndrome and aplastic anaemia as adverse reactions. Therefore, the current terms of the marketing authorisation(s) should be varied[15].
- In the next PSUR, the MAH should provide a cumulative review of cases of arthralgia and should propose to update the product information as warranted.

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

6.1.8. Roxadustat - EVRENZO (CAP) - PSUSA/00010955/202112

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Anna Mareková

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 Evrenzo, a centrally authorised medicine containing roxadustat 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 Evrenzo (roxadustat) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add secondary hypothyroidism and blood thyroid stimulating hormone decreased as warnings and as undesirable effects with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[16].
- In the next PSUR, the MAH should provide cumulative reviews of cases of thrombotic vascular events and serious infections.

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.

[15] Update of SmPC sections 4.2, 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion.
[16] Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion.

6.1.9. Rucaparib - RUBRACA (CAP) - PSUSA/00010694/202112

Applicant: Clovis Oncology Ireland Limited

PRAC Rapporteur: Annika Folin

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 Rubraca, a centrally authorised medicine containing rucaparib 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 Rubraca (rucaparib) 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 submit a cumulative review of cases of vascular occlusive events, including a thorough causality assessment and a discussion of potential mechanistic plausibility.

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

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

See also Annex I 16.2.

6.2.1. Edotreotide - SOMAKIT TOC (CAP); NAP - PSUSA/00010552/202112

Applicant(s): Advanced Accelerator Applications (SomaKit TOC), various

PRAC Rapporteur: Ronan Grimes

Scope: Evaluation of a PSUSA procedure

Background

Edotreotide is a somatostatin analogue indicated, for diagnostic use only. After radiolabelling with gallium (68Ga) chloride solution, the combined solution is indicated for positron emission tomography (PET) imaging of somatostatin receptor overexpression in adult patients with confirmed or suspected well-differentiated gastroenteropancreatic neuroendocrine tumours (GEP-NET) for localising primary tumours and their metastases. It is also indicated in imaging of meningioma.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of edotreotide-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the existing warning on errors of interpretation of gallium (^{68}Ga) edotreotide image and to add a description of cases in which physiological uptake of gallium (^{68}Ga) edotreotide by splenic tissue has been misdiagnosed as neuroendocrine tumour, leading to unnecessary intervention. Therefore, the current terms of the marketing authorisations should be varied[17].
- In the next PSUR, the MAH should provide further reviews of cases of hypersensitivity, embryofoetal toxicity, impact on fertility, and occupational and inadvertent exposure as important potential risks. In addition, the MAH should present any new information arising on the possible interaction of curcumin (turmeric) with (^{68}Ga) edotreotide arising from spontaneous reports, the literature, or any other relevant data sources.

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.

6.2.2. Erlotinib - TARCEVA (CAP); NAP - PSUSA/00001255/202111

Applicant(s): Roche Registration GmbH (Tarceva), various

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Evaluation of a PSUSA procedure

Background
Erlotinib is a reversible tyrosine kinase inhibitor (TKI) indicated for the treatment of non-small luncg cancer (NSCLC) and pancreatic cancer, subject to certain conditions.
Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of Tarceva, a centrally authorised medicine containing erlotinib, and nationally authorised medicines containing erlotinib and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of erlotinib-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add hepatitis and acute hepatitis as undesirable effects with a frequency 'rare' and 'not known' respectively, as well as to add pneumatosis with a frequency 'rare'. In addition, the product information

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

should be updated to amend the existing warning/precaution regarding hepatotoxicity. Therefore, the current terms of the marketing authorisations should be varied[18].

- In the next PSUR, the MAHs should provide literature reviews on relevant safety information for the class epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKI). In addition, the MAHs should provide cumulative reviews of cases of microangiopathic haemolytic anaemia, hair texture abnormal, mental status changes, cerebrovascular accident, acute myocardial infarction, cardiac arrest and pulmonary embolism, including a causality assessment and a discussion on the potential mechanisms. The MAHs should also discuss whether the risk of renal failure with erlotinib is sufficiently and adequately covered in the product information based on, but not limited to, the results of the *Choi HD et al. (2020)*[19] .The MAHs should also discuss whether the risk of ocular toxicity is sufficiently covered in the product information or if the ocular disorders relating to dry eye, cataract and visual impairment/vision blurred should be reflected, as well as provide a critical analysis of certain publications related to the important identified risk of cutaneous toxicity. Moreover, the MAHs should provide a critical assessment of the publication by *Ehrenstein et al (2021)*[20] and discuss whether further investigations or actions are warranted particularly concerning the safety outcomes of interest which are currently unlisted. The MAHs should propose 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.

6.2.3. Sufentanil - DZUVEO (CAP); ZALVISO (CAP); NAP - PSUSA/00002798/202111

Applicants: FGK Representative Service GmbH (Zalviso), Laboratoire Aguettant (Dzuveo), various

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

Background

Sufentanil is a synthetic potent opioid with highly selective binding to μ-opioid receptors indicated for the management of acute moderate to severe pain in adult patients in a medically monitored setting (sublingual use), as well as an analgesic adjunct during induction and maintenance of balanced general anaesthesia, and as an anaesthetic agent for induction and maintenance of anaesthesia in patients undergoing major surgical procedures (intravenous use), subject to certain conditions.

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

[18] Update of SmPC section 4.4. and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion.
[19] Choi HD, Chang MJ. Eye, hepatobiliary, and renal disorders of erlotinib in patients with non-small-cell lung cancer: A meta-analysis. PLoS One. 2020 Jul14;15(7):e0234818
[20] Ehrenstein V, Huang K, Kahlert J, et al. Outcomes in patients with lung cancer treated with crizotinib and erlotinib in routine clinical practice: a post authorsation safety cohort study conducted in Europe and in the United States. Pharmacoepidemiology and drug safety (2021)

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of sufentanil-containing product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add a warning/precaution regarding opioid induced hyperalgesia and on sleep-related breathing disorders, as well as to amend the existing warning on tolerance and opioid use disorder (abuse and dependence). In addition, the product information should be updated to add the interactions with gabapentinoids. In addition, the product information should be updated to include a warning concerning ileus and spasm of sphincter of Oddi. Therefore, the current terms of the marketing authorisations should be varied[21].

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

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

See also Annex I 16.3.

6.3.1. Chlormadinone acetate, ethinylestradiol (NAP) - PSUSA/00000679/202111

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

Chlormadinone is a progestin derivative and ethinylestradiol a derivative of natural occurring oestradiol. In combination, chlormadinone acetate/ethinylestradiol is indicated for hormonal contraception (HC), for the treatment of papulopustular acne, seborrhoea oleosa, androgenic alopecia and hirsutism and in women with break-through bleedings with lower dose combined hormonal contraceptives (CHCs).

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing chlormadinone acetate/ethinylestradiol 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 chlormadinone acetate/ethinylestradiol-containing product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add the contraindication and the interaction of ethinylestradiol with sofosbuvir/velpatasvir/voxilaprevir and to

[21] Update of SmPC section 4.4 and 4.5. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion.

remove the warning on transaminase (ALT) elevations. Therefore, the current terms of the marketing authorisation(s) should be varied[22].

- In the next PSUR, the MAHs should provide a sub-analysis in adolescents, patients between 18-30 years of age, 31-40 years of age, 41-50 years of age and older women to gain more clarity on the patient population using chlormadinone acetate-containing CHCs and the development of the age distribution.

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

PRAC considered that the risk of elevated liver enzymes is also relevant for medicinal products containing ethinylestradiol as single agent and in fixed-dose combinations. Further consideration is to be given at the level of CMDh.

6.3.2. Donepezil (NAP) - PSUSA/00001160/202111

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

Donepezil is a selective reversible inhibitor of acetylcholinesterase (AChE) and is indicated for the symptomatic treatment of mild to moderately severe Alzheimer's dementia. In some Member States, it is also indicated for severe Alzheimer's disease, vascular dementia and dementia with Lewy bodies.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing donepezil 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 donepezil-containing product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add libido increased, hypersexuality, and pleurothotonus (Pisa syndrome) as undesirable effects with a frequency 'not known'. In addition, the product information should be updated to amend the information about the timing of the intake in case of sleep-related undesirable effects. Therefore, the current terms of the marketing authorisation(s) should be varied[23].

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.

[22] Update of SmPC section 4.3, 4.4 and 4.5. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position.
[23] Update of SmPC section 4.2 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position.

6.3.3. Hydromorphone (NAP) - PSUSA/00001686/202111

Applicant(s): various

PRAC Lead: Polona Golmajer

Scope: Evaluation of a PSUSA procedure

Background

Hydromorphone is a semisynthetic opioid indicated for the treatment of severe (malignant and sometime non-malignant) pain when not successfully controlled by other analgesics.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing hydromorphone 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 hydromorphone-containing product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to strengthen the warning on the risk of opioid use disorder (abuse and dependence) and to add sleep-related breathing disorders as a warning and central sleep apnoea syndrome as an undesirable effect with a frequency 'not known'. In addition, the product information should be updated to add drug-drug interaction between hydromorphone and gabapentinoids. Therefore, the current terms of the marketing authorisation(s) should be varied[24].
- In the next PSUR, the MAH(s) should provide a literature review regarding the opioids class effect, as well as reviews of cases of pancreatitis and sphincter of Oddi spasm. In addition, the MAH Mundipharma[25] should discuss and propose routine risk minimisation measures (RMMs) to prevent the risk of dependence/addiction. This includes a discussion on the possibility to add a waning on the outer packaging.

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. Ketamine (NAP) - PSUSA/00001804/202112

Applicant(s): various

PRAC Lead: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

Background

Ketamine is a non-barbiturate anaesthetic indicated as an anaesthetic agent for diagnostic and surgical procedures that do not require skeletal muscle relaxation. Ketamine is also indicated for the induction of anaesthesia prior to the administration of other general

[24] Update of SmPC sections 4.4, 4.5 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position.
[25] MAH of originator hydromorphone-containing product(s)

anaesthetic agents, in obstetrics, for vaginal delivery or in caesarean section, as well as to supplement low-potency agents, such as nitrous oxide.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of ketamine-containing product(s) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisations should be maintained.
- In the next PSUR, the MAH(s) should continue to monitor the off-label use of ketamine. In addition, the MAH(s) should analyse whether further risk minimisation measures are necessary for ketamine concerning endocrine disorders such as increases in cortisol or prolactin levels.

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

PRAC considered that cases related to hepatotoxicity and biliary disorders should be further assessed. Further consideration is to be given at the level of CMDh.

6.3.5. Tapentadol (NAP) - PSUSA/00002849/202111

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

Tapentadol is a centrally acting synthetic analgesic indicated for moderate to severe chronic pain, which can be adequately managed only with opioid analgesics, subject to certain conditions.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing tapentadol 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 tapentadol-containing product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to strengthen the warning on the risk of opioid use disorder (abuse and dependence), to add drug-drug interaction between tapentadol and gabapentinoids (gabapentin and pregabalin) and to include additional explanation on symptoms in association with sleep-related breathing

disorders, the latter only in the package leaflet. Therefore, the current terms of the marketing authorisation(s) should be varied[26].

- In the next PSUR, the MAH(s) should further monitor/present the signal on central sleep apnoea (for all opioids). In addition, the MAH(s) should further monitor cases of drug abuse and drug dependence (including drug diversion), convulsion, overdose as important identified risks and potential medication errors, accidental exposure, serotonin syndrome with concomitant use of serotonergic medications, suicidal ideation and behaviour as important potential risks. Moreover, the MAH(s) should further monitor the following concerns as missing information: use in paediatric patients with chronic pain, use in paediatric patients outside the hospital setting, use during pregnancy.

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

6.4. Follow-up to PSUR/PSUSA procedures

See Annex I 16.4.

6.5. Variation procedure(s) resulting from PSUSA evaluation

None

6.6. Expedited summary safety reviews[27]

6.6.1. Coronavirus (COVID-19) vaccine (recombinant, adjuvanted) - NUVAXOVID (CAP) - EMEA/H/C/005808/MEA 014.3

Applicant: Novavax CZ, a.s.

PRAC Rapporteur: Brigitte Keller-Stanislawski

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

Background

Coronavirus (COVID-19) vaccine (recombinant, adjuvanted) is indicated, as Nuvaxovid, for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older.

PRAC assessed the fourth expedited summary safety report (SSR) for the safety monitoring of Nuvaxovid (Coronavirus (COVID-19) vaccine (recombinant, adjuvanted)). PRAC endorsed the conclusions at the current meeting.

Summary of advice/conclusion(s)

[26] Update of SmPC sections 4.4 and 4.5. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position.
[27] Submission of expedited summary safety reports for review in addition to the requirements for submission of PSUR(s) falling within the pandemic period and requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c (7) of Directive 2001/83/EC

- The MAH should submit to EMA, a variation[28] to amend the warning on anaphylaxis and to add anaphylaxis, paraesthesia and hypoesthesia as undesirable effects with a frequency 'not known'.
- In the next SSR, the MAH should provide a review of cases of pericarditis/myocarditis cases, including observed versus expected (O/E) analyses, reporting rates and an updated analysis from clinical trials, together with a causality assessment. In addition, the MAH should provide a review of cases of menstrual disorders in particular heavy menstrual bleedings and heart rhythm disorders in particular tachycardia (not related to myo-/pericarditis). The MAH should propose to update of the product information as warranted.

