18 August 2023
EMA/PRAC/332783/2023
Human Medicines Division

Pharmacovigilance Risk Assessment Committee (PRAC)

Minutes of PRAC meeting on 10-12 May 2023

Chair: Sabine Straus – Vice-Chair: Martin Huber

Disclaimers

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

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

Note on access to documents

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

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1. Introduction

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

The Chairperson opened the meeting by welcoming all participants. The meeting was held remotely.

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

1.2. Agenda of the meeting on 10-12 May 2023

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

1.3. Minutes of the previous meeting on 11-14 April 2023

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

Post-meeting note: the PRAC minutes of the meeting held on 11-14 April 2023 were published on the EMA website on 07 July 2023 (EMA/PRAC/280418/2023).

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

2.1. Newly triggered procedures

None

2.2. Ongoing procedures

None

2.3. Procedures for finalisation

None

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

3.1. Newly triggered procedures

3.1.1. Hydroxyprogesterone (NAP) - EMEA/H/A-31/1528

Applicant(s): various

PRAC Rapporteur: Amelia Cupelli; PRAC Co-rapporteur: Nathalie Gault

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

Hydroxyprogesterone caproate (17-OHPC) is a synthetic ester of 17-OH progesterone, an endogenous progestogen with an affinity for progesterone receptors. It is indicated for the treatment of disorders of progesterone deficiency, sterility due to luteal insufficiency, artificial cycle in association with an oestrogen, as well as for threatened abortion or prevention of repeated abortion by proven luteal insufficiency and threat of premature deliver in connection with uterine hypermobility. It is also indicated for dysfunctional juvenile and climacteric metrorrhagia, primary and secondary amenorrhea, protection of pregnancy in the event of surgery and luteal insufficiency.

The French Medicine Agency (ANSM) sent a letter of notification dated 05 May 2023 triggering a referral under article 31 of Directive 2001/83/EC for the review of hydroxyprogesterone-containing products following the results of a pharmacoepidemiological study by *Murphy et al*[1] that showed that *in utero* exposure to 17-OHPC may be associated with a higher risk of cancer in the offspring. In addition, the results from another study by *Blackwell et al*[2] suggested that 17-OHPC is no more effective than placebo in preventing recurrent premature birth or medical complications due to prematurity in the newborn infant.

Considering the seriousness of the events occurring in the offspring of women treated during their pregnancy with 17-OHPC and the indications for which the medicines are approved, ANSM referred the matter to PRAC in the interest of the Union for further evaluation and requested that it gives its recommendation as to whether the marketing authorisation(s) for hydroxyprogesterone-containing product(s) should be maintained, varied, suspended or revoked.

Discussion

PRAC noted the notification letter from ANSM.

PRAC appointed Amelia Cupelli as Rapporteur and Nathalie Gault as Co-Rapporteur for the procedure.

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

Summary of recommendation(s)/conclusions

[1] Murphy CC, et al. In utero exposure to 17α-hydroxyprogesterone caproate and risk of cancer in offspring. Am J Obstet Gynecol. 2022 Jan;226(1):132.e1-132.e14. doi:10.1016/j.ajog.2021.10.035
[2] Blackwell, S. C. et al. 17-OHPC to prevent recurrent preterm birth in singleton gestations (PROLONG Study): A multicenter, international, randomized double-blind trial. Am J Perinatol. 2020 Jan;37(2):127-136. doi:10.1055/s-0039-3400227

- The Committee adopted a LoQ to the MAHs (EMA/PRAC/194264/2023) and a timetable for the procedure (EMA/PRAC/194263/2023).
- PRAC discussed the option to conduct a public hearing in the context of the current procedure according to the pre-defined criteria set out in the rules of procedure (EMA/11523/2023 Rev 2). It was agreed by the Committee that at this stage in the assessment, in light of the currently available data and the need to determine the appropriate approach to stakeholder engagement, a public hearing would not be appropriate. PRAC can reconsider this at a later stage of the procedure, as needed.

See EMA press release (EMA/203354/2023) entitled 'Review of hydroxyprogesterone started'.

3.2. Ongoing procedures

3.2.1. Pseudoephedrine (NAP); pseudoephedrine, acetylsalicylic acid (NAP); pseudoephedrine, acetylcysteine, paracetamol (NAP); pseudoephedrine, acrivastine (NAP); pseudoephedrine, ascorbic acid, paracetamol (NAP); pseudoephedrine, cetirizine (NAP); pseudoephedrine, ebastine (NAP); pseudoephedrine, guaifenesin (NAP); pseudoephedrine, ibuprofen (NAP); pseudoephedrine, chlorphenamine (NAP); pseudoephedrine, chlorphenamine, codeine (NAP); pseudoephedrine, chlorphenamine, dextromethorphan (NAP); pseudoephedrine, chlorphenamine, paracetamol (NAP); pseudoephedrine, chlorphenamine, dextromethorphan, paracetamol (NAP); pseudoephedrine, dextromethorphan (NAP); pseudoephedrine, dextromethorphan, paracetamol (NAP); pseudoephedrine, dextromethorphan, ascorbic acid, paracetamol (NAP); pseudoephedrine, dextromethorphan, guaifenesin, paracetamol (NAP); pseudoephedrine, dextromethorphan, guaifenesin, triprolidine (NAP); pseudoephedrine, dextromethorphan, triprolidine (NAP); pseudoephedrine, diphenhydramine, paracetamol (NAP); pseudoephedrine, doxylamine, paracetamol (NAP); pseudoephedrine, loratadine (NAP); pseudoephedrine, paracetamol (NAP); pseudoephedrine, paracetamol, pholcodine (NAP); pseudoephedrine, triprolidine (NAP); pseudoephedrine, triprolidine, guaifenesin (NAP); pseudoephedrine, triprolidine, paracetamol (NAP); pseudoephedrine, desloratadine - AERINAZE (CAP) – EMA/H/A-31/1526

Applicant(s): various

PRAC Rapporteur: Eva Jirsová; PRAC Co-rapporteur: Krõõt Aab

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

Background

A referral procedure under Article 31 of Directive 2001/83/EC is ongoing for pseudoephedrine-containing products following the assessment of the PSUR single assessment (PSUSA) procedure on ibuprofen/pseudoephedrine (PSUSA/00001711/202207) concluded in February 2023. The data submitted by the MAHs within the PSUSA procedure suggested a causal relationship between posterior reversible encephalopathy syndrome (PRES), reversible cerebral vasoconstriction syndrome (RCVS) and pseudoephedrine use, based on the compatible and suggestive time to onset, the biological plausibility and the lack of alternative aetiologies for some patients without any risk factors. Considering the seriousness of PRES and RCVS, the overall safety profile of pseudoephedrine and the indications for which the medicines are approved, the matter was referred to PRAC for further evaluation. For further background, see PRAC minutes January 2023 and PRAC minutes February 2023.

Summary of recommendation(s)/conclusions

- PRAC discussed the assessment reports issued by the Rapporteurs.
- PRAC adopted a list of outstanding issues (LoOI) to be addressed by the MAHs in accordance with a revised timetable (EMA/PRAC/55340/2023 Rev. 1).
- PRAC also adopted a list of questions (LoQ) for an ad-hoc expert group (AHEG) meeting.

3.3. Procedures for finalisation

None

3.4. Re-examination procedures[3]

None

3.5. Others

None

4. Signals assessment and prioritisation[4]

4.1. New signals detected from EU spontaneous reporting systems

See also Annex I 14.1.

4.1.1. Mepolizumab – NUCALA (CAP)

Applicant: GlaxoSmithKline Trading Services Limited

PRAC Rapporteur: Gabriele Maurer

Scope: Signal of arthralgia

EPITT 19919 – New signal

Lead Member State(s): DE

Background

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

During routine signal detection activities, a signal of arthralgia was identified by Spain based on 31 cases retrieved from the national database. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by PRAC.

Discussion

[3] Re-examination of PRAC recommendation under Article 32 of Directive 2001/83/EC
[4] 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.

Having considered the available evidence in EudraVigilance and literature, PRAC agreed that further evaluation on the signal of arthralgia with Nucala (mepolizumab) is warranted.

Summary of recommendation(s)

- In the next PSUR[5], the MAH for Nucala (mepolizumab) should submit to EMA a cumulative review of cases of arthralgia and discuss the plausibility and possible mechanism(s) of action. The MAH should propose to update the product information and/or RMP as warranted.

4.2. New signals detected from other sources

See also Annex I 14.2.

4.3. Signals follow-up and prioritisation

4.3.1. Elasomeran - SPIKEVAX (CAP) - EMEA/H/C/005791/SDA/090

Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Signal of myositis

EPITT 19884 – follow up to January 2023

Background

For background information, see PRAC minutes January 2023.

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

Discussion

Having considered the available evidence, including the MAH's responses and Rapporteur's assessment, PRAC concluded that there is insufficient evidence at present to confirm a causal association between Spikevax (elasomeran) and myositis.

Summary of recommendation(s)

- The MAH for Spikevax (elasomeran) should continue to monitor any cases of idiopathic inflammatory myopathies (IIM)/myositis and their flares in the next PSURs. The MAH should also include a follow-up on cases of IIM/myositis in the final study report of EU PASS study mRNA-1273-P904 to be submitted in December 2023.

See also EMA/PRAC/207872/2023 published on 5 June 2023 on the EMA website.

4.3.2. Lenvatinib - LENVIMA (CAP) - EMEA/H/C/004224/SDA/018; KISPLYX (CAP) - EMEA/H/C/003727/SDA/021

Applicant: Eisai GmbH

PRAC Rapporteur: Ulla Wändel Liminga (Lenvima); David Olsen (Kisplyx)

[5] Data lock point: 23 September 2023

Scope: Signal of adrenal insufficiency

EPITT 19870 – follow up to January 2023

Background

For background information, see PRAC minutes January 2023.

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

Discussion

Having considered the available evidence, including non-clinical and literature data, taking also into account the plausible biological mechanism, PRAC agreed that a causal association between lenvatinib and adrenal insufficiency is considered at least a reasonable possibility. Therefore, PRAC agreed that an update of the product information of lenvatinib is warranted to add adrenal insufficiency as an undesirable effect with a frequency 'uncommon' for the monotherapy/combination treatment with everolimus, and with a frequency 'common' for the combination treatment with pembrolizumab.

Summary of recommendation(s)

- The MAH for Lenvima and Kisplyx (lenvatinib) should submit to EMA, within 60 days, a variation to amend the product information[6].

See also EMA/PRAC/207872/2023 published on 5 June 2023 on the EMA website.

4.3.3. Progesterone (NAP)

Applicant: various

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of meningioma

EPITT 19871 – follow up to January 2023

Background

For background information, see PRAC minutes January 2023.

The MAHs Besins Healthcare Ireland Ltd and Merck A/S replied to the request for information on the signal of meningioma and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence, including the MAH's responses and Rapporteur's assessment, PRAC has concluded that there is insufficient evidence to establish a causal relationship between progesterone and meningioma at present.

Summary of recommendation(s)

- In the next PSUR, the MAHs for progesterone-containing products should continue to monitor cases of meningioma.

See also EMA/PRAC/207872/2023 published on 5 June 2023 on the EMA website.

[6] Update of SmPC section 4.8. The package leaflet is to be updated accordingly.

4.3.4. Tozinameran - COMIRNATY (CAP) - EMEA/H/C/005735/SDA/063

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Signal of myositis

EPITT 19883 – follow up to January 2023

Background

For background information, PRAC minutes January 2023.