7. Post-authorisation safety studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)[29]

See also Annex I 17.1.

7.1.1. Lisocabtagene maraleucel - BREYANZI (CAP) - EMEA/H/C/PSP/S/0098

Applicant: Bristol-Myers Squibb Pharma EEIG, ATMP[30]

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Submission of a non-interventional, PASS of patients treated with commercially available liso-cel (lisocabtagene maraleucel) for relapsed/refractory diffuse large B-cell lymphoma, primary mediastinal B-cell lymphoma, and follicular lymphoma Grade 3B after 2 or more lines of systemic therapy in the postmarketing setting to characterize the incidence and severity of selected adverse drug reactions (ADRs), as outlined in the SmPC, and to monitor for potential clinically important adverse events (AEs) that have not yet been identified as part of the liso-cel safety profile

Background

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

In order to fulfil a specific obligation to conduct a PASS (Annex II-D) imposed in accordance with Article 107n(3) of Directive 2001/83/EC, the MAH of Breyanzi (lisocabtagene maraleucel) submitted to EMA a protocol 1.0 version for a study entitled: 'non-interventional, PASS of patients treated with commercially available liso-cel (lisocabtagene maraleucel) for relapsed/refractory diffuse large B-cell lymphoma, primary mediastinal B-cell lymphoma, and follicular lymphoma grade 3B after 2 or more lines of systemic therapy in the post-marketing setting)' for review by PRAC. PRAC is responsible for evaluating the PASS protocol.

Endorsement/Refusal of the protocol

- Having considered the protocol dated 20 January 2022 in accordance with Article 107o of Directive 2001/83/EC, PRAC objected to the draft protocol for the above-listed

[28] Update of SmPC section 4.8. The package leaflet is updated accordingly.
[29] In accordance with Article 107n of Directive 2001/83/EC
[30] Advanced therapy medicinal product

medicinal product(s). PRAC agreed that the PASS is non-interventional, but the study design does not fulfil the study objectives at this stage.

- PRAC considered that the MAH should provide sufficiently detailed information to demonstrate that the framework to conduct the study is in place and practicable, including information regarding allocation of responsibilities and lines of communication between involved parties, as well as on data transfer and management.
- 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)[31]

See also Annex I 17.2.

7.2.1. Vosoritide - VOXZOGO (CAP) - EMEA/H/C/005475/MEA 005.1

Applicant: BioMarin International Limited

PRAC Rapporteur: Zane Neikena

Scope: MAH's response to MEA 005.1 [protocol for study 111-603: a multicentre, non-interventional study to evaluate long-term safety in patients with achondroplasia treated with Voxzogo (vosoritide)]

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 Voxzogo (vosoritide), the MAH was required to conduct a PASS in order to address 'missing information', 'long-term safety including skeletal effects as impaired function of extremities and joints' and 'immunogenic potential' as safety concerns in the RMP. 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

- Based on the review of protocol version 3 and the assessment from the Rapporteur, PRAC considered the protocol for Voxzogo (vosoritide) is acceptable.

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

None

7.4. Results of PASS non-imposed in the marketing authorisation(s)[33]

See Annex I 17.4.

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

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

See Annex I 17.5.

7.6. Others

See Annex I 17.6.

7.7. New Scientific Advice

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

7.8. Ongoing Scientific Advice

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

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

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

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

8.1. Annual reassessments of the marketing authorisation

See Annex I 18.1.

8.2. Conditional renewals of the marketing authorisation

See Annex I 18.2.

8.3. Renewals of the marketing authorisation

See Annex I 18.3.

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

Applicant: STEBA Biotech S.A

PRAC Rapporteur: Maia Uusküla

Scope: 5-year renewal of the marketing authorisation

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.

The MAH submitted an application for renewal of the marketing authorisation for opinion by CHMP. PRAC is responsible for providing advice to CHMP on this renewal with regard to safety and risk management aspects.

Summary of advice

- Based on the review of the available pharmacovigilance data for Tookad (padeliporfin), the MAH's responses and the CHMP Rapporteur's assessment report, PRAC considered that the renewal of the marketing authorisation could be granted with unlimited validity.

9. Product related pharmacovigilance inspections

9.1. List of planned pharmacovigilance inspections

None

9.2. Ongoing or concluded pharmacovigilance inspections

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

9.3. Others

None

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

10.1. Safety related variations of the marketing authorisation

None

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

None

10.3. Other requests

None

10.4. Scientific Advice

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

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

11.1. Safety related variations of the marketing authorisation

11.1.1. Ibuprofen (NAP) - DE/H/0392/II/032/G

Applicant: Johnson & Johnson GmbH (Dolormin für Kinder Ibuprofensaft 20 mg/mL)

PRAC Lead: Martin Huber

Scope: Second PRAC consultation on a grouped type II variations (DE/H/0392/II/032/G) on the use of ibuprofen during pregnancy, on request of Germany (first PRAC consultation concluded in April 2022)

Background

Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID) indicated in the treatment of pain, fever and inflammation under certain conditions.

In the context of the evaluation of a grouped variation procedure for Dolormin für Kinder Ibuprofensaft 20 mg/mL (ibuprofen) on the use of ibuprofen during pregnancy, Germany as reference Member State (RMS) for the medicinal product, requested a second PRAC advice on its assessment. For background, see PRAC minutes April 2022.

Summary of advice

- Based on the review of the available information, PRAC agreed that an update of the product information of the medicinal product in the context of the current variation (DE/H/0392/II/032/G) regarding the use in pregnancy is warranted. In addition, PRAC agreed that the respective product information updates would be applicable to other ibuprofen-containing products for systemic use (including fixed dose combinations), as well as to all other NSAID-containing products for systemic use (including fixed dose combinations), except for the centrally authorised product Pedea[34]. However, in case the product information already includes a stricter advice on use in pregnancy, the stricter advice remains valid and should remain. Regarding implementation of the updates in the product information for acetylsalicylic acid containing products, PRAC supported that the MAH Bayer should submit a work-sharing variation application to implement the amended NSAID class wording and discuss the applicability of the wording for low-dose acetylsalicylic acid. Finally, PRAC was of the view that no further advice can be given for topical NSAIDs and their use during pregnancy at this stage. This should be reviewed in the context of the upcoming PSURs for relevant medicinal products.

11.2. Other requests

None

[34] Paediatric indication

12. Organisational, regulatory and methodological matters

12.1. Mandate and organisation of the PRAC

12.1.1. PRAC membership

The PRAC Chair welcomed Valentina Di Giovanni as the new alternate for Italy. The PRAC Chair also welcomed as Lucia Kuráková as the new alternate for Slovakia, replacing Anna Mareková who took over the role of member.

12.1.2. Vote by proxy

None

12.2. Coordination with EMA Scientific Committees or CMDh-v

None

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

None

12.4. Cooperation within the EU regulatory network

12.4.1. Coronavirus (COVID-19) pandemic - update

The EMA Secretariat updated PRAC on the activities of the COVID-19 EMA pandemic Task Force (ETF), including an overview of ongoing clinical trials and epidemiological studies and initiatives, as well as a summary of medicines in development as potential treatments for COVID-19, as well as authorised medicines and their effectiveness against new coronavirus SARS-CoV-2 variants and their safety surveillance.

12.5. Cooperation with International Regulators

None

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

None

12.7. PRAC work plan

None

12.8. Planning and reporting

12.8.1. Marketing authorisation applications (MAA) forecast for 2022 – planning update dated Q2 2022

At the organisational, regulatory and methodological matters (ORGAM) meeting on 20 July 2022, the EMA Secretariat presented for information to PRAC a quarterly updated report on marketing authorisation applications planned for submission (the business 'pipeline') in 2022. For previous update, see PRAC minutes April 2022.

12.8.2. European Commission (EC) report on performance of pharmacovigilance tasks - third three-yearly report – status update

The EMA Secretariat presented to PRAC an update on the preparation of the upcoming report to the EC on the performance of the EU Member States activities relating to the pharmacovigilance (Article 108b of Directive 2001/83/EC and Article 29 of Regulation 726/2004). For further background, see PRAC minutes May 2015, PRAC minutes July 2015 and PRAC minutes July 2018. The presentation included the timelines as well as the actions envisaged for the EU Member States for the next months. The EMA Secretariat informed PRAC that the draft report will be circulated in July 2022. PRAC members/Member States were invited to provide their comments in writing. Further update will be given in due course.

12.9. Pharmacovigilance audits and inspections

12.9.1. Pharmacovigilance systems and their quality systems

None

12.9.2. Pharmacovigilance inspections

None

12.9.3. Pharmacovigilance audits

None

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

12.10.1. Periodic safety update reports

None

12.10.2. Granularity and Periodicity Advisory Group (GPAG)

None

12.10.3. PSURs repository

None

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

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

12.11. Signal management

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

PRAC lead: Menno van der Elst

PRAC was updated on the progress from the SMART working group meeting on Methods held on 15 June 2022, including the group's objectives and deliverables, as well as further information about lessons learned on observed versus -expected (O/E) analyses to support COVID-19 vaccine safety monitoring, on masking and other effects in EudraVigilance related to COVID-19 vaccines.

12.12. Adverse drug reactions reporting and additional reporting

12.12.1. Management and reporting of adverse reactions to medicinal products

None

12.12.2. Additional monitoring

None

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

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

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

12.13. EudraVigilance database

12.13.1. Activities related to the confirmation of full functionality

None

12.14. Risk management plans and effectiveness of risk minimisations

12.14.1. Risk management systems

None

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

None

12.15. Post-authorisation safety studies (PASS)

12.15.1. Post-authorisation Safety Studies – imposed PASS

None

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

None

12.16. Community procedures

12.16.1. Referral procedures for safety reasons

None

12.17. Renewals, conditional renewals, annual reassessments

None

12.18. Risk communication and transparency

12.18.1. Public participation in pharmacovigilance

None

12.18.2. Safety communication

None

12.19. Continuous pharmacovigilance

12.19.1. Incident management

None

12.20. Impact of pharmacovigilance activities

None

12.21. Others

12.21.1. EMA records management system – update on SharePoint migration

At the organisational, regulatory and methodological matters (ORGAM) meeting on 20 July 2022, the EMA Secretariat updated PRAC on the impact and timelines of the implementation of SharePoint as the Agency's records management system. PRAC noted the information.

13. Any other business

None

14. Annex I – Signals assessment and prioritisation[35]

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[36].

14.1.1. Diphtheria, tetanus, pertussis (acellular, component), poliomyelitis (inactivated) vaccine (adsorbed) (NAP); diphtheria, tetanus, pertussis (acellular, component), poliomyelitis (inactivated) vaccine (adsorbed, reduced antigen(s) content) (NAP)

Applicant(s): various

PRAC Rapporteur: Anette Kirstine Stark

Scope: Signal of immune thrombocytopenia

EPITT: 19831 – New signal

Lead Member State(s): DK

[35] 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

[36] 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

14.2. New signals detected from other sources

14.2.1. Cetuximab – ERBITUX (CAP)

Applicant: Merck Europe B.V.

PRAC Rapporteur: Annika Folin

Scope: Signal of nephrotic syndrome

EPITT 19819 – 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. Plerixafor - EMEA/H/C/005943

Scope: Treatment of lymphoma and multiple myeloma

15.1.2. Teriflunomide - EMEA/H/C/005960

Scope: Treatment of multiple sclerosis (MS)

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

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

15.2.1. Alemtuzumab - LEMTRADA (CAP) - EMEA/H/C/003718/II/0041

Applicant: Sanofi Belgium

PRAC Rapporteur: Anette Kirstine Stark

Scope: Submission of an updated RMP (version 10.0) in order to include the new important identified risk of 'autoimmune encephalitis' and to introduce changes in accordance to the Rapporteurs' requests made in the conclusions of variation II/0038 finalised in January 2022

15.2.2. Estrogens conjugated, bazedoxifene - DUAVIVE (CAP) - EMEA/H/C/002314/II/0032

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Martin Huber

Scope: Submission of an updated RMP version 3.2 in order to reflect the updated study milestones and completion of the post authorisation safety study of CE/BZA in the United States (US PASS, Study B2311060) previously assessed as part of II/0030 (MEA002.15), as well as to update the post marketing data with the data lock point of 31 October 2021

15.2.3. Fentanyl - EFFENTORA (CAP); NAP - EMEA/H/C/000833/WS2212/0060

Applicant: Teva B.V.

PRAC Rapporteur: Martin Huber

Scope: Submission of an updated RMP (version 5.1) in order to bring it in line with revision 2 of GVP module V on 'Risk management systems' and to implement PRAC requests arising from previous assessments as follows: 1) revision of the list of safety concerns; 2) update of the key messages of the educational materials in line with another centrally authorised product containing fentanyl (Instanyl (fentanyl)). As a result, Annex II on additional risk minimisation measures is updated accordingly

15.2.4. Fentanyl - PECFENT (CAP) - EMEA/H/C/001164/II/0054

Applicant: Kyowa Kirin Holdings B.V.

PRAC Rapporteur: Martin Huber

Scope: Submission of an updated RMP (version 7.1) in line with the outcome of the last PSUR single assessment (PSUSA) procedure (PSUSA 00001369/202004) finalised in January 2021 in order to update the key messages of the educational materials in line with another centrally authorised product containing fentanyl (Instanyl (fentanyl)). As a result, Annex II-D on 'Conditions or restrictions with regard to the safe and effective use of the medicinal product' is updated accordingly. Finally, the MAH took the opportunity to bring the RMP in line with revision 2 of GVP module V on 'Risk management systems' and the product information in line with the latest quality review of documents (QRD) template (version 10.2)

15.2.5. Nintedanib - VARGATEF (CAP) - EMEA/H/C/002569/II/0044

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Georgia Gkegka

Scope: Submission of an updated RMP (version 10.0) in order to remove safety concerns that were classified as important identified risks, important potential risks and missing information, based on cumulative post-marketing experience. The MAH also proposed an update of the anatomical therapeutic chemical (ATC) code, an update of post-marketing exposure, the removal of adverse event follow-up forms and an update of search strategies

15.2.6. Selexipag - UPTRAVI (CAP) - EMEA/H/C/003774/II/0035

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Nathalie Gault

Scope: Submission of an updated RMP (version 9.3) in order to reflect amendments to the protocol of ongoing EXPOSURE PASS study: an international, observational, cohort study of pulmonary arterial hypertension (PAH) patients newly treated with either Uptravi (selexipag) or any other PAH-specific therapy, in clinical practice; to add the EXTRACT study (67896049PAH0002): a retrospective medical chart review of patients with PAH newly treated with either Uptravi (selexipag) or any other PAH-specific therapy as an additional pharmacovigilance activity; and to reflect amendments to the protocol of study EDUCATE (listed as category 3 study in the RMP): a PASS to evaluate risk minimisation measures for medication errors with Uptravi (selexipag) during the titration phase in patients with PAH in clinical practice (assessed and approved in MEA 003.4)

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

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

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

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Update of sections 4.4 and 4.8 of the SmPC based on updated safety data from the full cumulative pool from ongoing long-term extension study B7451015: a phase 3 multicentre, long-term extension study investigating the efficacy and safety of abrocitinib, with or without topical medications, administered to subjects aged 12 years and older with moderate to severe atopic dermatitis. The RMP (version 1.0) is updated accordingly. In addition, MAH took the opportunity to implement editorial changes in the SmPC and to update the contact details of the local representatives in the package leaflet

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

Applicant: Kite Pharma EU B.V., ATMP[37]

PRAC Rapporteur: Anette Kirstine Stark

Scope: Extension of indication to include treatment of adult patients with relapsed or refractory (r/r) diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL). As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 5.3) are updated in accordance. In addition, the MAH took the opportunity to update the product information with minor editorial changes

[37] Advanced therapy medicinal product

15.3.3. Baricitinib - OLUMIANT (CAP) - EMEA/H/C/004085/II/0028

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Extension of indication to include treatment of coronavirus disease 2019 (COVID-19) in hospitalised adult and paediatric patients aged 10 years and older who require low-flow oxygen or non-invasive ventilation/high flow oxygen. As a consequence, sections 4.1, 4.2, 4.4, 4.6, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated. Annex II, the package leaflet and the RMP (version 11.1) are updated in accordance

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

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Liana Gross-Martirosyan

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

15.3.5. Brexucabtagene autoleucel - TECARTUS (CAP) - EMEA/H/C/005102/II/0008/G, Orphan

Applicant: Kite Pharma EU B.V., ATMP[38]

PRAC Rapporteur: Menno van der Elst

Scope: Grouped variations consisting of: 1) extension of indication to include treatment of adult patients with relapsed or refractory (r/r) B-cell acute lymphoblastic leukaemia (B-ALL); 2) change the drug product dose specification for the new indication. As a consequence, sections 2.2, 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The package leaflet, labelling and the RMP (version 1.1) are updated in accordance. Furthermore, the product information is brought in line with the latest quality review of documents (QRD) template (version 10.2)

15.3.6. Burosumab - CRYSVITA (CAP) - EMEA/H/C/004275/II/0028, Orphan

Applicant: Kyowa Kirin Holdings B.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, to split immunogenicity data into paediatric and adult populations and to update clinical efficacy in paediatric patients upon request by CHMP, following procedures P46/006, P46/007 and variations II/04 and II/10/G finalised in October 2019 and July 2020 respectively, based on the final results from: 1) study UX023-CL201: a randomised, open-label, dose finding, phase 2 study to assess the pharmacodynamics and

[38] Advanced therapy medicinal product

safety of KRN23 (burosumab) in paediatric patients with X-linked hypophosphatemia (XLH); 2) study UX023-CL205: an open-label, phase 2 study to assess the safety, pharmacodynamics, and efficacy of KRN23 in children from 1 to 4 years old with XLH; 3) study UX023-CL301: randomized, open-label, phase 3 study to assess the efficacy and safety of krn23 versus oral phosphate and active vitamin D treatment in paediatric patients with XLH. In addition, the MAH proposed to delete the remaining specific obligation (SO) for study UX023-CL205 from Annex II, and to request a switch from a conditional marketing authorisation (MA) to standard MA. The package leaflet and the RMP (version 5.0) are updated accordingly

15.3.7. Cenobamate - ONTOZRY (CAP) - EMEA/H/C/005377/II/0009

Applicant: Angelini S.p.A.

PRAC Rapporteur: Jean-Michel Dogné

Scope: Update of section 5.3 of the SmPC in order to update information on toxicity to reproduction and development based on final results from nonclinical study "Effects of Cenobamate (YKP3089) on Embryo-Fetal Development in Rats after Twice Daily Oral Administration". The RMP version 3.0 has also been submitted

15.3.8. Clopidogrel - ISCOVER (CAP) - EMEA/H/C/000175/WS2150/0146; PLAVIX (CAP) - EMEA/H/C/000174/WS2150/0145; clopidogrel, acetylsalicylic acid - DUOPLAVIN (CAP) - EMEA/H/C/001143/WS2150/0060

Applicant: sanofi-aventis groupe

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Extension of indication to include clopidogrel in combination with acetylsalicylic acid in ST segment elevation acute myocardial infraction (STEMI) patients undergoing percutaneous coronary intervention (PCI). As a consequence, sections 4.1, 4.2 and 5.1 of the SmPC are updated. The RMP (version 1.5) for Iscover/Plavix (clopidogrel) is updated accordingly. In addition, the MAH took the opportunity to introduce an editorial update in the labelling

15.3.9. Coronavirus (COVID-19) vaccine (recombinant, adjuvanted) (NVX-CoV2373) - NUVAXOVID (CAP) - EMEA/H/C/005808/II/0014

Applicant: Novavax CZ, a.s.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of sections 4.2, 4.8 and 5.1 of the SmPC in order to include a 0.5 mL third dose for Nuvaxovid, to boost subjects that have previously completed a primary vaccination series with Nuvaxovid (homologous booster dose) or with an authorised mRNA or adenoviral vector vaccine (heterologous booster dose), based on interim data from study 2019nCoV-101 (Part 2), a Phase 1/2, Randomized, Observer-Blinded Study to Evaluate the Safety and Immunogenicity of a SARS-CoV-2 Recombinant Spike Protein Nanoparticle Vaccine (SARS-CoV-2 rS) With or Without Matrix-M Adjuvant in Healthy Subjects (NCT04368988), final data from study 2019nCoV-501, a Phase 2a/b, Randomized, Observer-Blinded, Placebo-Controlled Study to Evaluate the Efficacy, Immunogenicity, and Safety of a SARS-CoV-2 Recombinant Spike Protein Nanoparticle Vaccine (SARS-CoV-2 rS)

With Matrix-M Adjuvant in South African Adult Subjects Living Without HIV; and Safety and Immunogenicity in Adults Living With HIV (NCT04533399) and data from the COV-BOOST study (Safety and immunogenicity of seven COVID-19 vaccines as a third dose (booster) following two doses of ChAdOx1 nCov-19 or BNT162b2 in the UK (COV-BOOST): a blinded, multicentre, randomised, controlled, phase 2 trial); the Package Leaflet is updated accordingly. The RMP version 1.2 has also been submitted. In addition, the Marketing Authorisation Holder (MAH) took the opportunity to make minor editorial corrections throughout the product information

15.3.10. Deferasirox - EXJADE (CAP) - EMEA/H/C/000670/II/0082/G

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Tiphaine Vaillant

Scope: Grouped variations consisting of: 1) submission of the final report from study CICL670F2202 (Calypso study) (listed as a category 3 study in the RMP): a randomized, open-label, multicentre, two arm, phase 2 study to evaluate treatment compliance, efficacy and safety of deferasirox (granules) in paediatric patients with iron overload; 2) removal of the risk of 'medication error' from the RMP and of the information related to the discontinuation of the dispersible tablets in the EU. The RMP (version 20.0) is updated accordingly

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

Applicant: sanofi-aventis groupe

PRAC Rapporteur: Kimmo Jaakkola

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

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

Applicant: sanofi-aventis groupe

PRAC Rapporteur: Kimmo Jaakkola

Scope: Extension of indication to include treatment of adults with moderate to severe prurigo nodularis (PN) who are candidates for systemic therapy, based on results from studies EFC16459 and EFC16460 (PRIME and PRIME2); these are two phase 3, 24-week, randomized, double-blind, placebo-controlled, multi-centre, parallel group studies undertaken to evaluate the efficacy and safety of dupilumab in patients 18 years of age and older with moderate to severe PN, who are inadequately controlled on topical prescription therapies or when those therapies are not advisable. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance.

Version 8.0 of the RMP has also been submitted. As part of this application, the MAH is also requesting a 1-year extension of the market protection

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

Applicant: AstraZeneca AB

PRAC Rapporteur: David Olsen

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

15.3.14. Durvalumab - IMFINZI (CAP) - EMEA/H/C/004771/II/0046

Applicant: AstraZeneca AB

PRAC Rapporteur: David Olsen

Scope: Extension of indication to include IMFINZI in combination with chemotherapy for the treatment of adults with locally advanced or metastatic biliary tract cancer (BTC), based on the second interim analysis from the ongoing pivotal study D933AC00001 (TOPAZ-1): a phase III randomized, double-blind, placebo-controlled, multi-regional, international study conducted to assess the efficacy and safety of durvalumab in combination with the current standard of care Gemcitabine/Cisplatin for the first-line treatment of patients with locally advanced or metastatic BTC. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated and the Package leaflet has been updated accordingly. Version 7.1 of the RMP has also been submitted

15.3.15. Emtricitabine, tenofovir alafenamide - DESCOVY (CAP) - EMEA/H/C/004094/II/0057

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Submission of the clinical study report and supporting modular summaries for study GS-US-311-1269: a phase 2/3, open label, multi-cohort switch study to evaluate emtricitabine/tenofovir alafenamide (F/TAF) in human immunodeficiency virus type 1 (HIV-1) infected children and adolescents virologically suppressed on a two nucleoside reverse transcriptase inhibitors (NRTI) containing regimen in fulfilment of the milestone for the category 3 additional pharmacovigilance activity to address long-term safety information in adolescents as missing information. The RMP (version 6.1) is updated accordingly

15.3.16. Fenfluramine - FINTEPLA (CAP) - EMEA/H/C/003933/II/0010/G, Orphan

Applicant: Zogenix ROI Limited

PRAC Rapporteur: Martin Huber

Scope: Grouped variations consisting of an update of section 5.3 of the SmPC in order to update the non-clinical information based on data from: 1) study 20147822: a 6-month carcinogenicity study of fenfluramine hydrochloride in mice; 2) study 8001993: a 2-year oral gavage carcinogenicity study of fenfluramine hydrochloride in rats, together with the final reports for dose range finding studies 20147821 and 20166554 and the final report for study 2021006-Z001-01: in-vitro evaluation of potential melanin binding by fenfluramine and norfenfluramine. The RMP (version 3.1) is updated accordingly

15.3.17. Fenfluramine - FINTEPLA (CAP) - EMEA/H/C/003933/II/0011/G, Orphan

Applicant: Zogenix ROI Limited

PRAC Rapporteur: Martin Huber

Scope: Grouped variations consisting of: 1) update of section 4.2 and 5.2 of the SmPC to include the relevant information regarding patients with renal impairment following the study 1902: a pharmacokinetic study of fenfluramine hydrochloride in subjects with varying degrees of impaired and normal renal function; 2) update of section 4.4 and 4.5 of the SmPC in order to reflect the relevant information on cytochrome (CYP)1A2 or CYP2B6 or CYP2D6 inducers following study 1904: a pharmacokinetic drug-drug interaction study of fenfluramine hydrochloride with and without fluvoxamine (CYP1A2 inhibitor), paroxetine (CYP2D6 inhibitor) and rifampin (CYP2B6 inducer) in healthy subjects. The RMP (version 2.2) is updated accordingly