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

Discussion

Having considered the available evidence, including the MAH's responses and Rapporteur's assessment, PRAC concluded that there is insufficient evidence for a causal association between vaccination with Comirnaty (tozinameran) and myositis at present.

Summary of recommendation(s)

- In the next PSUR, the MAH for Comirnaty (tozinameran) should continue to monitor cases of idiopathic inflammatory myopathies (IIM)/myositis and their flares. Moreover, the MAH should include and follow-up on cases of IIM/myositis in any of the ongoing PASSs listed in the pharmacovigilance plan of the RMP.

See also EMA/PRAC/207872/2023 published on 5 June 2023 on the EMA website.

4.4. Variation procedure(s) resulting from signal evaluation

None

5. Risk management plans (RMPs)

5.1. Medicines in the pre-authorisation phase

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

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

See also Annex I 15.1.

5.1.1. Cabotegravir - EMEA/H/C/005756

Scope: Pre-exposure prophylaxis of HIV-1 infection

5.1.2. Crisantaspase - EMEA/H/C/005917

Scope: Indicated as a component of a multi-agent chemotherapeutic regimen for the treatment of acute lymphoblastic leukaemia (ALL) and lymphoblastic lymphoma (LBL)

5.1.3. Dabrafenib - EMEA/H/C/005885, Orphan

Applicant: Novartis Europharm Limited

Scope: Treatment of glioma

5.1.4. Decitabine, cedazuridine - EMEA/H/C/005823, Orphan

Applicant: Otsuka Pharmaceutical Netherlands B.V.

Scope: Treatment of myeloid leukaemia

5.1.5. Elacestrant - EMEA/H/C/005898

Scope: Treatment of postmenopausal woman and men with breast cancer

5.1.6. Epcoritamab - EMEA/H/C/005985, Orphan

Applicant: AbbVie Deutschland GmbH & Co. KG

Scope: Treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL)

5.1.7. Exagamglogene autotemcel - EMEA/H/C/005763, PRIME, Orphan

Applicant: Vertex Pharmaceuticals (Ireland) Limited, ATMP[7]

Scope: Treatment of transfusion-dependent β-thalassaemia and sickle cell disease

5.1.8. Masitinib - EMEA/H/C/005897, Orphan

Applicant: AB Science

Scope: In combination with riluzole for the treatment of adult patients with amyotrophic lateral sclerosis (ALS)

5.1.9. Oteseconazole - EMEA/H/C/005682

Scope: Treatment and prevention of recurrent vulvovaginal candidiasis (RVVC) including the acute episodes of RVVC in adult women

5.1.10. Palovarotene - SOHONOS (CAP MAA) - EMEA/H/C/004867, Orphan

Applicant: Ipsen Pharma

Scope (under re-examination): Treatment of fibrodysplasia ossificans progressive

[7] Advanced therapy medicinal product

5.1.11. Quizartinib - EMEA/H/C/005910, Orphan

Applicant: Daiichi Sankyo Europe GmbH

Scope: Treatment of adult patients with diagnosed acute myeloid leukaemia (AML)

5.1.12. Ritlecitinib - EMEA/H/C/006025

Scope: Treatment of severe alopecia areata in adults and adolescents 12 years of age and older

5.1.13. Sparsentan - EMEA/H/C/005783, Orphan

Applicant: Vifor France

Scope: Treatment of primary immunoglobulin A nephropathy (IgAN)

5.1.14. Trametinib - EMEA/H/C/005886, Orphan

Applicant: Novartis Europharm Limited

Scope: Treatment of paediatric patients aged 1 year and older with glioma

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

None

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

See also Annex I 15.3.

5.3.1. Sacubitril, valsartan - ENTRESTO (CAP) - EMEA/H/C/004062/WS2465/0051; NEPARVIS (CAP) - EMEA/H/C/004343/WS2465/0049

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Anette Kirstine Stark

Scope: Submission of the final report from study CLCZ696B2320 listed as a category 3 study in the RMP in order to fulfil MEA/001. This is a multicentre, randomised, double-blind, active-controlled study to evaluate the effects of LCZ696 compared to valsartan on cognitive function in patients with chronic heart failure and preserved ejection fraction. The RMP version 6 has also been submitted

Background

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

CHMP is evaluating a worksharing variation procedure for Entresto and Neparvis, centrally authorised products containing sacubitril/valsartan to submit the final report from study CLCZ696B2320 listed as a category 3 study in the RMP. PRAC is responsible for providing advice to CHMP on the necessary updates to the RMP to support this procedure.

Summary of advice

- The RMP version 6 for Entresto and Neparvis (sacubitril,valsartan) in the context of the variation under evaluation by CHMP is considered acceptable.
- PRAC agreed with the summary of safety concern in the RMP, as proposed by the Applicant. In addition, PRAC agreed that the study CLCZ696B2320 can be removed from the list of additional pharmacovigilance activities from the RMP.

5.3.2. Vosoritide - VOXZOGO (CAP) - EMEA/H/C/005475/II/0007, Orphan

Applicant: BioMarin International Limited

PRAC Rapporteur: Zane Neikena

Scope: Type II B. IV.1.z Change of a measuring or administration device: to register an alternative CE-marked Transfer Needle and Administration Syringe from an alternate supplier, with consequential changes to the instructions for use in the product information (SmPC and PL)

Background

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

CHMP is evaluating a line extension for Voxzogo, a centrally authorised product containing vosoritide, to include a change of the administration device to an alternative CE-marked transfer needle and administration syringe from an alternate supplier, with consequential changes to the instructions for use in the product information. PRAC is responsible for providing advice to CHMP on the necessary updates to the RMP to support this procedure.

Summary of advice

- The MAH's justification for not submitting an RMP was not considered acceptable by PRAC.
- PRAC considered that the direct healthcare professional communication (DHPC) to inform HCPs about a change to the administration syringe and needle leading to product administration in units (U) instead of mL, as proposed by the Applicant, should address the important potential risk 'medication errors related to the change of the type of the syringe' as an additional risk minimisation measure. The MAH should submit an updated RMP to include a discussion regarding the potential risk of medication errors, considering the change of the type of the syringe, and provide a justification for not proposing an update to the summary of safety concern. In addition, the MAH should provide a revised DHPC and communication plan.

Post-meeting note 1: The MAH submitted RMP version 2.2 and agreed to provide an updated RMP in line with the request for supplementary information (RSI) as part of the ongoing variation procedure EMEA/H/C/005475/II/0006.

Post-meeting note 2: PRAC adopted the content of a direct healthcare professional communication (DHPC) along with a communication plan for its distribution via written procedure.

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. Asciminib - SCEMBLIX (CAP) - PSUSA/00011008/202210

Applicant: Novartis Europharm Limited

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 Scemblix, a centrally authorised medicine containing asciminib 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 Scemblix (asciminib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add hypersensitivity as an undesirable effect with a frequency 'uncommon'. Therefore, the current terms of the marketing authorisation(s) should be varied[8].
- In the next PSUR, the MAH should provide cumulative reviews of cases of cardiac failure and pericarditis, as well as of gynecomastia and related terms ('HLT Breast disorders NEC', HLT 'Breast signs and symptoms') along with a discussion on the need for an update of the product information (PI). Furthermore, the MAH should evaluate the cases reporting constipation and discuss an update of the PI as warranted. The MAH should discuss the need to update the RMP as warranted concerning additional pharmacovigilance activities for hepatitis B virus infection reactivation. In addition, the MAH should provide a review of cases of hyperglycaemia with treatment interruption/termination and cases of patients with *de novo* diabetes, along with a discussion on the need for updating the PI.

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. Conestat alfa - RUCONEST (CAP) - PSUSA/00000873/202210

Applicant: Pharming Group N.V

[8] 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: Jan Neuhauser

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Ruconest (conestat alfa) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add hypersensitivity reactions and anaphylaxis as undesirable effects with frequency 'not known' and 'common', respectively. In addition, the product information should be updated to add thromboembolic events as a warning and to amend the warning on hypersensitivity reactions. Therefore, the current terms of the marketing authorisation(s) should be varied[9].
- In the next PSUR, the MAH should closely monitor reports of medication error, allergic reactions, off label and intentional product use, thromboembolic events (also in conjunction with self- or home-administration), lack of efficacy, pharyngeal swelling and of cardiac events. The MAH should also discuss the imbalance of serious adverse events between intervention and standard of care groups as observed in study NCT04414631[10]. Furthermore, the MAH should investigate the occurrence of pharyngeal swelling in detail and discuss the need for inclusion of a restriction of indication in the EU marketing authorisation.

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

6.1.3. Edoxaban - LIXIANA (CAP); ROTEAS (CAP) - PSUSA/00010387/202210

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

PRAC Rapporteur: Nathalie Gault

Scope: Evaluation of a PSUSA procedure

Background

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

[9] 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.
[10] Conestat Alfa in the Prevention of Severe SARS-CoV-2 Infection in Hospitalized Patients With COVID-19

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Lixiana and Roteas, centrally authorised medicines containing edoxaban 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 Lixiana (edoxaban) and Roteas (edoxaban) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add a drug-drug interaction between clarithromycin and edoxaban, as well as to add anticoagulated-related nephropathy as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[11].
- In the next PSUR, the MAH should continue to closely monitor cases of medication errors related to non-compliance with dosage criteria or contra-indications as well as to assess the effectiveness of the prescriber guide. In addition, the MAH should discuss fatal intracranial bleeding cases connected to head trauma, taking into account also cases of subdural haematoma, even without a reported fall, for the analysis of deaths due to intracranial haemorrhage associated with a fall, as well as all cases of interstitial lung disease or lung injuries. Finally, the MAH should discuss cases of gastrointestinal haemorrhage taking into account all deaths related to digestive haemorrhage, regardless of the gastrointestinal haemorrhage site.

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. Ivacaftor, tezacaftor, elexacaftor - KAFTRIO (CAP) - PSUSA/00010868/202210

Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

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

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Kaftrio, a centrally authorised medicine containing ivacaftor/tezacaftor/elexacaftor 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, and the data presented by the MAH in the context of an oral explanation, the benefit-risk balance of Kaftrio (ivacaftor/tezacaftor/elexacaftor) in the approved indication(s) remains unchanged.

[11] Update of SmPC sections 4.5 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion.

- Nevertheless, the product information should be updated to include depression as a warning and 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 a review of cases of anaphylaxis for Kalydeco (ivacaftor), Orkambi (lumacaftor/ivacaftor), Symdeko (tezacaftor/ivacaftor and ivacaftor), and Trikafta (tezacaftor/ivacaftor/elexacaftor and ivacaftor) and discuss if there is a need for an update of the product information for Kaftrio (ivacaftor/tezacaftor/elexacaftor). The MAH should also provide a review of cases where the recommended intake was changed to overcome fatigue and/or insomnia and discuss if any update of the product information is warranted. In addition, the MAH should provide a review of cases of psychiatric events, including depression and any changes in mental health, and to discuss whether the measures that are currently in place to minimise depression are sufficient or whether additional measures/activities should be taken. The MAH should also provide a review of cases of birth defects, abortion and pregnancies, focusing on the duration of treatment before and 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.

6.1.5. Pemigatinib - PEMAZYRE (CAP) - PSUSA/00010923/202210

Applicant: Incyte Biosciences Distribution B.V.