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

Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Maria del Pilar Rayon

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

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

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

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

15.3.20. Ivacaftor, tezacaftor, elexacaftor - KAFTRIO (CAP) - EMEA/H/C/005269/II/0017/G, Orphan

Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Martin Huber

Scope: Grouped variations consisting of: 1) update of section 5.3 of the SmPC in order to update the non-clinical information based on final results from study VX-445-TX-015: a 2-year oral carcinogenicity study in rats evaluating the carcinogenic potential of up to 10 mg/kg/day of elexacaftor. The RMP (version 6.0) is updated accordingly; 2) submission of the final report for study VX-661-TX-038: a tezacaftor juvenile toxicity study

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

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Submission of an updated RMP version 5.0 to revise plans for conduct of hepatic impairment studies. The RMP is updated to reflect the termination of the hepatic impairment study B7461009: a phase 1 study to evaluate the effect of hepatic impairment on the pharmacokinetics and safety of lorlatinib in advanced cancer patients and to include new hepatic impairment study b7461040: a phase 1, open-label, single-dose, parallel-group study to evaluate the plasma pharmacokinetics and safety of lorlatinib in participants with moderate and severe hepatic impairment relative to participants with normal hepatic function

15.3.22. Metreleptin - MYALEPTA (CAP) - EMEA/H/C/004218/II/0025, Orphan

Applicant: Amryt Pharmaceuticals DAC

PRAC Rapporteur: Adam Przybylkowski

Scope: Proposal for an alternative study to the currently agreed protocol for study AEGR-734-002 (specific obligation SOB002): a 24-month, multicentre, open label phase 4 post-authorisation efficacy study (PAES) to evaluate the efficacy, safety and immunogenicity of daily subcutaneous metreleptin treatment in patients with partial lipodystrophy due to the challenges of implementing the existing protocol. Annex II and the RMP (version 2.1) are updated accordingly. The MAH took the opportunity to update the RMP in line with the outcome of previous procedures and to include editorial changes

15.3.23. Olaparib - LYNPARZA (CAP) - EMEA/H/C/003726/II/0053

Applicant: AstraZeneca AB

PRAC Rapporteur: Amelia Cupelli

Scope: Extension of indication to include treatment of adults with metastatic castration resistant prostate cancer (mCRPC) with olaparib in combination with abiraterone and prednisone or prednisolone, based on the results of the pivotal study D081SC00001 (PROpel study): a phase 3, randomised, double-blind, placebo-controlled, multicentre study evaluating olaparib vs placebo in combination with abiraterone as first line treatment for men with mCRPC, and supportive evidence from study D081DC00008 (study 8): a

randomised, double-blind, placebo-controlled, multicentre phase 2 study to compare the efficacy, safety and tolerability of olaparib versus placebo when given in addition to abiraterone treatment in patients with mCRPC who have received prior chemotherapy containing docetaxel. Consequently, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC for Lynparza (olaparib) tablets are updated. In addition, sections 4.4 and 4.8 of the SmPC for Lynparza (olaparib) hard capsules are revised based on the updated safety data analysis. The package leaflet and the RMP (version 24) are updated accordingly

15.3.24. Oritavancin - TENKASI (CAP) - EMEA/H/C/003785/X/0036

Applicant: Menarini International Operations Luxembourg S.A.

PRAC Rapporteur: Adam Przybylkowski

Scope: Extension application to add a new strength of 1200 mg for powder for concentrate for solution for infusion. The RMP (version 4) is updated accordingly

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

Applicant: Takeda Pharmaceuticals International AG

PRAC Rapporteur: Rhea Fitzgerald

Scope: Submission of the updated protocol from study SHP634-403 listed as a Specific Obligation in the Annex II of the Product Information with twice-daily (BID) as the proposed alternative dosing regimen to be evaluated. This is a Randomized, 2-Arm, Double-Blind, Phase 4 Study to Evaluate Once Daily (QD) Versus Twice Daily (BID) Administration of Recombinant Human Parathyroid Hormone (rhPTH[1-84]; NATPARA®) for the Treatment of Adults with Hypoparathyroidism (HPT). The Annex II and the RMP (submitted version 3.4) are updated accordingly

15.3.26. Peginterferon alfa-2a - PEGASYS (CAP) - EMEA/H/C/000395/II/0112

Applicant: Zr Pharma & GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of section 4.8 of the SmPC in order to include information on post-treatment recovery in growth based on final results from study YV25718 listed as a category 3 study in the RMP; this is a Phase IIIb parallel group, open label study of pegylated interferon alfa-2a monotherapy (PEG-IFN, RO0258310) compared to untreated control in children with HBeAg-Positive Chronic Hepatitis B in the immune active phase. The RMP version 9.1 has also been submitted. In addition, the MAH took the opportunity to implement editorial changes in the Package Leaflet

15.3.27. Pembrolizumab - KEYTRUDA (CAP) - EMEA/H/C/003820/II/0121

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication to include Keytruda as monotherapy for the adjuvant treatment of adults with Stage IB (T2a ≥ 4 cm), II or IIIA non-small cell lung carcinoma (NSCLC) who have undergone complete resection, based on study KEYNOTE-091: an

ongoing Phase 3, randomized, triple-blinded, placebo-controlled, multicentre study of pembrolizumab versus placebo in patients with early-stage NSCLC after resection and completion of standard adjuvant therapy. As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are being updated and the Package Leaflet is updated in accordance. An updated RMP version 39.1 was also submitted

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

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

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

15.3.29. Ravulizumab - ULTOMIRIS (CAP) - EMEA/H/C/004954/X/0027/G

Applicant: Alexion Europe SAS

PRAC Rapporteur: Kimmo Jaakkola

Scope: Grouped application consisting of: 1) extension application to introduce a new pharmaceutical form (solution for injection) associated with new strength (245 mg) and route of administration (subcutaneous use); 2) update of the Summary of product characteristics and Labelling for Ultomiris intravenous formulation (IV) in order to align with the proposed Ultomiris subcutaneous formulation (SC). The RMP (version 5.0) is updated in accordance

15.3.30. Remdesivir - VEKLURY (CAP) - EMEA/H/C/005622/II/0034/G

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Eva Jirsová

Scope: Grouped variations consisting of: 1) update sections 5.1 and 5.2 of the SmPC as a consequence of the submission of the final component of specific obligation (SO) 012 agreed in the renewal procedure of the conditional marketing authorisation (CMA) (R/0015) finalised in April 2021 and listed in Annex II of the product information. This submission includes the adaptive COVID-19 treatment trial (ACTT-1) final sequencing and phenotyping

analysis and the full virology report including activity against variants. The package leaflet and the RMP (version 3.1) are updated accordingly

15.3.31. Risdiplam - EVRYSDI (CAP) - EMEA/H/C/005145/II/0005/G, Orphan

Applicant: Roche Registration GmbH

PRAC Rapporteur: Jan Neuhauser

Scope: Grouped variations consisting of: 1) extension of indication to include treatment of patients below 2 months of age based on interim results from pivotal study BN40703 (RAINBOWFISH): an ongoing phase 2 multicentre, open-label, and single-arm study designed to evaluate the efficacy, safety, tolerability, and pharmacokinetic/pharmacodynamic (PK/PD) of risdiplam in pre-symptomatic infants below 2 months of age who were genetically diagnosed with spinal muscular atrophy (SMA). As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. In addition, the MAH took the opportunity to make some editorial improvements in the product information; 2) update of Evrysdi (risdiplam) pack configuration. As a consequence, section 6.5 of the SmPC and the labelling are updated; 3) removal of a device. As a consequence, section 6.5 of the SmPC and the labelling are updated. The package leaflet and the RMP (version 1.1) are updated in accordance

15.3.32. Selpercatinib - RETSEVMO (CAP) - EMEA/H/C/005375/II/0014/G

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Grouped variations consisting of: 1) extension of indication to include first-line treatment of advanced rearranged during transfection (RET)-mutant medullary thyroid cancer (MTC) in adults and adolescents 12 years and older based on interim results from Study LIBRETTO-001 (LOXO-RET-17001) on the clinical safety and efficacy of selpercatinib in patients with RET-mutant MTC who are cabozantinib and vandetanib treatment-naïve (MTC:-Cab/-Van). LIBRETTO-001 is a global, multicohort, open-label, Phase 1/2 study in adult and adolescent patients with advanced RET-altered tumours. As a consequence, sections 4.1 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 2.1 of the RMP has also been submitted; 2) submission of an updated Phase II Environmental Risk Assessment in order to reflect the patient population as per the approved indication. As part of the application, the MAH is requesting a 1-year extension of the market protection

15.3.33. Setmelanotide - IMCIVREE (CAP) - EMEA/H/C/005089/II/0002/G, Orphan

Applicant: Rhythm Pharmaceuticals Netherlands B.V.,

PRAC Rapporteur: Anna Mareková

Scope: Grouped variations consisting of: 1) addition of a new therapeutic indication for the treatment of obesity and the control of hunger associated with genetically confirmed Bardet-Biedl syndrome (BBS). As a consequence, sections 4.1, 4.2, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The package leaflet and the RMP (version 1.0) are updated accordingly; 2) addition of a new therapeutic indication for the treatment of obesity and the control of hunger associated with genetically confirmed Alström syndrome (AS). As a

consequence, sections 4.1, 4.2, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated accordingly. The package leaflet and the RMP (version 1.0) are updated in accordance

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

Applicant: Novartis Europharm Limited, ATMP[39]

PRAC Rapporteur: Brigitte Keller-Stanislawski

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

15.3.35. Trastuzumab emtansine - KADCYLA (CAP) - EMEA/H/C/002389/II/0064

Applicant: Roche Registration GmbH

PRAC Rapporteur: Anette Kirstine Stark

Scope: Submission of the final report from study BO28407 (KAITLIN): A randomized, multicentre, open-label, Phase III trial comparing trastuzumab plus pertuzumab plus a taxane following anthracyclines versus trastuzumab emtansine plus pertuzumab following anthracyclines as adjuvant therapy in patients with operable HER2-positive primary breast cancer listed as a category 3 study in the RMP. The RMP version 15.0 has also been submitted

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

Applicant: medac Gesellschaft fur klinische Spezialpraparate mbH

PRAC Rapporteur: Julia Pallos

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

15.3.37. Treosulfan - TRECONDI (CAP) - EMEA/H/C/004751/II/0013, Orphan

Applicant: medac Gesellschaft fur klinische Spezialpraparate mbH

PRAC Rapporteur: Julia Pallos

Scope: Update of section 5.3 of the SmPC in order to update the description of non-clinical information regarding musculoskeletal and connective tissue disorders in form of lympho-histiocytic infiltration in the skeletal muscles and renal and urinary disorders which show up as haematuria. These new determinations are based on results from study LPT 37259. A revised RMP version 1.0 was also submitted

[39] Advanced therapy medicinal product

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

Applicant: medac Gesellschaft fur klinische Spezialpraparate mbH

PRAC Rapporteur: Julia Pallos

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

15.3.39. Turoctocog alfa pegol - ESPEROCT (CAP) - EMEA/H/C/004883/II/0010, Orphan

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of sections 4.4 and 4.8 of the SmPC to add a new warning and update the list of adverse drug reactions (ADRs) based on post-marketing data concerning a lack of factor VIII activity in patients switching from a similar factor VIII product to Esperoct (turoctocog alfa pegol). The package leaflet is updated accordingly. In addition, the MAH took the opportunity to introduce minor editorial changes to the product information and to bring the product information in line with the latest quality review of documents (QRD) (template 10.2). The RMP (version 2.0) is updated accordingly

15.3.40. Velmanase alfa - LAMZEDE (CAP) - EMEA/H/C/003922/II/0027, Orphan

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Jan Neuhauser

Scope: Update of section 4.2 the SmPC in order to include the home infusion statement, following the assessment of PSUSA/00010677/202009, based on results from LAMAN-07, Sparkle and Italian Patient Support Program (PSP). The Package Leaflet and Annex II are updated accordingly. The RMP version 9.1 has also been submitted

15.3.41. Volanesorsen - WAYLIVRA (CAP) - EMEA/H/C/004538/II/0017/G, Orphan

Applicant: Akcea Therapeutics Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: Update of sections 4.8 and 5.1 of the SmPC based on the final results from study

ISIS 304801 CS7: a multicentre open label extension study of volanesorsen administered subcutaneously to patients with familial chylomicronemia syndrome. The package leaflet and the RMP (version 2.1) are updated accordingly. The RMP is updated: 1) to reflect a change in the distribution methodology of the educational materials and to clarify what is meant by the prescriber kit; 2) to reflect the final results from study ISIS 304801 (CS17): a phase 2/3 double blind, randomized, placebo controlled study, with an open label extension of volanesorsen (ISIS 304801) administered subcutaneously to patients with familial partial lipodystrophy. In addition, the MAH took the opportunity to implement editorial changes to the product information in order to align with the latest quality review of documents (QRD) template and to introduce minor linguistic update to Annex III of the product information to support product launch

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

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

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

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

16.1.1. Angiotensin II - GIAPREZA (CAP) - PSUSA/00010785/202112

Applicant: Paion Deutschland GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.2. Atidarsagene autotemcel - LIBMELDY (CAP) - PSUSA/00010899/202112

Applicant: Orchard Therapeutics (Netherlands) BV

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.3. Berotralstat - ORLADEYO (CAP) - PSUSA/00010930/202112

Applicant: BioCryst Ireland Limited

PRAC Rapporteur: Julia Pallos

Scope: Evaluation of a PSUSA procedure

16.1.4. Betibeglogene autotemcel - ZYNTEGLO[40] (CAP) - PSUSA/00010769/202111

Applicant: bluebird bio (Netherlands) B.V, ATMP[41]

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.5. Blinatumomab - BLINCYTO (CAP) - PSUSA/00010460/202112

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Eva Jirsová

Scope: Evaluation of a PSUSA procedure

16.1.6. Cholera vaccine, oral, live - VAXCHORA (CAP) - PSUSA/00010862/202112

Applicant: Emergent Netherlands B.V.

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

16.1.7. Delafloxacin - QUOFENIX (CAP) - PSUSA/00010822/202112

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

PRAC Rapporteur: Željana Margan Koletić

Scope: Evaluation of a PSUSA procedure

16.1.8. Dengue tetravalent vaccine (live, attenuated) - DENGVAXIA (CAP) - PSUSA/00010740/202112

Applicant: Sanofi Pasteur

PRAC Rapporteur: Sonja Hrabcik

Scope: Evaluation of a PSUSA procedure

16.1.9. Elotuzumab - EMPLICITI (CAP) - PSUSA/00010500/202111

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.10. Entrectinib - ROZLYTREK (CAP) - PSUSA/00010874/202112

Applicant: Roche Registration GmbH

PRAC Rapporteur: Menno van der Elst

[40] European Commission (EC) decision on the withdrawal of the marketing authorisation (MA) for Zynteglo dated 24 March 2022

[41] Advanced therapy medicinal product

Scope: Evaluation of a PSUSA procedure

16.1.11. Fondaparinux - ARIXTRA (CAP) - PSUSA/00001467/202112

Applicant: Mylan Ire Healthcare Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.12. Formoterol fumarate dihydrate, glycopyrronium bromide, budesonide - TRIXEO AEROSPHERE (CAP) - PSUSA/00010908/202112

Applicant: AstraZeneca AB

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.1.13. Inotuzumab ozogamicin - BESPONSA (CAP) - PSUSA/00010659/202112

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.14. Lamivudine[42] - EPIVIR (CAP); lamivudine, zidovudine - COMBIVIR (CAP) - PSUSA/00009207/202111

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Nathalie Gault

Scope: Evaluation of a PSUSA procedure

16.1.15. Latanoprost, netarsudil - ROCLANDA (CAP) - PSUSA/00010905/202112

Applicant: Santen Oy

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.16. Levodopa - INBRIJA (CAP) - PSUSA/00107800/202112

Applicant: Acorda Therapeutics Ireland Limited

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Evaluation of a PSUSA procedure

16.1.17. Luspatercept - REBLOZYL (CAP) - PSUSA/00010860/202112

Applicant: Bristol-Myers Squibb Pharma EEIG

[42] Treatment of human immunodeficiency virus (HIV) infections only

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

16.1.18. Metformin, saxagliptin - KOMBOGLYZE (CAP) - PSUSA/00002686/202111

Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.19. Olaparib - LYNPARZA (CAP) - PSUSA/00010322/202112

Applicant: AstraZeneca AB

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.1.20. Pertuzumab, trastuzumab - PHESGO (CAP) - PSUSA/00010906/202112

Applicant: Roche Registration GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.21. Polatuzumab vedotin - POLIVY (CAP) - PSUSA/00010817/202112

Applicant: Roche Registration GmbH

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

16.1.22. Sapropterin - KUVAN (CAP) - PSUSA/00002683/202112

Applicant: BioMarin International Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

16.1.23. Saquinavir - INVIRASE (CAP) - PSUSA/00002684/202112

Applicant: Roche Registration GmbH

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.1.24. Satralizumab - ENSPRYNG (CAP) - PSUSA/00010944/202111

Applicant: Roche Registration GmbH

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.1.25. Semaglutide - OZEMPIC (CAP); RYBELSUS (CAP); WEGOVY (CAP) - PSUSA/00010671/202111

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

16.1.26. Sofosbuvir - SOVALDI (CAP) - PSUSA/00010134/202112

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.1.27. Sucroferric oxyhydroxide - VELPHORO (CAP) - PSUSA/00010296/202111

Applicant: Vifor Fresenius Medical Care Renal Pharma France

PRAC Rapporteur: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

16.1.28. Thyrotropin alfa - THYROGEN (CAP) - PSUSA/00002940/202111

Applicant: Genzyme Europe BV

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

16.1.29. Tirbanibulin - KLISYRI (CAP) - PSUSA/00010943/202112

Applicant: Almirall, S.A.

PRAC Rapporteur: Anna Mareková

Scope: Evaluation of a PSUSA procedure

16.1.30. Tozinameran - COMIRNATY (CAP) - PSUSA/00010898/202112

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.31. Tralokinumab - ADTRALZA (CAP) - PSUSA/00010937/202112

Applicant: LEO Pharma A/S

PRAC Rapporteur: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

16.1.32. Trastuzumab deruxtecan - ENHERTU (CAP) - PSUSA/00010894/202112

Applicant: Daiichi Sankyo Europe GmbH

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Evaluation of a PSUSA procedure

16.1.33. Turoctocog alfa pegol - ESPEROCT (CAP) - PSUSA/00010782/202112

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.34. Venetoclax - VENCLYXTO (CAP) - PSUSA/00010556/202112

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Eva Jirsová

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. Bimatoprost, timolol - GANFORT (CAP); NAP - PSUSA/00002961/202111

Applicant: AbbVie Deutschland GmbH & Co. KG (Ganfort), various

PRAC Rapporteur: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

16.2.2. Doxorubicin - CAELYX PEGYLATED LIPOSOMAL (CAP); MYOCET LIPOSOMAL (CAP); NAP - PSUSA/00001172/202111

Applicant: Baxter Holding B.V. (Caelyx pegylated liposomal), Teva B.V. (Myocet liposomal), various

PRAC Rapporteur: Eva Jirsová

Scope: Evaluation of a PSUSA procedure

16.2.3. Levetiracetam - KEPPRA (CAP); NAP - PSUSA/00001846/202111

Applicant: UCB Pharma S.A. (Keppra), various

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

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

16.3.1. Aprotinin, calcium chloride, human factor XIII, human fibrinogen, human thrombin (NAP); aprotinin, fibrinogen, fibronectin, human coagulation factor XIII, plasma protein fraction, plasminogen, thrombin (NAP); aprotinin, human fibrinogen, thrombin, calcium chloride (NAP); aprotinin, calcium chloride, factor XIII, human thrombin, human clottable protein containing mainly fibrinogen and fibronectin (NAP); bovine aprotinin, calcium chloride, human fibrinogen, factor XIII, fibronectin, plasminogen, human thrombin (NAP); bovine aprotinin, calcium chloride, human fibrinogen, factor XIII, fibronectin, human thrombin (NAP); bovine aprotinin, human fibrinogen, calcium chloride dihydrate, plasma fibronectin, thrombin, human coagulation factor XIII (NAP), bovine aprotinin, human fibrinogen, calcium chloride dihydrate, plasma protein fraction, fibronectin, thrombin, human coagulation factor XIII (NAP); bovine aprotinin, human fibrinogen, plasminogen, human thrombin, human coagulation factor XIII, human fibronectin (NAP) - PSUSA/00010346/202111

Applicant(s): various

PRAC Lead: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.3.2. Bisoprolol, hydrochlorothiazide (NAP) - PSUSA/00000420/202111

Applicant(s): various

PRAC Lead: Nathalie Gault

Scope: Evaluation of a PSUSA procedure

16.3.3. Caffeine, ergotamine (NAP) - PSUSA/00000485/202111

Applicant(s): various

PRAC Lead: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

16.3.4. Cefazolin (NAP) - PSUSA/00000589/202111

Applicant(s): various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.3.5. Ceftobiprole (NAP) - PSUSA/00010734/202111

Applicant(s): various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.3.6. Ciprofibrate (NAP) - PSUSA/00000771/202112

Applicant(s): various

PRAC Lead: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

16.3.7. Hydroxycarbamide[43] (NAP) - PSUSA/00009182/202112

Applicant(s): various

PRAC Lead: Nikica Mirošević Skvrce

Scope: Evaluation of a PSUSA procedure

16.3.8. Indapamide, perindopril (NAP) - PSUSA/00010230/202111

Applicant(s): various

PRAC Lead: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Evaluation of a PSUSA procedure

16.3.9. Metoclopramide (NAP) - PSUSA/00002036/202111

Applicant(s): various

PRAC Lead: Karen Pernille Harg

Scope: Evaluation of a PSUSA procedure

16.3.10. Quinine (NAP) - PSUSA/00002598/202111

Applicant(s): various

PRAC Lead: Ronan Grimes

Scope: Evaluation of a PSUSA procedure

16.4. Follow-up to PSUR/PSUSA procedures

16.4.1. Ocrelizumab - OCREVUS (CAP) - EMEA/H/C/004043/LEG 008

Applicant: Roche Registration GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Cumulative review of cases of colitis, diarrhoea, alopecia/alopecia aerate and appendicitis, as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00010662/202103) adopted in November 2021

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

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)[44]

17.1.1. Afamelanotide - SCENESSE (CAP) - EMEA/H/C/PSA/S/0076.2

Applicant: Clinuvel Europe Limited

PRAC Rapporteur: Martin Huber

Scope: MAH's response to PSA/0076.1 [substantial amendment to a protocol previously agreed in March 2016 (PSP/0022.1.A.1 (PSA/0002)) for study CUV-PA001: a post-authorisation disease registry safety study to generate data on the long-term safety and clinical effectiveness of Scenesse (afamelanotide) in patients with erythropoietic protoporphyria (EPP)] as per the request for supplementary information (RSI) adopted in February 2022

17.1.2. Axicabtagene ciloleucel - YESCARTA (CAP) - EMEA/H/C/PSA/S/0087

Applicant: Kite Pharma EU B.V., ATMP[45]

PRAC Rapporteur: Anette Kirstine Stark

Scope: Amendment to a previously agreed protocol [EMEA/H/C/PSP/S/0079] for study KT-EU-471-0117 (EU PAS Register no.: EUPAS32539): a long-term, imposed non-interventional study of recipients of Yescarta for treatment of relapsed or refractory diffuse large B-cell lymphoma and primary mediastinal B-cell lymphoma

17.2. Protocols of PASS non-imposed in the marketing authorisation(s)[46]

17.2.1. Avacopan - TAVNEOS (CAP) - EMEA/H/C/005523/MEA 002

Applicant: Vifor Fresenius Medical Care Renal Pharma France

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Protocol for study CS-AVA-2022-0016 (listed as category 3 study in the RMP): avacopan real world evidence in anti-neutrophil cytoplasmic autoantibody (ANCA) associated vasculitis - characterisation of the safety concerns of avacopan (i.e. liver injury, serious infections, malignancies and cardiovascular events) beyond the known safety profile based on clinical trial data limited to 52 weeks of exposure

[44] In accordance with Article 107n of Directive 2001/83/EC
[45] Advanced therapy medicinal product
[46] In accordance with Article 107m of Directive 2001/83/EC, supervised by PRAC in accordance with Article 61a (6) of Regulation (EC) No 726/2004

17.2.2. Benralizumab - FASENRA (CAP) - EMEA/H/C/004433/MEA 004.5

Applicant: AstraZeneca AB

PRAC Rapporteur: David Olsen

Scope: MAH's response to MEA 004.3 [substantial amendment to a protocol previously agreed in July 2019 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] as per the request for supplementary information (RSI) adopted in December 2020

17.2.3. Brodalumab - KYNTHEUM (CAP) - EMEA/H/C/003959/MEA 002.6

Applicant: LEO Pharma A/S

PRAC Rapporteur: Eva Segovia

Scope: Amendment to a protocol previously agreed in 2019 for PASS KYNTHEUM-1345: The BRodalumab Assessment of Hazards: A Multinational Safety (BRAHMS) study in electronic healthcare databases – an observational post-authorisation safety study of suicidal behaviour, serious infections, major adverse cardiac events (MACE) and malignancy in psoriasis patients treated with brodalumab (Kyntheum)

17.2.4. Coronavirus (COVID-19) vaccine (recombinant, adjuvanted) (NVX-CoV2373) - NUVAXOVID (CAP) - EMEA/H/C/005808/MEA 004

Applicant: Novavax CZ, a.s.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Protocol for study 2019nCoV-402: UK Post-Authorisation Safety Study Using the Clinical Practice Research Datalink (CPRD): A surveillance study to characterise the safety profile of Nuvaxovid in adults aged 18 years and older in the real-world setting using the UK CPRD

17.2.5. Coronavirus (COVID-19) vaccine (recombinant, adjuvanted) (NVX-CoV2373) - NUVAXOVID (CAP) - EMEA/H/C/005808/MEA 005