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 Pemazyre, a centrally authorised medicine containing pemigatinib 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 Pemazyre (pemigatinib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include cutaneous calcification as an undesirable effect with a frequency 'uncommon'. Therefore, the current terms of the marketing authorisation(s) should be varied[13].

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.

[12] 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.
[13] 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.

6.1.6. Rivaroxaban - XARELTO (CAP) - PSUSA/00002653/202209

Applicant: Bayer AG

PRAC Rapporteur: Mari Thorn

Scope: Evaluation of a PSUSA procedure

Background

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

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Xarelto, a centrally authorised medicine containing rivaroxaban 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 Xarelto (rivaroxaban) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add anticoagulant related nephropathy as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[14].
- In the next PSUR, the MAH should present any new cases of confirmed vasculitis, as well as data on long-term treatment with rivaroxaban.

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. Tobramycin[15] [16] - VANTOBRA (CAP) - PSUSA/00010370/202209

Applicant: PARI Pharma GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

Background

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

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

Summary of recommendation(s) and conclusions

[14] Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion
[15] Nebuliser solution
[16] Centrally authorised product(s) only

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Vantobra (tobramycin) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add the increased risk of aminoglycoside-associated ototoxicity in patients with mitochondrial rRNA mutations as a warning. Therefore, the current terms of the marketing authorisation(s) should be varied[17].
- In the next PSUR, the MAH should present an updated cumulative review on cases of increased systemic levels of tobramycin in lung transplanted cystic fibrosis patients, and to provide any new data related to the drug-drug interaction between tobramycin and azithromycin that may lead to a lower effectiveness.

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

6.1.8. Vortioxetine - BRINTELLIX (CAP) - PSUSA/00010052/202209

Applicant: H. Lundbeck A/S

PRAC Rapporteur: Jo Robays

Scope: Evaluation of a PSUSA procedure

Background

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

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Brintellix, a centrally authorised medicine containing vortioxetine 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 Brintellix (vortioxetine) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add the following undesirable effects: dyspepsia with a frequency 'common', movement disorders (akathisia, bruxism, restless leg syndrome, trismus) with a frequency 'not known', tremor with a frequency 'uncommon', sexual dysfunction with a frequency 'very common', discontinuation syndrome with a frequency 'very common', blurred vision with a frequency 'uncommon' and galactorrhoea with a frequency 'not known'. In addition, the product information should be updated to amend the information regarding treatment discontinuation. Therefore, the current terms of the marketing authorisation(s) should be varied[18].

[17] Update of SmPC section 4.4. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion.
[18] Update of SmPC sections 4.2 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 cumulative review of cases of hepatic disorders and discuss whether an update of the product information is warranted.

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

Post-meeting note: The CHMP noted the PRAC recommendation to add sexual dysfunction as an adverse reaction to the SmPC table in 4.8 as well as the MAH objection regarding the frequency category recommended by PRAC for this adverse reaction. The CHMP took into consideration all available data and furthermore, gave the opportunity to the MAH to present their position in the context of an oral explanation.

CHMP concluded not to add sexual dysfunction as an adverse reaction to the SmPC table in 4.8 as recommended by PRAC, but agreed to reflect the new information from post-marketing experience in the relevant part of the 4.8 in SmPC, as also recommended by PRAC. See CHMP minutes May 2023.

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

See Annex I 16.2.

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

See also Annex I 16.3.

6.3.1. Carbidopa, levodopa (NAP) - PSUSA/00000548/202210

Applicant(s): various

PRAC Lead: Nikica Mirošević Skvrce

Scope: Evaluation of a PSUSA procedure

Background

Carbidopa is an immediate precursor of dopamine and levodopa a peripheral dopa-decarboxylase inhibitor. In combination, it is indicated for the treatment of Parkinson's disease.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing carbidopa/levodopa 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 carbidopa/levodopa-containing medicinal products in the approved indication(s) remains unchanged.

- Nevertheless, the product information should be updated to include urinary tract infections as an undesirable effect with a frequency 'very common'. Therefore, the current terms of the marketing authorisation(s) should be varied[19].
- In the next PSUR, the MAHs for carbidopa/levodopa-containing medicinal products should provide a review of cases of atrial fibrillation, cardiac arrest and cardiac failure, dehydration, gout/gout flare up, osteoporosis, syndrome of inappropriate antidiuretic hormone secretion (SIADH), fibroma, as well as of MedDRA SMQs[20] for embolic and thrombotic events, malignancies, breast neoplasms, malignant and unspecified, prostate neoplasms, malignant and unspecified. Finally, all MAHs should include polyneuropathy (if not already included) as important potential risk in the list of safety concerns within the PSURs.

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

6.3.2. Clenbuterol (NAP) - PSUSA/00000794/202209

Applicant(s): various

PRAC Lead: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

Background

Clenbuterol is a beta2-adrenergic agonist, indicated for the prophylaxis and symptomatic bronchodilatory treatment of asthma and other conditions with reversible airway narrowing, such as chronic obstructive bronchitis with or without emphysema.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing clenbuterol 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 clenbuterol-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include product abuse as a warning in order to discourage such behaviour by highlighting the health related risks and to amend the signs and symptoms of overdose. Therefore, the current terms of the marketing authorisation(s) should be varied[21].
- In the next PSUR, the MAHs should provide a cumulative review of cases of non-infectious myocarditis/pericarditis and discuss the need for an update of the product information as warranted.

[19] Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position
[20] Standardised MedDRA Queries
[21] Update of SmPC sections 4.4 and 4.9. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position.

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

6.3.3. Famotidine (NAP) - PSUSA/00001350/202209

Applicant(s): various

PRAC Lead: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

Background

Famotidine is a histamine (H)2-receptor antagonist and it is indicated in adults for diseases that require a reduction of the gastric acid production, such as duodenal ulcer, benign gastric ulcer, hypersecretory conditions such as Zollinger-Ellison syndrome, prevention of relapse of duodenal or benign gastric ulcer, symptomatic relief of gastroesophageal reflux disease, healing of oesophageal erosion or ulceration associated with gastroesophageal reflux disease (GERD), prevention of relapse of symptoms and erosions or ulcerations associated with GERD.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing famotidine 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 famotidine-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add the drug-drug interactions between famotidine and posaconazole oral suspension, and between famotidine and tyrosines kinase inhibitors (TKIs) such as dasatinib, erlotinib, gefitinib and pazopanib. Therefore, the current terms of the marketing authorisation(s) should be varied[22]. In case the product information already includes a stricter advice regarding these drug-drug interactions, the stricter advice remains valid and should be kept in the product information.
- In the next PSUR, the MAH should provide a cumulative review of cases of QT prolongation, in particular, but not restricted, to patients with renal problems or electrolyte disorder, and discuss the chronology between famotidine administration and the event.

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. Fenoterol[23] (NAP) - PSUSA/00001366/202209

Applicant(s): various

[22] Update of SmPC section 4.5. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position.
[23] Respiratory indication(s) only

PRAC Lead: Nikica Mirošević Skvrce

Scope: Evaluation of a PSUSA procedure

Background

Fenoterol is a short-acting sympathomimetic agent, indicated, among others, in respiratory indications for the symptomatic treatment of acute asthma attacks and other conditions with reversible airway narrowing, e.g. chronic obstructive bronchitis, and as prophylaxis of exercise induced asthma in adults (including elderly patients), adolescents and children (including infants).

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing fenoterol 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 fenoterol-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the existing warning on the use of fenoterol reliever (i.e. pressurised inhalation, solution) to indicate that it is no longer recommended for the treatment of asthma symptoms as monotherapy (excluding in prophylaxis of exercise induced asthma) and add short-acting beta-agonists (SABAs) overuse as a warning. Therefore, the current terms of the marketing authorisation(s) should be varied[24].
- In the next PSUR, the MAH(s) should provide an updated review of cases of dysgeusia, and should broaden the search criteria for the important identified risk 'arrhythmia' to MedDRA SMQ[25] Cardiac arrhythmias. The MAH(s) should amend the list of safety concerns in the RMP to include SABA overuse as an important identified risk.

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

6.3.5. Polystyrene sulfonate (NAP) - PSUSA/00002472/202210

Applicant(s): various

PRAC Lead: Jana Lukačišinová

Scope: Evaluation of a PSUSA procedure

Background

Polystyrene sulfonate is a non-absorbable cation-exchange resin indicated for the treatment of hyperkalaemia in patients with acute or chronic kidney disease, including patients undergoing dialysis and in patients with kidney replacement therapy who are at risk of hyperkalaemia.

[24] Update of SmPC section 4.4. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position.
[25] Standardised MedDRA Queries

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing polystyrene sulfonate 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 polystyrene sulfonate-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add a warning on the use of polystyrene sulfonate in patients with compromised gastrointestinal mobility. Therefore, the current terms of the marketing authorisation(s) should be varied[26].

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

6.3.6. Ropivacaine (NAP) - PSUSA/00002662/202209

Applicant(s): various

PRAC Lead: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

Background

Ropivacaine is an aminoamide local anaesthetic indicated in adults for intrathecal administration for surgical anaesthesia, in adults and adolescents above 12 years of age for continuous epidural infusion or intermittent bolus administration during postoperative or labour pain, field blocks, continuous peripheral nerve block via a continuous infusion or intermittent bolus injections (e.g. postoperative pain management), epidural blocks for surgery including Caesarean section and major nerve blocks, in infants from 1 year and children up to and including 12 years of age (per- and post-operative) for single and continuous peripheral nerve block, and in neonates, infants and children up to and including 12 years of age for (per-and post-operative) for caudal epidural block and continuous epidural infusion, subject to certain conditions.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing ropivacaine 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 ropivacaine-containing medicinal products in the approved indication(s) remains unchanged.

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

- Nevertheless, the product information should be updated to add anaphylactic shock as an undesirable effect with a frequency 'rare'. Therefore, the current terms of the marketing authorisation(s) should be varied[27].
- In the next PSUR, the MAH(s) should amend the list of safety concerns within the PSUR and remove all safety concerns classified as important identified risks and missing information.

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

6.4.1. Cabozantinib - CABOMETYX (CAP) - EMEA/H/C/004163/LEG 007.1

Applicant: Ipsen Pharma

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to LEG 007 [Causality assessment of pneumonia cases already reported as confounded by the MAH as well as of any newly reported cases, as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00010180/202111) adopted in July 2022] as per request for supplementary information (RSI) adopted in December 2022

Background

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

Following the evaluation of the most recently submitted PSUR(s) for the above-mentioned medicine(s), PRAC requested the MAH to submit further data on selected cases of pneumonia that were previously deemed confounded by the MAH. The responses were assessed by the Rapporteur for further PRAC advice. For further background, see PRAC minutes July 2022 and PRAC minutes December 2022[28].

Summary of advice/conclusion(s)

- Based on the available data and the Rapporteur's assessment, PRAC agreed there is sufficient evidence to establish a causal relationship between Cabometyx (cabozantinib) and pneumonia. Therefore, the product information[29] should be amended in order to add pneumonia as an undesirable effect following cabozantinib monotherapy.
- The MAH should submit to EMA, within 60 days, a variation to amend the product information.

6.4.2. Cabozantinib - COMETRIQ (CAP) - EMEA/H/C/002640/LEG 022.1

Applicant: Ipsen Pharma

[27] Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position.
[28] Held on 28 November-01 December 2022
[29] 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 a position.

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to LEG 022 [Causality assessment of pneumonia cases already reported as confounded by the MAH as well as of any newly reported cases, as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00010180/202111) adopted in July 2022] as per request for supplementary information (RSI) adopted in December 2022

Background

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

Following the evaluation of the most recently submitted PSUR(s) for the above-mentioned medicine(s), PRAC requested the MAH to submit further data on selected cases of pneumonia that were previously deemed confounded by the MAH. The responses were assessed by the Rapporteur for further PRAC advice. For further background, see PRAC minutes July 2022 and PRAC minutes December 2022[30].

Summary of advice/conclusion(s)

- Based on the available data and the Rapporteur's assessment, PRAC agreed that no further regulatory action is deemed necessary for Cabometriq(cabozantinib), as pneumonia is already listed as undesirable effect in the product information.

6.4.3. Inotersen - TEGSEDI (CAP) - EMEA/H/C/004782/LEG 008

Applicant: Akcea Therapeutics Ireland Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Submission of the seventh periodic benefit-risk evaluation report covering the reporting interval of 06 July 2021 to 05 July 2022 together with the WHO-UMC causality of additional cases and drug-induced liver injury signal investigation as requested in the conclusions of periodic safety update single assessment (PSUSA) procedure (PSUSA/00010697/202207) adopted in February 2023

Background

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

Following the evaluation of the most recently submitted PSUR(s) for the above-mentioned medicine(s), PRAC requested the MAH to submit further data cases of drug-induced liver injury (DILI). The responses were assessed by the Rapporteur for further PRAC advice. For further background, see PRAC minutes February 2023.

Summary of advice/conclusion(s)

- Based on the available data and the Rapporteur's assessment, PRAC agreed that an update of the product information[31] is needed to amend the existing warning on liver monitoring and DILI, and to add DILI as an undesirable effect with a frequency 'not

[30] Held on 28 November-01 December 2022
[31] 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 a position.

known'. In addition, the MAH should amend the list of safety concerns in the RMP to include hepatotoxicity as an important identified risk, and update the patient card accordingly.

- The MAH should submit to EMA, within 60 days, a variation to update the product information.

6.4.4. Pralsetinib - GAVRETO (CAP) - EMEA/H/C/005413/LEG 009

Applicant: Roche Registration GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of a DHPC (Direct Health Care Professional Communication) and a communication plan aiming at informing health care professionals about the risk of tuberculosis and the measures as requested in the conclusions of periodic safety update single assessment (PSUSA) procedure (PSUSA/00010961/202209) adopted in April 2023

Background

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

Following the evaluation of the most recently submitted PSUR(s) for the above-mentioned medicine(s), PRAC requested the MAH to submit a proposal for a Direct Health Care Professional Communication (DHPC) and a communication plan aimed at informing health care professionals about the new risk on tuberculosis as well as the measures to be taken to minimise it. The responses were assessed by the Rapporteur for further PRAC advice. For further background, see PRAC minutes April 2023.

Summary of advice/conclusion(s)

- Based on the available data and the Rapporteur's assessment, PRAC agreed on the DHPC and the communication plan aimed at informing health care professionals about the new risk on tuberculosis, as well as to amend the product information in order to include tuberculosis as a warning.

6.5. Variation procedure(s) resulting from PSUSA evaluation

6.5.1. Coronavirus (COVID-19) vaccine (Ad26.COV2-S, recombinant) - JCOVDEN (CAP) - EMEA/H/C/005737/II/0072/G

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of section 4.4 of the SmPC in order to add a new warning on pericarditis and myocarditis and update of section 4.8 of the SmPC to add myocarditis and pericarditis to the list of adverse drug reactions (ADRs) with frequency not known based on post-marketing data and three observational claims databases in US as requested in the conclusions of periodic safety update single assessment (PSUSA) procedure (PSUSA/00010916/202208) adopted in April 2023. The package leaflet is updated accordingly. The RMP version 6.2 has also been submitted. In addition, the MAH took the opportunity to update the ATC Code as amended by the WHO

Background

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

Following the evaluation of the most recently submitted PSUR(s) for the above-mentioned medicine(s), PRAC requested the MAH to submit a variation to address the new conclusion that myo-/peri-carditis is an important identified risk for Jcovden (Coronavirus (COVID-19) vaccine (Ad26.COV2-S, recombinant)) and to discuss the need for an update of the product information and/or RMP as warranted. PRAC is responsible for adopting an outcome based on the assessment report from the PRAC Rapporteur, to be further considered at the level of CHMP, responsible for adopting an opinion on this variation. For further background, see PRAC minutes April 2023.

Summary of recommendation(s)

- Based on the available data and the Rapporteur's assessment, PRAC agreed to update the product information[32] in order to add myocarditis and pericarditis as warnings and as undesirable effects with a frequency 'not known', as well as to include myocarditis and pericarditis as important identified risks in the RMP.

6.5.2. Nirmatrelvir, ritonavir - PAXLOVID (CAP) - EMEA/H/C/005973/II/0032

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Martin Huber

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

Background

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

Following the evaluation of a safety review for hypertension (EMEA/H/C/005973/LEG 006), PRAC requested the MAH to submit a variation to discuss if an update of the product information to include a warning to further alert prescribers on the risk of hypertension and to recommend a monitoring of blood pressure during Paxlovid therapy is warranted. PRAC is responsible for adopting an outcome based on the assessment report from the PRAC Rapporteur, to be further considered at the level of CHMP, responsible for adopting an opinion on this variation. For further background, see PRAC minutes October 2022[33].

Summary of recommendation(s)

- Based on the available data and the Rapporteur's assessment, PRAC agreed to update the product information[34] in order to add hypertension as a warning and as an

[32] 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 a position.
[33] Held on 26-29 September 2022
[34] Update of SmPC sections 4.4 and 4.8. The package leaflet is updating accordingly

undesirable effect with a frequency 'uncommon', as well as to include the need for monitoring of blood pressure during Paxlovid therapy.

6.6. Expedited summary safety reviews[35]

None

7. Post-authorisation safety studies (PASS)

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

See also Annex I 17.1.

7.1.1. Tabelecleucel - EBVALLO (CAP) - EMEA/H/C/PSP/S/0104

Applicant: Pierre Fabre Medicament, ATMP[37]

PRAC Rapporteur: Amelia Cupelli

Scope: An observational PASS to describe the safety and effectiveness of tabelecleucel in patients with Epstein-Barr Virus positive (EBV+) Post-Transplant Lymphoproliferative Disease (PTLD) in a real-world setting in Europe

Background

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

In order to fulfil the specific obligation to conduct a PASS (Annex II-E) imposed in accordance with Article 107n(3) of Directive 2001/83/EC, the MAH Pierre Fabre Medicament submitted to EMA a protocol version 1.0 for a study entitled: 'An observational, Post-Authorisation Safety Study (PASS) to describe the safety and effectiveness of tabelecleucel in patients with Epstein-Barr Virus positive (EBV+) Post-Transplant Lymphoproliferative Disease (PTLD) in a real-world setting in Europe' for review by PRAC. PRAC is responsible for evaluating the PASS protocol.

Endorsement/Refusal of the protocol

- Having considered the protocol version 1.0 in accordance with Article 107n of Directive 2001/83/EC, PRAC objected to the draft protocol for the above-listed medicinal product(s). PRAC agreed that the PASS is non-interventional, but the study design does not fulfil the study objectives at this stage.
- The MAH should provide clarifications on data collection strategy for data transfer and management allocation of responsibilities between involved parties, as well as on lines of communication between involved parties, data transfer arrangements, data management, including missing data, as well as on handling of study limitations and efforts to reduce bias during data entry.

[35] Submission of expedited summary safety reports for review in addition to the requirements for submission of PSUR(s) falling within the pandemic period and requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC
[36] In accordance with Article 107n of Directive 2001/83/EC
[37] Advanced therapy medicinal product

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

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

See also Annex I 17.2.

7.2.1. Ponesimod - PONVORY (CAP) - EMEA/H/C/005163/MEA 004.3

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Anette Kirstine Stark

Scope: MAH's response to MEA 004.2 [protocol for study PCSNSP003693 (listed as a category 3 study in the RMP): a survey among healthcare professionals (neurologists treating patients with multiple sclerosis (MS) along with MS specialist nurses) in selected European countries to evaluate knowledge and behaviours required for the safe use of ponesimod] as per the request for supplementary information (RSI) adopted in November 2022

Background

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

As part of the RMP for Ponvory (ponesimod), the MAH was requested to conduct a study to evaluate the effectiveness of educational materials aimed at minimising risks related to the use of ponesimod. The MAH Janssen-Cilag International N.V submitted to EMA the protocol 4.0 for the study 'survey to assess the effectiveness of Ponvory educational materials for additional risk minimisation measures in the European Union' which was assessed by the Rapporteur. PRAC was requested to provide advice to CHMP on the protocol submitted by the MAH. For further background, see PRAC minutes November 2022[39].

Summary of advice

- Based on the review of the protocol and the assessment from the Rapporteur, considered that the protocol version 4.0 for Ponvory (ponesimod) is acceptable.
- PRAC concluded that despite the well-known limitations, the study could deliver relevant information to estimate the effectiveness of the risk minimisation measures in place for Ponvory (ponesimod). PRAC discussed the issue of non-response and emphasised, in agreement with the MAH, that recruitment must continue until the required sample size is achieved, so that the pre-defined sample size is met regardless of the low response rate. Although it is acknowledged that the non-response bias will not be completely eliminated, this will ensure an acceptable precision of the results.

[38] In accordance with Article 107m of Directive 2001/83/EC, supervised by PRAC in accordance with Article 61a (6) of Regulation (EC) No 726/2004
[39] Held on 24-27 October 2022

7.3. Results of PASS imposed in the marketing authorisation(s)[40]

7.3.1. Valproate[41] (NAP) - EMEA/H/N/PSR/J/0043

Applicant: Sanofi-Aventis Recherche & Développement

PRAC Rapporteur: Liana Gross-Martirosyan

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

Background

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

Further to the conclusions dated 2018 of the referral procedure under Article 31 of Directive 2001/83/EC (EMEA/H/A-31/1454) conducted by PRAC for valproate-containing medicines, MAHs were requested as a condition to the marketing authorisation(s) (Annex IV) to conduct a retrospective observational study to investigate the association between paternal exposure to valproate and the risk of congenital anomalies and neurodevelopmental disorders including autism in offspring.

The MAH Sanofi-Aventis Recherche & Développement, on behalf of a consortium, submitted to EMA the final results of the study 'A post-authorisation safety study (PASS) to evaluate the paternal exposure to valproate and the risk of neurodevelopmental disorders including autism spectrum disorders as well as congenital abnormalities in offspring – a population-based retrospective study'. PRAC discussed the final study results. PRAC is responsible for evaluating the PASS final results.

Summary of recommendation(s) and conclusions

- Based on the review of the study final report and the assessment from the Rapporteur, PRAC considered that a request for supplementary information (RSI) was necessary before a final recommendation could be issued.
- In particular, the MAH should provide additional analyses in order to improve the interpretation of the study results and to gain more insight into study robustness, such a distribution of different types of epilepsy among the treatment groups, sensitivity analyses using a different definition for defining children with diagnosis of neurodevelopmental disorders and 'former user' analysis to account for potential indication bias.
- The MAH should submit responses to the RSI, within 60 days, to EMA. A 60 days-assessment timetable will be followed.