Applicant: Novavax CZ, a.s.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Protocol for study 2019nCoV-405: Global Safety Surveillance Study of Pregnancy and Infant Outcomes Study Using C-VIPER. A registry-based observational cohort safety surveillance study to characterise the population of pregnant women who are vaccinated with Nuvaxovid, estimate the frequency of selected adverse pregnancy outcomes in women and selected adverse foetal/neonatal/infant outcomes at birth and up to the first 12 months of life of infants from pregnancies in women who received Nuvaxovid during pregnancy

17.2.6. Drospirenone, estetrol - DROVELIS (CAP) - EMEA/H/C/005336/MEA 001.2

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

PRAC Rapporteur: Martin Huber

Scope: MAH's response to MEA 001.1 [protocol for an international active surveillance study (INAS-NEES): a prospective non-interventional comparative cohort observational study to characterize and compare the risks of estetrol/drospirenone with combined oral contraceptive-containing levonorgestrel (COC-LNG) in a study population that is representative of the actual users of these preparations. The main clinical outcome of interest is venous thromboembolism (VTE), specifically deep venous thrombosis (DVT) and pulmonary embolism (PE)] as per the request for supplementary information (RSI) adopted in March 2022

17.2.7. Drospirenone, estetrol - LYDISILKA (CAP) - EMEA/H/C/005382/MEA 001.2

Applicant: Estetra SRL

PRAC Rapporteur: Martin Huber

Scope: MAH's response to MEA 001.1 [protocol for an international active surveillance study (INAS-NEES): a prospective non-interventional comparative cohort observational study to characterize and compare the risks of estetrol/drospirenone with combined oral contraceptive-containing levonorgestrel (COC-LNG) in a study population that is representative of the actual users of these preparations. The main clinical outcome of interest is venous thromboembolism (VTE), specifically deep venous thrombosis (DVT) and pulmonary embolism (PE) [final study report expected in December 2029] (from initial opinion/marketing authorisation (MA))] as per the request for supplementary information (RSI) adopted in March 2022

17.2.8. Elasomeran - SPIKEVAX (CAP) - EMEA/H/C/005791/MEA 065

Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Protocol for study mRNA-1273-P910: clinical course, outcomes and risk factors of myocarditis following administration of mRNA-1273 (Spikevax)

17.2.9. Elasomeran - SPIKEVAX (CAP) - EMEA/H/C/005791/MEA 066

Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Protocol for study mRNA-1273-P911: long-term outcomes of myocarditis following administration of Spikevax (COVID-19 vaccine mRNA)

17.2.10. Fenfluramine - FINTEPLA (CAP) - EMEA/H/C/003933/MEA 006.2

Applicant: Zogenix ROI Limited

PRAC Rapporteur: Martin Huber

Scope: MAH's response to MEA 006.1 [protocol for study ZX008-2104: a European study of the effectiveness of risk minimisation measures for fenfluramine in Dravet syndrome] as per the request for supplementary information (RSI) adopted April 2022

17.2.11. Lutetium (^{177}Lu) oxodotreotide - LUTATHERA (CAP) - EMEA/H/C/004123/MEA 001.10

Applicant: Advanced Accelerator Applications

PRAC Rapporteur: Adam Przybylkowski

Scope: Amendment to a protocol previously agreed in 2018 for study A-LUT-T-E02-402 (SALUS study) (listed as a category 3 study in the RMP): an international post-authorisation safety registry to assess the long-term safety of Lutathera (lutetium (^{177}Lu)) for unresectable or metastatic, somatostatin receptor positive gastroenteropancreatic neuroendocrine tumours (GEP-NETs)

17.2.12. Naltrexone hydrochloride, bupropion hydrochloride - MYSIMBA (CAP) - EMEA/H/C/003687/MEA 003.12

Applicant: Orexigen Therapeutics Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: MAH's response to MEA 003.11 [protocol for study NB-451: an observational retrospective drug utilisation study (DUS) of Mysimba (naltrexone hydrochloride/bupropion hydrochloride) in Europe and the United States to describe the demographic and baseline characteristics of users of Mysimba (naltrexone hydrochloride/bupropion hydrochloride), evaluate patterns of Mysimba (naltrexone hydrochloride/bupropion hydrochloride) initiation and use] as per the request for supplementary information (RSI) adopted in February 2022

17.2.13. Netarsudil - RHOKIINSA (CAP) - EMEA/H/C/004583/MEA 001.4

Applicant: Santen Oy

PRAC Rapporteur: Eva Segovia

Scope: MAH Response to MEA 001.3 [protocol for study AR-13324-OBS02: a non-interventional, observational cohort study of 2-year of treatment with Rhokiinsa (netarsudil) compared with non-Rhokiinsa (netarsudil) ocular hypotensive therapy in patients with elevated intraocular pressure due to primary open angle glaucoma or ocular hypertension] as per request for supplementary information (RSI) adopted in April 2022

17.2.14. Setmelanotide - IMCIVREE (CAP) - EMEA/H/C/005089/MEA 001.1

Applicant: Rhythm Pharmaceuticals Netherlands B.V.,

PRAC Rapporteur: Anna Mareková

Scope: MAH's response to MEA 001 [protocol for study RM-IMC-901 (listed as a category 3 study in the RMP): a registry of patients with biallelic homozygous pro-opiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), or leptin receptor (LEPR) deficiency obesity treated with setmelanotide (from initial opinion/marketing authorisation)] as per the request for supplementary information (RSI) adopted in February 2022

17.2.15. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/MEA 015.3

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Amendment to a protocol previously agreed in November 2020 for study A3921334 (listed as a category 3 study in the RMP): a non-interventional PASS to evaluate the effectiveness of additional risk minimisation measures (aRMM) materials for Xeljanz (tofacitinib) in Europe via a survey of healthcare professionals (HCPs), as requested in the conclusions of the referral procedure under Article 20 of Regulation (EC) No 726/2004 (EMEA/H/A-20/1485) finalised in November 2019

17.2.16. Tozinameran - COMIRNATY (CAP) - EMEA/H/C/005735/MEA 017.4

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

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

17.2.17. Upadacitinib - RINVOQ (CAP) - EMEA/H/C/004760/MEA 013.1

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Revised protocol for study P20-390: a cohort study of long-term safety of upadacitinib in the treatment of atopic dermatitis in Denmark and Sweden

17.3. Results of PASS imposed in the marketing authorisation(s)[47]

None

17.4. Results of PASS non-imposed in the marketing authorisation(s)[48]

17.4.1. Autologous CD34+ enriched cell fraction that contains CD34+ cells transduced with retroviral vector that encodes for the human adenosine deaminase (ADA) complementary deoxyribonucleic acid (cDNA) sequence - STRIMVELIS (CAP) - EMEA/H/C/003854/II/0033, Orphan

Applicant: Orchard Therapeutics (Netherlands) BV, ATMP[49]

PRAC Rapporteur: Menno van der Elst

Scope: Submission of the final report from study STRIM-001 (listed as a category 3 study in the RMP): a cross-sectional study evaluating referring healthcare providers' and

[47] In accordance with Article 107p-q of Directive 2001/83/EC
[48] 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
[49] Advanced therapy medicinal product

parents/carers' understanding of specific risks associated with Strimvelis treatment. The RMP (version 6.1) is updated accordingly

17.4.2. Coronavirus (COVID-19) vaccine (Ad26.COV2-S, recombinant) - JCOVDEN (CAP) - EMEA/H/C/005737/II/0048/G

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of the final reports from four exploratory studies conducted to further characterise the potential mechanisms underlying the important identified risk of thrombosis with thrombocytopenia syndrome (TTS). These studies evaluated the levels of anti-PF4 antibodies using clinical samples, both from Ad26.COV2.S and other non-COVID-19 Ad26-based vaccine clinical studies. Interim results from an additional exploratory study are provided and the submission milestone for the final results has been updated. The RMP version 4.1 has been submitted and updated in line with this procedure and the ongoing procedure EMEA/H/C/005737/II/0047/G. In addition, the MAH removed the important identified risk of anaphylaxis from the list of safety concerns (PSUSA/00010916/202108), updated the routine pharmacovigilance activities section and took the opportunity to implement other administrative updates in the RMP in alignment with procedure EMEA/H/C/005737/II/033

17.4.3. Dasabuvir - EXVIERA (CAP) - EMEA/H/C/003837/WS2216/0052; glecaprevir, pibrentasvir - MAVIRET (CAP) - EMEA/H/C/004430/WS2216/0049; ombitasvir, paritaprevir, ritonavir - VIEKIRAX (CAP) - EMEA/H/C/003839/WS2216/0064

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Submission of the final report from study B20-146 listed as a category 3 study in the RMP. This is a non-imposed joint post-authorisation safety study to evaluate the risk of de novo hepatocellular carcinoma in patients with compensated cirrhosis treated with direct-acting antivirals for chronic hepatitis C (HCC De Novo PASS)

17.4.4. Defibrotide - DEFITELIO (CAP) - EMEA/H/C/002393/II/0058/G, Orphan

Applicant: Gentium S.r.l.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Grouped variation consisting of: 1) submission of the final study report of the DEFIFrance registry (listed as category 3 study in the RMP): a national, post-registration observational study of the long-term safety and health outcome of patients treated with Defitelio, including patients with severe hepatic veno-occlusive disease (VOD) after haematopoietic stem cell transplantation (HSC T). The submission of the study report addresses LEG/011.3. In addition, the MAH took the opportunity to provide two errata to the clinical study reports of studies #R09-1425 and #2006-05. Consequential changes to RMP version 9.2 have been implemented; 2) submission of the updated RMP version 9.2 in order to remove reproductive toxicity as a potential risk

17.4.5. Elbasvir, grazoprevir - ZEPATIER (CAP) - EMEA/H/C/004126/II/0033

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Submission of the final report for study B20-146 (listed as a category 3 study in the RMP): a non-imposed joint PASS to evaluate the risk of de novo hepatocellular carcinoma (HCC) in patients with compensated cirrhosis treated with direct-acting antivirals (DAA) for chronic hepatitis C (HCC de novo PASS)

17.4.6. Idebenone - RAXONE (CAP) - EMEA/H/C/003834/II/0031, Orphan

Applicant: Santhera Pharmaceuticals (Deutschland) GmbH

PRAC Rapporteur: Amelia Cupelli

Scope: Update of sections 4.2, 4.4, 4.9 and 5.1 of the SmPC based on the final study report from study SNT-IV-003 (PAROS) (listed as a category 2 study in the RMP and Annex II (SOB003)): a non-interventional study of clinical experience in patients prescribed Raxone (idebenone) for the treatment of Leber's hereditary optic neuropathy (LHON). Annex II and the RMP (version 1.14) are updated accordingly

17.4.7. Sapropterin - KUVAN (CAP) - EMEA/H/C/000943/II/0073

Applicant: BioMarin International Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Submission of the final report from study BMN 162-501 KAMPER (formerly EMR700773-001) (listed as a category 3 study in the RMP): an observational drug registry to assess the long-term safety in subjects treated with Kuvan (in fulfilment of MEA 020). The RMP version 15.1 has also been submitted

17.4.8. Sofosbuvir - SOVALDI (CAP) - EMEA/H/C/002798/WS2222/0077; sofosbuvir, ledipasvir - HARVONI (CAP) - EMEA/H/C/003850/WS2222/0104; sofosbuvir, velpatasvir - EPCLUSA (CAP) - EMEA/H/C/004210/WS2222/0064; sofosbuvir, velpatasvir, voxilaprevir - VOSEVI (CAP) - EMEA/H/C/004350/WS2222/0054

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Submission of the final report from study B20-146 (listed as a category 3 study in the RMP): a non-imposed joint post-authorisation safety study to evaluate the risk of de novo hepatocellular carcinoma (HCC) in patients with compensated cirrhosis treated with direct-acting antivirals for chronic hepatitis C (HCC De Novo PASS)

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

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Tiphaine Vaillant

Scope: Update of section 5.1 of the SmPC in order to update information based on final results from study B3461029 listed as a Specific Obligation in the Annex II of the Product

Information. This is a non-interventional PASS sub-study evaluating effects of tafamidis on disease progression in patients with non-Val30Met mutations and symptomatic neuropathy. Consequently, the MAH proposes a switch from marketing authorisation under exceptional circumstances to full marketing authorisation given the fulfilment of the SOB. The Annex II and Package Leaflet are updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet

17.4.10. Velaglucerase alfa - VPRIV (CAP) - EMEA/H/C/001249/II/0049, Orphan

Applicant: Takeda Pharmaceuticals International AG

PRAC Rapporteur: Martin Huber

Scope: Submission of final physician data study results for study EUPASS 14255: an evaluation of the effectiveness of risk minimisation measures - a survey among healthcare professionals (HCPs) and patient/caregivers to assess their knowledge and attitudes on prescribing and home administration conditions of velaglucerase alfa (Vpriv) in 6 European countries. Annex II was updated in order too include new agreed key elements for the educational material. The RMP (version 11.0) was updated accordingly

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

Applicant: H. Lundbeck A/S

PRAC Rapporteur: Jean-Michel Dogné

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

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

17.5.1. Arsenic trioxide - TRISENOX (CAP) - EMEA/H/C/000388/MEA 050.4

Applicant: Teva B.V.