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

See Annex I 17.4.

[40] In accordance with Article 107p-q of Directive 2001/83/EC
[41] Valproic acid, sodium valproate, valproate pivoxil, valproate semisodium, valpriomide, valproate bismuth, calcium valproate, valproate magnesium
[42] In accordance with Article 61a (6) of Regulation (EC) No 726/2004, in line with the revised variations regulation for any submission as of 4 August 2013

7.5. 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 also Annex I 18.3.

8.3.1. Axicabtagene ciloleucel - YESCARTA (CAP) - EMEA/H/C/004480/R/0056 (with RMP)

Applicant: Kite Pharma EU B.V., ATMP[43]

PRAC Rapporteur: Anette Kirstine Stark

Scope: 5-year renewal of the marketing authorisation

Background

[43] Advanced therapy medicinal product

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.

Yescarta, a centrally authorised medicine containing axicabtagene ciloleucel, was authorised in 2018.

The MAH submitted an application for renewal of the marketing authorisation for opinion by CHMP. PRAC is responsible for providing advice to CAT and 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 Yescarta (axicabtagene ciloleucel) and the CAT Rapporteur's assessment report, PRAC considered that the renewal of the marketing authorisation could be granted with unlimited validity.

8.3.2. Voretigene neparvovec - LUXTURNA (CAP) - EMEA/H/C/004451/R/0040 (without RMP)

Applicant: Novartis Europharm Limited, ATMP[44]

PRAC Rapporteur: Gabriele Maurer

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.

Luxturna, a centrally authorised medicine containing voretigene neparvovec, was authorised in 2018.

The MAH submitted an application for renewal of the marketing authorisation for opinion by CHMP. PRAC is responsible for providing advice to CAT and 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 Luxturna (voretigene neparvovec) and the CHMP Rapporteur's assessment report, PRAC advised that an additional five-year renewal of the marketing authorisation should be considered.

9. Product related pharmacovigilance inspections

9.1. List of planned pharmacovigilance inspections

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

Scope: Pharmacovigilance inspection programme 2023-2026 (first revision for 2023)

[44] Advanced therapy medicinal product

The EMA Secretariat presented the pharmacovigilance inspection programme for 2023-2026.

9.2. Ongoing or concluded pharmacovigilance inspections

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

9.3. Others

None

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

10.1. Safety related variations of the marketing authorisation

10.1.1. Ibandronic acid - BONDRONAT (CAP) - EMEA/H/C/000101/WS2451/0090; BONVIVA (CAP) - EMEA/H/C/000501/WS2451/0075

Applicant: Atnahs Pharma Netherlands B.V.

PRAC Rapporteur: Anette Kirstine Stark

Scope: PRAC consultation on a worksharing variation procedure to update the product information of Bonviva and Bondronat regarding the risk of 'atypical fractures of long bones other than femour' based on literature

Background

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

A worksharing variation procedure proposing to update the product information of Bonviva and Bondronat regarding the risk of 'atypical fractures of long bones other than femour' based on literature is under evaluation at CHMP. PRAC was requested to provide advice on this variation.

Summary of advice

- Based on the review of the available information, PRAC agreed that data consistently show a plausible relationship between atypical fractures of long bones other than the femur, and long-term bisphosphonate use, including ibandronate. Therefore, PRAC agreed to update the product information to rename the existing warning and undesirable effect on the risk of 'atypical fractures of the femur' to 'atypical fractures of the long bones' for both Bonviva and Bondronat. Moreover, PRAC agreed to reclassify the risk of atypical femoral fracture from 'important potential risk' to 'important identified risk' in the RMP for ibandronic acid, and to extend the risk to 'atypical fractures of long bones'. PRAC did not agree with the proposed introduction of a temporary treatment discontinuation for Bonviva, and did not support the proposed wording in product information for prescribers to consider a temporary drug holiday after 3-5 years of treatment in patients not at high risk of osteoporotic fractures. Finally, PRAC

considered it appropriate for the product information and RMPs of the other authorised bisphosphonates to be updated accordingly, provided that applicability is confirmed within individual product-specific assessments.

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

None

10.3. Other requests

None

10.4. Scientific Advice

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

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

11.1. Safety related variations of the marketing authorisation

None

11.2. Other requests

None

12. Organisational, regulatory and methodological matters

12.1. Mandate and organisation of PRAC

12.1.1. PRAC membership

None

12.1.2. PRAC working group - Best practice guide on using PRAC plenary time efficiently and effectively – update on the implementation of quantitative goals – Q1 2023

In line with the adopted PRAC best practice guidance (BPG) on Committee efficiency (see PRAC minutes May 2016 and PRAC minutes June 2018) and the adopted implementation plan for the BPG including goals to measure compliance with the recommendations (see PRAC minutes June 2016 and PRAC minutes June 2018), the EMA Secretariat updated PRAC at the organisational, regulatory and methodological matters (ORGAM) meeting on 23 May 2023, on the quantitative measures collected for Q1 2023 of PRAC meetings. For previous update, see PRAC minutes February 2023.

12.1.3. PRAC assessors' trainings – organisational matters

PRAC lead: Martin Huber

At the organisational, regulatory and methodological matters (ORGAM) meeting on 23 May 2023, the EMA Secretariat presented to PRAC a new way of collaborating and knowledge sharing within the pharmacovigilance network under the format of more focused practical training sessions on different pharmacovigilance issues to possibly replace the yearly PRAC Assessor's training. PRAC noted the information.

12.1.4. 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 the ongoing clinical trials to evaluate the safety and efficacy of medicines in development as potential treatments for COVID-19, as well as study results on effectiveness of COVID-19 mRNA vaccines' (booster dose and adapted mRNA bivalent vaccines). The EMA Secretariat also updated PRAC on monkey pox, as well as on influenza, Ebola and Marburg virus outbreaks.

12.4.2. PRAC strategic review and learning meeting (SRLM) under the Swedish presidency of the European Union (EU) Council – Uppsala, Sweden, 24 - 26 May 2023 - agenda

PRAC lead: Ulla Wändel Liminga, Mari Thorn

PRAC was informed on the final agenda for the 'PRAC strategic review and learning meeting (SRLM)', to be held on 24-26 May 2023 in Uppsala, Sweden, under the Swedish presidency of the Council of the European Union (EU). The topics to be discussed cover effectiveness of risk minimisation measures, risk communication, as well as methods and tools for pharmacovigilance activities.

12.5. Cooperation with International Regulators

None

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

None

12.7. PRAC work plan

None

12.8. Planning and reporting

12.8.1. EU Pharmacovigilance system - quarterly workload measures and performance indicators – Q1 2023 and predictions

At the organisational, regulatory and methodological matters (ORGAM) meeting on 23 May 2023, the EMA Secretariat presented to PRAC an overview of the quarterly figures on the EMA pharmacovigilance system-related workload and performance indicators. For previous update, see PRAC minutes February 2023.

12.8.2. PRAC workload statistics – Q1 2023

At the organisational, regulatory and methodological matters (ORGAM) meeting on 23 May 2023, the EMA secretariat presented to PRAC the quarterly and cumulative figures to estimate the evolution of the PRAC workload for Q1 2023, by reflecting on the number of procedures and agenda items covered at each PRAC plenary meeting. For previous update, see PRAC minutes February 2023.

12.8.3. MAAs 3-year forecast report for March 2023 - December 2025

At the organisational, regulatory and methodological matters (ORGAM) meeting on 23 May 2023, the EMA Secretariat presented the 3-year forecast report on marketing authorisation applications planned for submission (the business 'pipeline') in the period 2023-2025 for information to PRAC. PRAC noted the information. For previous update, see PRAC minutes May 2022.

12.9. Pharmacovigilance audits and inspections

12.9.1. Pharmacovigilance systems and their quality systems

None

12.9.2. Pharmacovigilance inspections

None

12.9.3. Pharmacovigilance audits

None

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

12.10.1. Periodic safety update reports

None

12.10.2. Granularity and Periodicity Advisory Group (GPAG)

None

12.10.3. PSURs repository

None

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

In line with the criteria for plenary presentation of updates to the EURD List adopted by PRAC in December 2021, PRAC endorsed the draft revised EURD list, version May 2023, reflecting the PRAC's comments impacting on the data lock point (DLP) and PSUR submission frequencies of the substances/combinations. PRAC endorsed the newly allocated Rapporteurs for upcoming PSUSAs in accordance with the principles previously endorsed by PRAC (see PRAC minutes April 2013).

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

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

PRAC lead: Sabine Straus, Martin Huber

PRAC's Vice chair Martin Huber presented to PRAC a follow-up on the proposal to remove the 'other considerations' section from the PSUSA assessment report (AR) for all PSUSA types (CAP only, mix CAP/NAP and NAPs only) in order to streamline the PSUSA AR and based on the previous discussions at both PRAC and CMDh levels (see PRAC minutes March 2023). PRAC agreed to implement the proposal in the context of a pilot phase of 6 months (with the PSUSA procedures starting on 01 June 2023). Guidance on how to further address topics that were previously included in section 'other consideration' was also discussed and agreed. During this course of the pilot phase, EMA will collect any examples and difficulties flagged by PRAC assessors and encountered in implementing this change at both PRAC and CMDh level. These will then be reviewed at the end of the pilot phase. PRAC will then re-discuss the decision based on the outcome of the pilot phase.

12.11. Signal management

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

None

12.12. Adverse drug reactions reporting and additional monitoring

12.12.1. Management and reporting of adverse reactions to medicinal products

None

12.12.2. Additional monitoring

None

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

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

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

12.13. EudraVigilance database

12.13.1. Activities related to the confirmation of full functionality

None

12.14. Risk management plans and effectiveness of risk minimisations

12.14.1. Risk management systems

None

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

None

12.14.3. Risk management plan (RMP) of medicinal product(s) - publication on EMA website

At the organisational, regulatory and methodological matters (ORGAM) meeting on 23 May 2023, the EMA Secretariat informed PRAC about the ongoing discussions related to the publication of RMPs on EMA website, following the comments received from the Member States. The EMA Secretariat will update PRAC on the final process once a decision is being made. For further information, see PRAC minutes April 2023.

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

12.20.1. Study of exposure and use patterns of alternatives to ranitidine-containing medicines in patients treated with ranitidine - PRAC Sponsors critical appraisal

PRAC lead: David Olsen

PRAC discussed the results of the 'Study of exposure and use patterns of alternatives to ranitidine-containing medicines in patients treated with ranitidine' (EUPAS44548) commissioned under the remit of the PRAC Strategy on measuring the impact of pharmacovigilance activities following suspension of all ranitidine-containing medicines in the EU in April 2020 due to the presence of N-nitrosodimethylamine (NDMA) impurities in context of referral EMEA/H/A-31/1491. The study concluded that after the referral, incident prescribing of ranitidine decreased to near zero levels in the six countries studied with an increase in the use of other antacids, mainly proton-pump inhibitors (PPIs), a trend already seen before the suspension of ranitidine. The study also showed that patients who switched

from ranitidine to alternative antacids mainly switched to PPIs and to a lesser extent to alternative H2-receptor antagonists, or permanently discontinued treatment. PRAC noted the missing indication of use in up to 85% of the exposed population as limitation and that the results are based on primary care data only. Overall, PRAC considered the risk minimisation measures (RMMs) were effective.

12.20.2. Study on the impact of EU label changes for fluoroquinolone-containing medicinal products for systemic and inhalation use: post-referral prescribing trends – finalisation of DHPC and communication plan

PRAC lead: Eva Jirsová, Martin Huber

PRAC agreed on the content of DHPC and the communication plan in order to remind healthcare professionals about the measures to be taken in order to reduce the risk of disabling, long-lasting and potentially irreversible side effects. For further information, see PRAC minutes January 2023, PRAC minutes February 2023 and PRAC minutes April 2023.

12.21. Others

12.21.1. Haematology WP reflection paper on novel therapies for Haemophilia

At the organisational, regulatory and methodological matters (ORGAM) meeting on 23 May 2023, Daniela Philadelphy, the Chair of the Haematology Working Party (WP), presented the finalised draft of the reflection paper on novel therapies for haemophilia in order to receive input on the clinical requirements for non-replacement therapy in congenital haemophilia A and B. PRAC members were invited to provide further comments on the reflection paper by 2 June 2023.

12.21.2. PRAC drafting group on the risks of dependence and addiction of opioids - preparation of Stakeholder consultation

The topic was postponed for the next PRAC plenary meeting (05-08 June 2023).

12.21.3. Report on experience with Real World Evidence (RWE) studies to support EMA scientific committees

At the organisational, regulatory and methodological matters (ORGAM) meeting on 23 May 2023, the EMA Secretariat presented to PRAC the EMA report on the experience with RWE studies conducted or commissioned by EMA. PRAC appreciated the information provided on the evaluation of the opportunities and challenges of RWE to support regulatory decision making and on the lessons learnt, as well as the provided recommendations and the focus that the report had on studies related to PRAC activities. An update on DARWIN EU® was also presented, including ongoing and planned studies.

13. Any other business

Next meeting on: 05-08 June 2023

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

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

14.1. New signals detected from EU spontaneous reporting systems

14.1.1. Azacitidine – AZACITIDINE ACCORD (CAP), AZACITIDINE BETAPHARM (CAP), AZACITIDINE MYLAN (CAP), ONUREG (CAP), VIDAZA (CAP)

Applicant(s): Accord Healthcare S.L.U. (Azacitidine Accord), betapharm Arzneimittel GmbH (Azacitidine betapharm), Bristol-Myers Squibb Pharma EEIG (Onureg, Vidaza), Mylan Ireland Limited (Azacitidine Mylan)

PRAC Rapporteur: Menno van der Elst

Scope: Signal of Cutaneous Vasculitis

EPITT 19929 – New signal

Lead Member State(s): NL

14.1.2. Baricitinib – OLUMIANT (CAP)

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Signal of interstitial lung disease

EPITT 19913 – New signal

Lead Member State(s): PL

14.1.3. Efgartigimod Alfa – VYVGART (CAP)

Applicant: Argenx

PRAC Rapporteur: Rhea Fitzgerald

Scope: Signal of anaphylactic reaction

EPITT 19926 – New signal

Lead Member State(s): IE

[45] Each signal refers to a substance or therapeutic class. The route of marketing authorisation is indicated in brackets (CAP for Centrally Authorised Products; NAP for Nationally Authorised Products including products authorised via Mutual Recognition Procedures and Decentralised Procedure). Product names are listed for reference Centrally Authorised Products (CAP) only. PRAC recommendations will specify the products concerned in case of any regulatory action required

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

14.1.4. Latanoprost[47] (NAP)

Applicant: various

PRAC Rapporteur: Jean-Michel Dogné

Scope: Signal of choroidal detachment and Choroidal effusion

EPITT 19936 – New signal

Lead Member State(s): BE

14.1.5. Pirfenidone – ESBRIET (CAP), PIRFENIDONE AXUNIO (CAP), PIRFENIDONE VIATRIS (CAP)

Applicant: Roche Registration GmbH

PRAC Rapporteur: Rhea Fitzgerald

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

EPITT 19920 – New signal

Lead Member State(s): IE

14.2. New signals detected from other sources

14.2.1. Rituximab – BLITZIMA (CAP), MABTHERA (CAP), RIXATHON (CAP), RIXIMYO (CAP), RUXIENCE (CAP), TRUXIMA (CAP)

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

PRAC Rapporteur: Anette Kirstine Stark

Scope: Signal of oral lichenoid reaction

EPITT 19916 – New signal

Lead Member State(s): DK

15. Annex I – Risk management plans

15.1. Medicines in the pre-authorisation phase

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

15.1.1. Aflibercept - EMEA/H/C/006022

Scope: Treatment of age-related macular degeneration (AMD) and visual impairment

[47] Except for products with paediatric indication

15.1.2. Sugammadex - EMEA/H/C/006115

Scope: Reversal of neuromuscular blockade induced by rocuronium or vecuronium

15.1.3. Tocilizumab - EMEA/H/C/005984

Scope: Treatment of rheumatoid arthritis, active systemic juvenile idiopathic arthritis (sJIA), juvenile idiopathic polyarthritis (pJIA), chimeric antigen receptor (CAR) T cell-induced cytokine release syndrome (CRS) and COVID-19

15.1.4. Tocilizumab - EMEA/H/C/005781

Scope: Treatment of rheumatoid arthritis, active systemic juvenile idiopathic arthritis (sJIA), juvenile idiopathic polyarthritis (pJIA), giant cell arteritis (GCA), chimeric antigen receptor (CAR) T cell-induced cytokine release syndrome (CRS) and COVID-19

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. 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 PASS of CE/BZA in the United States (US PASS, Study B2311060) previously assessed as part of II/0030 (MEA 002.15), as well as to update the post marketing data with the data lock point of 31 October 2021

15.2.2. Fremanezumab - AJOVY (CAP) - EMEA/H/C/004833/II/0039

Applicant: TEVA GmbH

PRAC Rapporteur: Kirsti Villikka

Scope: Submission of an updated RMP version 4.0 in order to replace PASS TV48125-MH-50039 with PASS TV48125-MH-40217 following MEA/005.3 and MEA/005.4

15.2.3. Glycopyrronium - SIALANAR (CAP) - EMEA/H/C/003883/II/0026

Applicant: Proveca Pharma Limited

PRAC Rapporteur: Zane Neikena

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

15.2.4. Imatinib - GLIVEC (CAP) - EMEA/H/C/000406/II/0133

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Monica Martinez Redondo

Scope: Submission of the final report from study CSTI571I2201 - A European observational registry collecting efficacy and safety data in newly diagnosed paediatric Ph+ acute lymphocytic leukaemia (ALL) patients treated with chemotherapy plus imatinib and with or without haematopoietic stem cell transplantation (HSCT), listed as an obligation in the Annex II of the product information. This study has been designed as an observational, multi-centre registry to collect efficacy and safety data in Ph+ ALL paediatric patients (ages 1 to <18 years old) treated with chemotherapy plus imatinib, with or without HSCT, primarily in European countries. The Annex II and the RMP (version 13.0) are updated accordingly

15.2.5. Measles, mumps, rubella and varicella vaccine (live) - PROQUAD (CAP) - EMEA/H/C/000622/WS2453/0160; Varicella vaccine (live) - ZOSTAVAX (CAP) - EMEA/H/C/000674/WS2453/0145

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Gabriele Maurer

Scope: Submission of updated RMPs for ProQuad and Zostavax versions 8.1 and 10.1 respectively, in order to remove the Varicella Zoster Virus Identification Program (VZVIP) as a routine pharmacovigilance activity beyond adverse reactions reporting and signal detection from the RMP Part III: pharmacovigilance plan

15.2.6. Sacubitril, valsartan - ENTRESTO (CAP) - EMEA/H/C/004062/WS2434/0049; NEPARVIS (CAP) - EMEA/H/C/004343/WS2434/0047

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Anette Kirstine Stark

Scope: Submission of an updated RMP version 5.0 for Ernestro and its duplicate marketing authorisation Neparvis to update the milestones for MEA 002 (study CLCZ696B2014) and MEA 004 (study CLCZ696B2015) from 31 December 2022 to 30 June 2024

15.2.7. Tadalafil - TADALAFIL MYLAN (CAP) - EMEA/H/C/003787/WS2431/0023

Applicant: Mylan Pharmaceuticals Limited

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Submission of an updated RMP (version 3) to develop follow-up forms in line with the reference product and to update Part III of RMP and Annex, Specific Adverse Drug Reaction Follow-up Forms accordingly, following CHMP and PRAC Rapporteurs Joint Assessment Report (EMEA/H/C/003787/R/0014, dated 15 April 2019); to adopt the safety concerns in the RMP in line with the ones available on CMDh website (Revision 35, dated Sep-2022) for generic RMP version 1.1 dated 01 April 2020 approved via procedure PT/H/1982/001-002/DC; to submit the updates in the new template (EMA/164014/2018 Rev.2.0.1 accompanying GVP Module V Rev.2)

15.2.8. Tecovirimat - TECOVIRIMAT SIGA (CAP) - EMEA/H/C/005248/II/0006

Applicant: SIGA Technologies Netherlands B.V.

PRAC Rapporteur: Martin Huber

Scope: Submission of substantial updates to the protocol of study SIGA-246-021 listed as a specific obligation in the Annex II of the product information in order to reflect the transfer of sponsorship from SIGA Technologies, Inc. to the NIH Division of Microbiology and Infection Disease protocol. This is a phase 4, observational field study to evaluate safety and clinical benefit in tecovirimat-treated patients following exposure to variola virus and clinical diagnosis of smallpox disease. The Annex II and the RMP submitted version 1.2 are updated accordingly

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. Adalimumab - YUFLYMA (CAP) - EMEA/H/C/005188/X/0022

Applicant: Celltrion Healthcare Hungary Kft.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension application to add a new strength (20 mg solution for injection). The indications for the new strength are identical to those already approved for the 40 mg strength. The RMP (version 2.1) has also been submitted. In addition, the MAH took the opportunity to include editorial changes in Mod. 2.3.A.1.2.2 and 3.2.A.1.2.2

15.3.2. Afamelanotide - SCENESSE (CAP) - EMEA/H/C/002548/II/0044, Orphan

Applicant: Clinuvel Europe Limited

PRAC Rapporteur: Martin Huber

Scope: Extension of indication for the prevention of phototoxicity in adolescent patients (12 to under 18 years of age) with erythropoietic protoporphyria (EPP), based on the analysis of the safety and efficacy data available. As a consequence, sections 4.1, 4.2 and 4.4 of the SmPC are updated. The package leaflet is updated in accordance. Version 9.4 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce a minor editorial correction to the product information

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

Applicant: PTC Therapeutics International Limited

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Update of sections 4.8 and 5.1 of the SmPC in order to update efficacy and safety information following results from study PTC124-GD-041-DMD, listed as a specific obligation in the Annex II; this is a Phase 3 multicentre, randomised, double-blind, 18-month, placebo-controlled study, followed by a 18-month open label extension to confirm the efficacy and safety of ataluren in the treatment of ambulant patients with nonsense

mutation Duchenne muscular dystrophy (mnDMD) aged 5 years or older. Annex II, and Annex IIB are updated to delete the SOB and to reflect the switch from conditional to full marketing authorisation. The package leaflet is updated accordingly. The RMP version 11.0 has also been submitted. Minor corrections were done to align the product information with the latest QRD templates