PRAC Rapporteur: Tiphaine Vaillant

Scope: Second interim report for study PASS C18477-ONC-50025: a post-authorisation long term safety cohort study in acute promyelocytic leukaemia (APL) patients treated with Trisenox (arsenic trioxide) to assess the long-term safety of all-trans retinoic acid (ATRA) + arsenic trioxide (ATO) in newly-diagnosed low to intermediate risk APL patients in a real-world clinical practice setting

17.5.2. Coronavirus (COVID-19) vaccine (ChAdOx1-S [recombinant]) - VAXZEVRIA (CAP) - EMEA/H/C/005675/MEA 007.6

Applicant: AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

Scope: First interim report for study D8111R00006: a post-authorisation/post-marketing

observational study using existing secondary health data sources to evaluate the association between exposure to AZD1222 and safety concerns

17.5.3. Coronavirus (COVID-19) vaccine (ChAdOx1-S [recombinant]) - VAXZEVRIA (CAP) - EMEA/H/C/005675/MEA 006.5

Applicant: AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

Scope: Third Quarterly Report for study D8110C00003: COVID-19 Vaccines International Pregnancy Registry of Women Exposed to AZD1222 Immediately Before or During Pregnancy (C-VIPER)

17.5.4. Elasomeran - SPIKEVAX (CAP) - EMEA/H/C/005791/MEA 003.6

Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Fifth interim report for a study (listed as a category 3 study in the RMP): a post authorisation safety of Spikevax (elasomeran) in the US - an enhanced pharmacovigilance study to provide additional evaluation of adverse events of special interest (AESI) and emerging validated safety signals [P903]

17.5.5. Elasomeran - SPIKEVAX (CAP) - EMEA/H/C/005791/MEA 004.6

Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Second 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

17.5.6. Elasomeran - SPIKEVAX (CAP) - EMEA/H/C/005791/MEA 034.3

Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: First interim report for study mRNA-1273-P905 [study monitoring the safety of Spikevax (COVID-19 vaccine) in pregnancy: an observational study using routinely collected health data in five European countries]

17.5.7. Ertugliflozin - STEGLATRO (CAP) - EMEA/H/C/004315/MEA 002.4

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to MEA 002.3 [first interim report for study MK8835-062: a PASS to

assess the risk of diabetic ketoacidosis among type 2 diabetes mellitus patients (T2DM) treated with ertugliflozin compared to patients treated with other antihyperglycemic agents] as per the request for supplementary information adopted in March 2022

17.5.8. Ertugliflozin, metformin hydrochloride - SEGLUROMET (CAP) - EMEA/H/C/004314/MEA 002.4

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to MEA 002.3 [first interim report for study MK-8835-062: a PASS to assess the risk of diabetic ketoacidosis (DKA) among type 2 diabetes mellitus (T2DM) patients treated with ertugliflozin compared to patients treated with other antihyperglycemic agents] as per the request for supplementary information adopted in March 2022

17.5.9. Ertugliflozin, sitagliptin - STEGLUJAN (CAP) - EMEA/H/C/004313/MEA 002.4

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to MEA 002.3 [first interim report for study MK-8835-062: a PASS to assess the risk of diabetic ketoacidosis (DKA) among type 2 diabetes mellitus (T2DM) patients treated with ertugliflozin compared to patients treated with other antihyperglycemic agents] as per the request for supplementary information adopted in March 2022

17.5.10. Infliximab - FLIXABI (CAP) - EMEA/H/C/004020/MEA 003.1

Applicant: Samsung Bioepis NL B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Annual interim report for a study (listed as a category 3 study in the RMP): a national prospective, observational, uncontrolled cohort study whose objectives are to evaluate the risk of selected adverse events (AEs) in rheumatoid arthritis (RA), juvenile idiopathic arthritis, and other rheumatic disease patients treated with infliximab using the Anti-Rheumatic Therapies in Sweden (ARTIS) national surveillance programme [final clinical study report (CSR) expected in 2027]

17.5.11. Infliximab - FLIXABI (CAP) - EMEA/H/C/004020/MEA 002.3

Applicant: Samsung Bioepis NL B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Annual interim report for a prospective study (listed as a category 3 study in the RMP) to treat patients with rheumatological disorders with biological agents to assess long-term toxicity of these agents in routine clinical practice using the British Society of Rheumatology Biologics Register for Rheumatoid Arthritis (BSRBR-RA): an established nationwide register [final clinical study report (CSR) expected in 2027]

17.5.12. Infliximab - FLIXABI (CAP) - EMEA/H/C/004020/MEA 005.3

Applicant: Samsung Bioepis NL B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Annual interim report for a study (listed as a category 3 study in the RMP): a prospective, observational cohort study whose objectives are to evaluate the long-term effectiveness, safety, and costs associated with tumour necrosis factor (TNF)-inhibitor therapies in the treatment of rheumatoid arthritis (RA) and to compare this to a cohort of RA patients who are treated with non-biologic disease-modifying antirheumatic drugs (DMARDs) [final clinical study report (CSR) expected in 2027]

17.5.13. Infliximab - FLIXABI (CAP) - EMEA/H/C/004020/MEA 006.3

Applicant: Samsung Bioepis NL B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Annual interim report for a study (listed as a category 3 in the RMP) conducted in the Spanish register of adverse events of biological therapies in rheumatic diseases (BIOBADASER) to identify relevant adverse events occurring during treatment of rheumatic diseases with biological therapies, to estimate the frequency of their occurrence; to identify unexpected adverse events; to identify relevant adverse events that occur following the suspension of the treatment, to estimate the relative risk of occurrence of adverse events with biological therapies in patients with rheumatoid arthritis (RA) compared to those not exposed to these treatments; to identify risk factors for suffering adverse reactions with these treatments; to evaluate, under non-experimental conditions, the treatment duration before the biological medications had been suspended in patients with rheumatic diseases, as well as the reasons for the interruption of the treatment [final clinical study report (CSR) expected in 2027]

17.5.14. Infliximab - FLIXABI (CAP) - EMEA/H/C/004020/MEA 009.2

Applicant: Samsung Bioepis NL B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Interim report for the Chronisch Entzündliche Darmerkrankungen, ein Unabhängiges Register (CEDUR) to describe the long-term effectiveness of treatment with inflammatory bowel disease (IBD)

17.5.15. Infliximab - FLIXABI (CAP) - EMEA/H/C/004020/MEA 010.2

Applicant: Samsung Bioepis NL B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Interim report for the Czech Register of inflammatory bowel disease (IBD) Patients on Biological Therapy (CREDIT) to monitor effectiveness of total population of IBD patients on biological medication in the Czech Republic and regular analytical evaluation of the effectiveness

17.5.16. Ivacaftor, tezacaftor, elexacaftor - KAFTRIO (CAP) - EMEA/H/C/005269/MEA 002.4

Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Martin Huber

Scope: MAH's response to MEA 002.3 [first annual interim report for study VX20-445-120: a five year-registry based study to assess real-world effects and utilisation patterns of elexacaftor/tezacaftor/ivacaftor combination therapy (ELX/TEZ/IVA) in patients with cystic fibrosis (CF)] as per the request for supplementary information (RSI) adopted in March 2022

17.5.17. Mexiletine - NAMUSCLA (CAP) - EMEA/H/C/004584/MEA 001.3

Applicant: Lupin Europe GmbH

PRAC Rapporteur: Eva Jirsová

Scope: Interim report for study LUP/MEX/2018/001: registry study to determine the long-term safety and tolerability of Namuscla for the symptomatic treatment of myotonia in adult patients with non-dystrophic myotonic disorder

17.5.18. Pegfilgrastim - NEULASTA (CAP) - EMEA/H/C/000420/MEA 059.3

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Interim report for study 20170701 (listed as category 3 study in the RMP): an observational study to assess the effectiveness of the Neulasta (pegfilgrastim) patient alert card (PAC) and to measure medication errors related to the use of the On-Body injector (OBI) to assess respondent awareness of key safety messages and behavioural intent to carry out recommended actions as described in the PAC and to estimate the proportion of OBI administrations associated with medication error

17.5.19. Pegvaliase - PALYNZIQ (CAP) - EMEA/H/C/004744/MEA 003.4

Applicant: BioMarin International Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: MAH's response to MEA 003.3 [first interim report for study 165-501: a multicentre, prospective global observational study to evaluate the long-term safety of subcutaneous injections of pegvaliase in patients with phenylketonuria] as per the request for supplementary information (RSI) adopted in March 2022

17.5.20. Pegvaliase - PALYNZIQ (CAP) - EMEA/H/C/004744/MEA 005.3

Applicant: BioMarin International Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: First interim report for study 165-504: a prospective global multicentre observational safety surveillance study to assess maternal, foetal and infant outcomes of exposure to Palynziq (pegvaliase) during pregnancy and breastfeeding

17.5.21. Prasterone - INTRAROSA (CAP) - EMEA/H/C/004138/ANX 001.1

Applicant: Endoceutics S.A.

PRAC Rapporteur: Menno van der Elst

Scope: Interim report for study ERC-243: a non-interventional PASS - Drug Utilisation Study (DUS) to describe the baseline characteristics, utilisation patterns of EU postmenopausal women initiating treatment with Intrarosa and to assess whether EU prescribers abide by the contraindications stated in the EU SmPC (protocol previously agreed in July 2021)

17.5.22. Tildrakizumab - ILUMETRI (CAP) - EMEA/H/C/004514/MEA 003.5

Applicant: Almirall S.A

PRAC Rapporteur: Adam Przybylkowski

Scope: MAH's response to MEA 003.4 [annual progress report 2021 for study M-14745-40: a European psoriasis registry to collect long-term safety data for tildrakizumab and to further characterise the long-term safety profile of tildrakizumab in the treatment of psoriasis under conditions of routine clinical practice] as per the request for supplementary information (RSI) adopted in March 2022

17.5.23. Tozinameran - COMIRNATY (CAP) - EMEA/H/C/005735/MEA 054

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Interim report for study C4591022: Pfizer-BioNTech COVID-19 Vaccine Exposure during Pregnancy: A Non-Interventional Post-Approval Safety Study of Pregnancy and Infant Outcomes in the Organization of Teratology Information Specialists (OTIS)/MotherToBaby Pregnancy Registry

17.5.24. Ulipristal acetate - ESMYA (CAP) - EMEA/H/C/002041/MEA 018.6

Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Annika Folin

Scope: Sixth yearly progress report for study PGL14-001: a prospective, multinational, multicentre, non-interventional study to evaluate the long-term safety of Esmya (ulipristal acetate) in particular the endometrial safety and the current prescription and management patterns of Esmya (ulipristal acetate) in a long-term treatment setting

17.5.25. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/MEA 044.14

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: Fourth interval safety registry for study CNTO1275PSO4056: an observational PASS of ustekinumab in the treatment of paediatric patients aged 12 years and older with moderate to severe plaque psoriasis (adolescent registry)

17.6. Others

17.6.1. Acalabrutinib - CALQUENCE (CAP) - EMEA/H/C/005299/MEA 002.4

Applicant: AstraZeneca AB

PRAC Rapporteur: Željana Margan Koletić

Scope: MAH's responses to MEA 002.2 [protocol for study D8220C00008 (listed as a category 3 study in the RMP): a phase 3b, multicentre, open-label, single-arm study in subjects with chronic lymphocytic leukaemia (ASSURE) to address missing information around moderate to severe cardiac impaired patients in subjects treated with Calquence (acalabrutinib)] as per the request for supplementary information (RSI) adopted in February 2022

17.6.2. Darolutamide - NUBEQA (CAP) - EMEA/H/C/004790/REC 004

Applicant: Bayer AG

PRAC Rapporteur: Jan Neuhauser

Scope: Submission of an addendum to the final clinical report for study (17712): efficacy and safety study of darolutamide (ODM-201) in men with high-risk non-metastatic castration-resistant prostate cancer (ARAMIS)

17.6.3. Fremanezumab - AJOVY (CAP) - EMEA/H/C/004833/MEA 005.3

Applicant: TEVA GmbH

PRAC Rapporteur: Kirsti Villikka

Scope: Protocol synopsis for a multi-country retrospective database study TV48125-MH-40217: 'A Long-Term Observational, Retrospective Cohort Study to Evaluate the Safety Including Cardiovascular Safety, of Fremanezumab in Patients with Migraine in Routine Clinical Practice in the United States and Europe' to replace the current ongoing prospective PASS (TV48125-MH-50039)

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. Amifampridine - FIRDAPSE (CAP) - EMEA/H/C/001032/S/0073 (without RMP)

Applicant: SERB SA

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Annual reassessment of the marketing authorisation