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

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Adam Przybylkowski

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

15.3.5. Brolucizumab - BEOVU (CAP) - EMEA/H/C/004913/II/0018

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Gabriele Maurer

Scope: Update of sections 4.2 and 5.1 of the SmPC in order to introduce an alternative posology regimen for wet age-related macular degeneration and update information based on modelling and simulation studies; the package leaflet is updated accordingly. The RMP version 9.0 has also been submitted

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

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Gabriele Maurer

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

15.3.7. Cerliponase alfa - BRINEURA (CAP) - EMEA/H/C/004065/II/0039, Orphan

Applicant: BioMarin International Limited

PRAC Rapporteur: Mari Thorn

Scope: Update of sections 4.2, 4.4, 4.8, 5.1, 5.2, 6.5 and 9 of the SmPC in order to state that clinical data are available for patients aged 1 year and older and to include updates to the frequency of adverse reactions, immunogenicity, pharmacokinetic, and paediatric population sections based on the final results from studies 190-203, listed as a specific obligation and 190-202 (submitted in P46/013). Study 190-203 was a Phase 2, open-label, multicentre study in paediatric patients < 18 years of age with CLN2 disease, confirmed by deficiency of TPP1 enzyme activity and mutation of the CLN2 gene. The package leaflet, Annex II and Annex IV are updated accordingly. The RMP version 4.0 has also been submitted

15.3.8. Coronavirus (COVID-19) vaccine (ChAdOx1-S [recombinant]) - VAXZEVRIA (CAP) - EMEA/H/C/005675/II/0089

Applicant: AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

Scope: Update of sections 4.8 and 5.1 of the SmPC in order to update the frequency of 'dizziness' and 'abdominal pain' in the list of adverse drug reactions (ADRs) to common and to update safety and efficacy information, based on final results and final pooled analysis for studies COV001, COV002, COV003 and COV005 as well as the final manuscript for COV004, listed as category 3 studies in the RMP. Study COV001 is phase I/II, single-blind, randomised, active-controlled, multicenter study in healthy adults aged 18-55 years; Study COV002 is a phase II/III, single-blind, randomised, active-controlled, multicenter study in adults ≥ 18 years of age and at high risk of exposure to COVID-19; Study COV003 is a phase III, single-blind, randomised, controlled, multicenter study in adults ≥ 18 years of age at high risk of exposure to SARS-CoV-2; Study COV005 is a phase I/II, double-blind, randomised, placebo-controlled, multicenter study in adults 18 to 65 years of age with or without HIV. Study COV004 a phase IB/II single-blind, randomised controlled trial of the (AZD1222) vaccine in adults in Kenya. The package leaflet is updated accordingly. The RMP version 7.0 has also been submitted

15.3.9. Denosumab - PROLIA (CAP) - EMEA/H/C/001120/II/0098

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Mari Thorn

Scope: Update of sections 4.2, 4.4, 5.1 and 5.2 in order to update efficacy, pharmacokinetic and safety information for paediatric population following the assessment of P46/043 and P46/044 based on final results from study 20130173, listed as a category 3 study in the RMP and study 20170534. Study 20130173 was a prospective, multicentre, open-label, single-arm phase 3 study to evaluate the safety, efficacy, and PK of denosumab in children 2 to 17 years of age with osteogenesis imperfecta (OI). Study 20170534 was an open-label, prospective, extension study of Study 20130173. The RMP version 31 has also been submitted. In addition, the MAH took this opportunity to introduce minor editorial changes

15.3.10. Fluticasone furoate, vilanterol - RELVAR ELLIPTA (CAP) - EMEA/H/C/002673/WS2438/0061/G; REVINTY ELLIPTA (CAP) - EMEA/H/C/002745/WS2438/0058/G

Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Monica Martinez Redondo

Scope: Grouped application consisting of 1) Update sections 4.2 and 5.1 of the SmPC to include results from study HZA107116. This is a randomised, double-blind, parallel group, multicentre, stratified, study evaluating the efficacy and safety of once daily fluticasone furoate (FF)/vilanterol (VI) inhalation powder compared to once daily fluticasone furoate inhalation powder in the treatment of asthma in participants aged 5 to 17 years old (inclusive) currently uncontrolled on inhaled corticosteroids. The package leaflet and labelling are updated accordingly. The RMP version 12.0 has also been submitted. In addition, the MAH took the opportunity to implement editorial changes to the SmPC; 2) Submission of final report from Phase 2b study HZA106855 (FF dose ranging) which gives information regarding the dose selection for FF combination in study HZA107116; 3) Submission of final report from Phase 2b study HZA106853 (VI dose ranging) which gives information regarding the dose selection for VI combination in study HZA107116

15.3.11. Givosiran - GIVLAARI (CAP) - EMEA/H/C/004775/II/0013/G, Orphan

Applicant: Alnylam Netherlands B.V.

PRAC Rapporteur: Martin Huber

Scope: Submission of the final reports from studies ALN-AS1-003 (Study 003) and ALN-AS1-002 (Study 002) listed as a category 3 studies in the RMP. Study 003 is a phase 3 randomised, double-blind, placebo-controlled multicenter study with an open-label extension to evaluate the efficacy and safety of givosiran in patients with acute hepatic porphyrias, while Study 002 is a multicentre, open-label extension study to evaluate the long-term safety and clinical activity of subcutaneously administered ALN AS1 in patients with acute intermittent porphyria who have completed a previous clinical study with ALN-AS1. The RMP version 2.2 has also been submitted

15.3.12. Golimumab - SIMPONI (CAP) - EMEA/H/C/000992/II/0113

Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of the final report from study CNTO148UCO1001 (PURSUIT PEDS PK) listed as a category 3 study in the RMP. This is a phase 1b open-label study to assess the safety and pharmacokinetics of subcutaneously administered golimumab, a human anti-TNFα antibody, in paediatric subjects with moderately to severely active ulcerative colitis. The RMP version 24.1 has also been submitted

15.3.13. Human normal immunoglobulin - HYQVIA (CAP) - EMEA/H/C/002491/II/0087

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Gabriele Maurer

Scope: Extension of indication to include treatment of Chronic Inflammatory Demyelinating

Polyneuropathy (CIDP) in adults for HyQvia, based on final results from studies 161403 and ABV-771-1001; and interim results from study 161505. 161403 and 161505 are interventional Phase III efficacy and safety studies respectively, while ABV-771-1001 is an interventional Phase I safety study. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and labelling are updated in accordance. Version 14.0 of the RMP has also been submitted

15.3.14. Ibandronic acid - BONDRONAT (CAP) - EMEA/H/C/000101/WS2451/0090; BONVIVA (CAP) - EMEA/H/C/000501/WS2451/0075

Applicant: Atnahs Pharma Netherlands B.V.

PRAC Rapporteur: Anette Kirstine Stark

Scope: Update of sections 4.2, 4.4 and 4.8 of the SmPC in order to add information regarding the risk of 'atypical fractures of long bones other than femour' based on literature. The package leaflet is updated accordingly. The RMP version 3.1 has also been submitted. In addition, the MAH took the opportunity to bring the product information in line with the latest QRD template version 10.3

15.3.15. Ivacaftor - KALYDECO (CAP) - EMEA/H/C/002494/X/0115/G

Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Monica Martinez Redondo

Scope: Grouped variation consisting of: 1) Extension application to introduce a new strength (13.4 mg of ivacaftor granules in sachet), grouped with a type II variation (C.I.6.a) in order to extend the indication of the granule presentations to include children with cystic fibrosis (CF) aged 1 to less than 4 months of age and weighing 3 kg or more who have an R117H CFTR mutation or one of the approved 9 gating (class III) mutations based on interim results from study VX15-770-124 (study 124); this is a phase 3, 2-part, open-label study to evaluate the safety, pharmacokinetics, and pharmacodynamics of ivacaftor (IVA) in subjects with CF who are less than 24 months of age at treatment initiation and have a CFTR gating mutation. As a consequence, sections 1, 2, 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2, 6.3 and 8 of the SmPC of the granules presentations and sections 4.2, 4.8, 5.1 and 5.2 of the SmPC of the tablets presentations are updated. The labelling for the 13.4 mg granule presentation and the package leaflet of the granules and tablets presentations are updated in accordance. Version 15.2 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the product information; 2) other quality related variations

15.3.16. Ivacaftor, tezacaftor, elexacaftor - KAFTRIO (CAP) - EMEA/H/C/005269/II/0035, Orphan

Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Martin Huber

Scope: Update of sections 4.8 and 5.1 of the SmPC based on interim results from study VX19-445-107 (Study 107) listed as a category 3 study in the RMP; this is a Phase III, open-label study evaluating the long-term safety and efficacy of VX445/TEZ/IVA combination therapy in subjects with cystic fibrosis who 6 years of age and older. The RMP version 7.0 has also been submitted. In addition, the MAH took the opportunity to

implement editorial changes in the SmPC

15.3.17. Maribavir - LIVTENCITY (CAP) - EMEA/H/C/005787/II/0004, Orphan

Applicant: Takeda Pharmaceuticals International AG Ireland Branch

PRAC Rapporteur: Adam Przybylkowski

Scope: Submission of the final report from study SHP620-302 listed as a category 3 study in the RMP. This is a Phase III, multicentre, randomised, double-blind, double-dummy, active-controlled study of maribavir compared to valganciclovir for the treatment of asymptomatic cytomegalovirus (CMV) infection in hematopoietic stem cell transplant (HSCT) recipients. The RMP version 2.0 has also been submitted

15.3.18. Methotrexate - NORDIMET (CAP) - EMEA/H/C/003983/II/0027

Applicant: Nordic Group B.V.

PRAC Rapporteur: Martin Huber

Scope: Extension of indication to include treatment of moderate to severe recalcitrant disabling psoriasis for Nordimet, based on literature. As a consequence, sections 4.1 and 4.2 of the SmPC are updated. The package leaflet is updated in accordance. The RMP (version 6.0) of the RMP has also been submitted

15.3.19. Nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/II/0130

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Martin Huber

Scope: Extension of indication to include OPDIVO for the adjuvant treatment of adults and adolescents 12 years of age and older with stage IIB or IIC melanoma who have undergone complete resection, based on results from study CA20976K; This is a phase III, randomised, double-blind study of adjuvant immunotherapy with nivolumab versus placebo after complete resection of stage IIB/C melanoma. As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The package leaflet is updated in accordance. Version 33.0 of the RMP has also been submitted

15.3.20. Odevixibat - BYLVAY (CAP) - EMEA/H/C/004691/II/0013, Orphan

Applicant: Albireo

PRAC Rapporteur: Adam Przybylkowski

Scope: Update of sections 4.4, 4.5 and 4.6 of the SmPC in order to update an existing warning, add drug-drug interaction (DDI) information with oral contraceptives and update information for women of childbearing potential, based on study A4250-022 listed as a category 3 study in the RMP; this is an open-label, phase 1 DDI study to evaluate the interaction of odevixibat with oral lipophilic contraceptives in healthy volunteers. The package leaflet is updated accordingly. The RMP version 4.1 has also been submitted

15.3.21. Pandemic influenza vaccine (surface antigen, inactivated, adjuvanted) - FOCLIVIA (CAP) - EMEA/H/C/001208/II/0081

Applicant: Seqirus S.r.l

PRAC Rapporteur: Amelia Cupelli

Scope: Extension of indication to include children from 6 months to less than 18 years of age for Foclivia, based on final results from study V87_30; this is a phase 2, randomised, observer-blind, multicentre study to evaluate the immunogenicity and safety of several doses of antigen and MF59 adjuvant content in a monovalent H5N1 pandemic influenza vaccine in healthy pediatric subjects 6 months to less than 9 years of age. As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The package leaflet is updated accordingly. Version 4.9 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the product information and to bring it in line with the latest QRD template