18.1.2. Chenodeoxycholic acid - CHENODEOXYCHOLIC ACID LEADIANT (CAP) - EMEA/H/C/004061/S/0020 (without RMP)

Applicant: Leadiant GmbH

PRAC Rapporteur: Adam Przybylkowski

Scope: Annual reassessment of the marketing authorisation

18.1.3. Clofarabine - EVOLTRA (CAP) - EMEA/H/C/000613/S/0076 (without RMP)

Applicant: Genzyme Europe BV

PRAC Rapporteur: Tiphaine Vaillant

Scope: Annual reassessment of the marketing authorisation

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

Applicant: Takeda Pharmaceuticals International AG Ireland Branch

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Annual reassessment of the marketing authorisation

18.1.5. Zanamivir - DECTOVA (CAP) - EMEA/H/C/004102/S/0013 (without RMP)

Applicant: GlaxoSmithKline Trading Services Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Annual reassessment of the marketing authorisation

18.2. Conditional renewals of the marketing authorisation

18.2.1. Amivantamab - RYBREVANT (CAP) - EMEA/H/C/005454/R/0002 (without RMP)

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Conditional renewal of the marketing authorisation

18.2.2. Ixazomib - NINLARO (CAP) - EMEA/H/C/003844/R/0040 (without RMP)

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Annika Folin

Scope: Conditional renewal of the marketing authorisation

18.2.3. Pralsetinib - GAVRETO (CAP) - EMEA/H/C/005413/R/0006 (without RMP)

Applicant: Roche Registration GmbH

PRAC Rapporteur: Annika Folin

Scope: Conditional renewal of the marketing authorisation

18.3. Renewals of the marketing authorisation

18.3.1. Benralizumab - FASENRA (CAP) - EMEA/H/C/004433/R/0044 (without RMP)

Applicant: AstraZeneca AB

PRAC Rapporteur: David Olsen

Scope: 5-year renewal of the marketing authorisation

18.3.2. Bevacizumab - MVASI (CAP) - EMEA/H/C/004728/R/0025 (without RMP)

Applicant: Amgen Technology (Ireland) Unlimited Company

PRAC Rapporteur: Anette Kirstine Stark

Scope: 5-year renewal of the marketing authorisation

18.3.3. Budesonide - JORVEZA (CAP) - EMEA/H/C/004655/R/0016 (without RMP)

Applicant: Dr. Falk Pharma GmbH

PRAC Rapporteur: Zane Neikena

Scope: 5-year renewal of the marketing authorisation

18.3.4. Emicizumab - HEMLIBRA (CAP) - EMEA/H/C/004406/R/0032 (without RMP)

Applicant: Roche Registration GmbH

PRAC Rapporteur: Amelia Cupelli

Scope: 5-year renewal of the marketing authorisation

18.3.5. Human fibrinogen, human thrombin - VERASEAL (CAP) - EMEA/H/C/004446/R/0018 (without RMP)

Applicant: Instituto Grifols, S.A.

PRAC Rapporteur: Amelia Cupelli

Scope: 5-year renewal of the marketing authorisation

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

Applicant: Diurnal Europe BV

PRAC Rapporteur: Annika Folin

Scope: 5-year renewal of the marketing authorisation

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

Applicant: Gen.Orph

PRAC Rapporteur: Ulla Wändel Liminga

Scope: 5-year renewal of the marketing authorisation

18.3.8. Naloxone - NYXOID (CAP) - EMEA/H/C/004325/R/0014 (without RMP)

Applicant: Mundipharma Corporation (Ireland) Limited

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: 5-year renewal of the marketing authorisation

18.3.9. Ocrelizumab - OCREVUS (CAP) - EMEA/H/C/004043/R/0033 (without RMP)

Applicant: Roche Registration GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: 5-year renewal of the marketing authorisation

18.3.10. Prasterone - INTRAROSA (CAP) - EMEA/H/C/004138/R/0022 (with RMP)

Applicant: Endoceutics S.A.

PRAC Rapporteur: Menno van der Elst

Scope: 5-year renewal of the marketing authorisation

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

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Menno van der Elst

Scope: 5-year renewal of the marketing authorisation

18.3.12. Semaglutide - OZEMPIC (CAP) - EMEA/H/C/004174/R/0030 (without RMP)

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Annika Folin

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 04-07 July 2022 meeting (marked as "a") and the 20 July 2022 ORGAM teleconference (marked as "b").

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

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Martin Huber [a, b]	Member (Vice-Chair)	Germany	No interests declared	
Brigitte Keller-Stanislawski [a, b]	Alternate	Germany	No interests declared	
Sofia Trantza [a, b]	Member	Greece	No interest declared	
Georgia Gkegka [a]	Alternate	Greece	No interest declared	
Julia Pallos [a, b]	Member	Hungary	No participation in final deliberations and voting on:	5.1.2. Deucravacitinib - TYCRUVA (CAP MAA) - EMEA/H/C/005755 5.1.8. Mavacamten - CAMZYOS (CAP MAA) - EMEA/H/C/005457 7.1.1. Lisocabtagene maraleucel - BREYANZI (CAP) - EMEA/H/C/PSP/S/0098 16.1.9. Elotuzumab - EMPLICITI (CAP) - PSUSA/00010500/202111 16.1.17. Luspatercept - REBLOZYL (CAP) - PSUSA/00010860/202112 16.3.7. Hydroxycarbamide (NAP) - PSUSA/00009182/202112
Melinda Palfi [b]	Alternate	Hungary	No interest declared	
Guðrún Stefánsdóttir [a]	Member	Iceland	No participation in final deliberations and voting on:	16.1.5. Blinatumomab - BLINCYTO (CAP) - PSUSA/00010460/202112

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				17.5.18. Pegfilgrastim - NEULASTA (CAP) - EMEA/H/C/000420 /MEA 059.3 18.3.2. Bevacizumab - MVASI (CAP) - EMEA/H/C/004728 /R/0025 (without RMP)
Rhea Fitzgerald [a]	Member	Ireland	No interests declared	
Ronan Grimes [a, b]	Alternate	Ireland	No interests declared	
Amelia Cupelli [a, b]	Member	Italy	No interests declared	
Valentina Di Giovanni [a]	Alternate (New membership as Alternate for Italy started on 24/06/2022)	Italy	No interests declared	
Zane Neikena [a, b]	Member	Latvia	No interests declared	
Zane Stade [b]	Alternate	Latvia	No interests declared	
Rugile Pilviniene [a]	Member	Lithuania	No interests declared	
Lina Seibokiene [a]	Alternate	Lithuania	No restrictions applicable to this meeting	
Nadine Petitpain [a]	Member	Luxembourg	No restrictions applicable to this meeting	
Benjamin Micallef [a]	Alternate	Malta	No interests declared	
Menno van der Elst [a]	Member	The Netherlands	No interests declared	
Liana Gross-Martirosyan [a]	Alternate	The Netherlands	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
David Olsen [a]	Member	Norway	No participation in final deliberations and voting on:	17.6.2. Darolutamide - NUBEQA (CAP) - EMEA/H/C/004790 /REC 004
Karen Pernille Harg [a]	Alternate	Norway	No interests declared	
Adam Przybylkowski [a]	Member	Poland	No interests declared	
Katarzyna Ziolkowska [a, b]	Alternate	Poland	No interests declared	
Ana Diniz Martins [a, b]	Member	Portugal	No interests declared	
Marcia Sofia Sanches de Castro Lopes Silva [a, b]	Alternate	Portugal	No interests declared	
Alexandra - Maria Spurni [a, b]	Alternate	Romania	No interests declared	
Anna Mareková [a]	Member (New membership as Member for Slovakia started on 24/06/2022)	Slovakia	No interests declared	
Lucia Kuráková [a, b]	Alternate (New membership as Alternate for Slovakia started on 24/06/2022)	Slovakia	No interests declared	
Polona Golmajer [a]	Member	Slovenia	No interests declared	
Milena Radoha-Bergoc [b]	Alternate	Slovenia	No participation in final deliberations and voting on:	4.1.1. 3-hydroxy 3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins): atorvastatin (NAP); fluvastatin (NAP); lovastatin

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				(NAP); pitavastatin (NAP); pravastatin (NAP); pravastatin, fenofibrate – PRAVAFENIX (CAP); rosuvastatin (NAP); simvastatin (NAP); simvastatin, fenofibrate – CHOLIB (CAP) 16.3.8. Indapamide, perindopril (NAP) - PSUSA/00010230/ 202111
Eva Segovia [a, b]	Member	Spain	No interests declared	
Maria del Pilar Rayon [a, b]	Alternate	Spain	No interests declared	
Ulla Wändel Liminga [a, b]	Member	Sweden	No interests declared	
Annika Folin [a]	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, b]	Member	Independent scientific expert	No interests declared	
Daniel Morales [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 the meeting	
Salvatore Antonio Giuseppe Messana [a]	Alternate	Healthcare Professionals' Representative	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Declan Noone [a, b]	Member	Patients' Organisation Representative	No interests declared	
Marko Korenjak [a]	Alternate	Patients' Organisation Representative	No participation in discussion, final deliberations and voting on:	6.1.1. Cabozantinib - CABOMETYX (CAP); COMETRIQ (CAP) - PSUSA/00010180/ 202111
Christelle Bizimungu [a]	Expert	Belgium	No restrictions applicable to this meeting	
Laurence de Fays [a]	Expert	Belgium	No interests declared	
Evelien De Clercq [a]	Expert	Belgium	No interests declared	
Piyush Jain [a]	Expert	Belgium	No restrictions applicable to the meeting	
Jo Robays [a]	Expert	Belgium	No restrictions applicable to the meeting	
Martine Sabbe [a]	Expert	Belgium	No interests declared	
Ane Blicher Schelde [a]	Expert	Denmark	No restrictions applicable to the meeting	
Kirsten Egebjerg Juul [a]	Expert	Denmark	No restrictions applicable to the meeting	
Karin Susanne Erneholm [a]	Expert	Denmark	No restrictions applicable to this meeting	
Lise Hobolth [a]	Expert	Denmark	No restrictions applicable to this meeting	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Pernille Lynge Gammelgaard [a, b]	Expert	Denmark	No interests declared	
Marian Hjortlund Allon [a]	Expert	Denmark	No interests declared	
Marie Holm Abildgaard [a]	Expert	Denmark	No interests declared	
Katrine Jønsson [a]	Expert	Denmark	No interests declared	
Line Michan [a]	Expert	Denmark	No interests declared	
Per Sindahl [a]	Expert	Denmark	No restrictions applicable to this meeting	
Josiane Uwera [a]	Expert	Denmark	No restrictions applicable to this meeting	
Julia Maslovskaja [a]	Expert	Estonia	No interests declared	
Nicolas Camhaji [a]	Expert	France	No restrictions applicable to this meeting	
Samuel Crommelynck [a]	Expert	France	No restrictions applicable to this meeting	
Pauline Dayani [a]	Expert	France	No interests declared	
Vincent Gazin [a]	Expert	France	No interests declared	
Stephanie Hueber [a]	Expert	France	No interests declared	
Leo Lambart [a]	Expert	France	No restrictions applicable to this meeting	
Marie-Caroline Pesquidous [a]	Expert	France	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
Youssef Shaim [a]	Expert	France	No restrictions applicable to this meeting	
Laure Tiquet [a]	Expert	France	No interests declared	
Faustine Vidil [a]	Expert	France	No interests declared	
Nicole Bick [a]	Expert	Germany	No interests declared	
Sabine Kudicke [a]	Expert	Germany	No interests declared	
Dennis Lex [a, b]	Expert	Germany	No restrictions applicable to this meeting	
Nerina Pflanz [a]	Expert	Germany	No interests declared	
Eamon O'Murchu [a]	Expert	Ireland	No interests declared	
Michal Pirozynski [a]	Expert	Malta	No restrictions applicable to this meeting	
Lisa Heltzel [a]	Expert	The Netherlands	No interests declared	
Bianca Mulder [a]	Expert	The Netherlands	No interests declared	
Evelyn Mulder-Olthof [a]	Expert	The Netherlands	No interests declared	
Paul ten Berg [a]	Expert	The Netherlands	No interests declared	
Fernanda Inês Carvalho Pereira Ribeiro Vaz [a]	Expert	Poland	No restrictions applicable to this meeting	
Carla Torre [a]	Expert	Portugal	No interests declared	
Charlotte Backman [a]	Expert	Sweden	No interests declared	
Karin Nylén [a]	Expert	Sweden	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Mari Thörn [a]	Expert	Sweden	No restrictions applicable to this meeting	
Lise Lotte Gluud [a]	Expert	Denmark	Expert witness for:	3.2.1. Terlipressin (NAP) - EMEA/H/A-31/1514
Meeting run with support from relevant EMA staff				

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

20. Annex III - List of acronyms and abbreviations

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

21. Explanatory notes

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

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

(Items 2 and 3 of the PRAC minutes)

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

Signals assessment and prioritisation

(Item 4 of the PRAC minutes)

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

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

Risk Management Plans (RMPs)

(Item 5 of the PRAC minutes)

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

Assessment of Periodic Safety Update Reports (PSURs)

(Item 6 of the PRAC minutes)

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

Post-authorisation Safety Studies (PASS)

(Item 7 of the PRAC minutes)

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

Product related pharmacovigilance inspections

(Item 9 of the PRAC minutes)

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

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