15.3.22. Pembrolizumab - KEYTRUDA (CAP) - EMEA/H/C/003820/II/0133

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication to include in combination with trastuzumab, fluoropyrimidine and platinum-containing chemotherapy for treatment of locally advanced unresectable or metastatic HER2- positive gastric or gastro-oesophageal junction adenocarcinoma for Keytruda, based on interim results from study KEYNOTE-811, an ongoing Phase 3, double-blind trial comparing trastuzumab plus chemotherapy and pembrolizumab with trastuzumab plus chemotherapy and placebo as first-line treatment in participants with HER2-positive advanced gastric or gastro-oesophageal junction adenocarcinoma. As a consequence, sections 4.1, 4.8, and 5.1 of the SmPC are updated. The package leaflet and Labelling are updated in accordance. Version 40.1 of the RMP has also been submitted

15.3.23. Pralsetinib - GAVRETO (CAP) - EMEA/H/C/005413/II/0010

Applicant: Roche Registration GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of sections 4.8, 5.1 and 5.2 of the SmPC in order to update efficacy and safety information in the treatment of adult patients with RET fusion-positive advanced non-small cell lung cancer (NSCLC) based on final results (NSCLC indication) from study ARROW/BO42863, a phase 1/2 study of the highly-selective RET inhibitor, BLU 667, in patients with thyroid cancer, NSCLC, and other advanced solid tumours listed as a specific obligation in the Annex II. The RMP version 1.5 has also been submitted

15.3.24. Remdesivir - VEKLURY (CAP) - EMEA/H/C/005622/II/0044/G

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Eva Jirsová

Scope: Update of sections 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC in order to change posology recommendations for patients with renal impairment, remove an existing warning on renal impairment and update the safety and efficacy information based on final results

from studies GS US 540 5912 and GS-US-540-9015, listed as category 3 studies in the RMP. Study GS US 540 5912 is a phase 3 randomised, double-blind, placebo-controlled, parallel group, multicentre study evaluating the efficacy and safety of remdesivir in participants with severely reduced kidney function who were hospitalised for COVID-19, while study GS-US-540-9015 is a phase 1, multicentre, open-label, single-dose study to evaluate the single-dose pharmacokinetic (PK) of remdesivir in participants with normal and impaired renal function. The package leaflet is updated accordingly. The RMP version 5.1 has also been submitted. In addition, the MAH took the opportunity to introduce minor edits to the product information

15.3.25. Rucaparib - RUBRACA (CAP) - EMEA/H/C/004272/II/0037

Applicant: Clovis Oncology Ireland Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of sections 4.8 and 5.1 of the SmPC in order to update the efficacy and safety information and the list of adverse drug reactions (ADRs) based on the final results from study CO-338-014 (ARIEL 3) listed as a category 1 PAES in the Annex II; this is a phase 3, multicentre, randomised, double-blind, placebo-controlled study of rucaparib as switch maintenance following platinum-based chemotherapy in patients with platinum-sensitive, high grade serous or endometrioid epithelial ovarian, primary peritoneal or fallopian tube cancer. The package leaflet is updated accordingly. The RMP version 6.4 has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the product information

15.3.26. Sodium phenylbutyrate - PHEBURANE (CAP) - EMEA/H/C/002500/X/0035

Applicant: Eurocept International B.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: Extension application to introduce a new pharmaceutical form associated with a new strength (350 mg/ml oral solution). The RMP (version 0.1) is updated in accordance

15.3.27. Sotorasib - LUMYKRAS (CAP) - EMEA/H/C/005522/II/0010/G

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Update of sections 4.2, 4.4, 4.8, 5.2 and 5.3 of the SmPC in order to change in the recommended dose and to update safety and efficacy information based on results from study 20190009 (CodeBreaK 200) listed as a specific obligation in the Annex II, in order to fulfil SOB/001; and results from study 20170543 (CodeBreak 100) phase 2 part B. Study 20190009 is a phase 3 multicentre, randomised, open-label, active-controlled study of AMG 510 versus docetaxel for the treatment of previously treated locally advanced and unresectable or metastatic non-small cell lung cancer (NSCLC) subjects with mutated KRAS p.G12C; while study 20170543 is a phase 1/2, open-label study evaluating the safety, tolerability, pharmacokinetics, pharmacodynamics and efficacy of AMG 510 monotherapy in subjects with advanced solid tumours with KRAS p.G12C mutation and AMG 510 combination therapy in subjects with advanced NSCLC with KRAS p.G12C mutation. The package leaflet is updated accordingly. The RMP version 2.0 has also been submitted. In

addition, the MAH took the opportunity to update Annex II of the SmPC

15.3.28. Tafasitamab - MINJUVI (CAP) - EMEA/H/C/005436/II/0008, Orphan

Applicant: Incyte Biosciences Distribution B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of section 4.4 of the SmPC in order to add a new warning on progressive multifocal leukoencephalopathy (PML) based on post-marketing data; the package leaflet is updated accordingly. The RMP version 2.0 has also been submitted. In addition, the MAH took the opportunity to implement editorial changes in the SmPC and to bring the product information in line with the latest QRD template version 10.3

15.3.29. Trientine - CUFENCE (CAP) - EMEA/H/C/004111/X/0014/G

Applicant: Univar Solutions BV

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Extension application to add a new strength (100 mg capsule, hard) grouped with a type IA variation (B.II.b.4.b) to introduce an alternate blend batch size range. The RMP (version 1.3) is updated in accordance. The marketing authorisation holder took the opportunity to align the product information to the latest QRD template (version 10.3)

15.3.30. Trifluridine, tipiracil - LONSURF (CAP) - EMEA/H/C/003897/II/0026

Applicant: Les Laboratoires Servier

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension of indication to include treatment of patients with refractory metastatic colorectal cancer, for LONSURF in combination with bevacizumab based on results from study SUNLIGHT (CL3-95005-007). This is an open-label, randomised, phase III study comparing trifluridine/tipiracil in combination with bevacizumab to trifluridine/tipiracil monotherapy in patients with refractory metastatic colorectal cancer. As a consequence, sections 4.1, 4.2, 4.4, 4.8, and 5.1 of the SmPC. The package leaflet is updated in accordance. The updated RMP version 9.1 has also been submitted. In addition, the MAH took the opportunity to update section 4.6 of the SmPC and the package leaflet accordingly

15.3.31. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/II/0098/G

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: –Grouped variations consisting of : 1) to add a new pre-filled pen (PFP) presentation, for Stelara 45 mg solution for injection (EU/1/08/494/00x); 2) to add a new PFP presentation for Stelara 90 mg Solution for injection (EU/1/08/494/00x); The RMP (Version 23.3) has been updated

15.3.32. Zanubrutinib - BRUKINSA (CAP) - EMEA/H/C/004978/II/0009

Applicant: BeiGene Ireland Ltd

PRAC Rapporteur: Menno van der Elst

Scope: Submission of the final report from study BGB-3111-113 - a drug-drug interaction study of zanubrutinib with moderate and strong CYP3A inhibitors in patients with B-cell malignancies, listed as a category 3 study in the RMP. The RMP version 3.0 has also been submitted

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

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

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

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

16.1.1. Andexanet alfa - ONDEXXYA (CAP) - PSUSA/00010764/202210

Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.2. Axicabtagene ciloleucel - YESCARTA (CAP) - PSUSA/00010703/202210

Applicant: Kite Pharma EU B.V., ATMP[48]

PRAC Rapporteur: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

16.1.3. Bezlotoxumab - ZINPLAVA (CAP) - PSUSA/00010576/202210

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.4. Brolucizumab - BEOVU (CAP) - PSUSA/00010829/202210

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Gabriele Maurer

[48] Advanced therapy medicinal product

Scope: Evaluation of a PSUSA procedure

16.1.5. Bupivacaine[49] - EXPAREL LIPOSOMAL (CAP) - PSUSA/00010889/202210

Applicant: Pacira Ireland Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

16.1.6. Cariprazine - REAGILA (CAP) - PSUSA/00010623/202210

Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.1.7. Chenodeoxycholic acid[50] [51] - CHENODEOXYCHOLIC ACID LEADIANT (CAP) - PSUSA/00010590/202210

Applicant: Leadiant GmbH

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.8. Choriogonadotropin alfa - OVITRELLE (CAP) - PSUSA/00000736/202209

Applicant: Merck Europe B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.9. Dapagliflozin - EDISTRIDE (CAP); FORXIGA (CAP) - PSUSA/00010029/202210

Applicant: AstraZeneca AB

PRAC Rapporteur: Mari Thorn

Scope: Evaluation of a PSUSA procedure

16.1.10. Delamanid - DELTYBA (CAP) - PSUSA/00010213/202210

Applicant: Otsuka Novel Products GmbH

PRAC Rapporteur: Jo Robays

Scope: Evaluation of a PSUSA procedure

[49] Liposomal formulations only
[50] Indicated for the treatment of inborn errors of primary bile acid synthesis due to sterol 27 hydroxylase deficiency (presenting as cerebrotendinous xanthomatosis (CTX)) in infants, children and adolescents aged 1 month to 18 years and adults
[51] Centrally authorised product(s) only

16.1.11. Dostarlimab - JEMPERLI (CAP) - PSUSA/00010931/202210

Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Inês Ribeiro-Vaz

Scope: Evaluation of a PSUSA procedure

16.1.12. Glycopyrronium bromide[52] - ENUREV BREEZHALER (CAP); SEEBRI BREEZHALER (CAP); TOVANOR BREEZHALER (CAP) - PSUSA/00010047/202209

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Evaluation of a PSUSA procedure

16.1.13. Herpes zoster vaccine (recombinant, adjuvanted) - SHINGRIX (CAP) - PSUSA/00010678/202210

Applicant: GlaxoSmithkline Biologicals SA

PRAC Rapporteur: Sonja Hrabcik

Scope: Evaluation of a PSUSA procedure

16.1.14. Histamine[53] - CEPLENE (CAP) - PSUSA/00001610/202210

Applicant: Laboratoires Delbert

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

16.1.15. Insulin degludec, liraglutide - XULTOPHY (CAP) - PSUSA/00010272/202209

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.16. Irinotecan[54] - ONIVYDE PEGYLATED LIPOSOMAL (CAP) - PSUSA/00010534/202210

Applicant: Les Laboratoires Servier

PRAC Rapporteur: David Olsen

Scope: Evaluation of a PSUSA procedure

16.1.17. Lasmiditan - RAYVOW (CAP) - PSUSA/00011011/202210

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Anna Mareková

[52] Centrally authorised product(s) indicated for chronic obstructive pulmonary disease
[53] Indicated for acute myeloid leukemia
[54] Liposomal formulation(s) only

Scope: Evaluation of a PSUSA procedure

16.1.18. Micafungin - MYCAMINE (CAP) - PSUSA/00002051/202210

Applicants: Astellas Pharma Europe B.V.

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.19. Nintedanib[55] - OFEV (CAP) - PSUSA/00010319/202210

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Evaluation of a PSUSA procedure

16.1.20. Pandemic influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) - FOCLIVIA (CAP); prepandemic influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) - AFLUNOV (CAP) - PSUSA/00010008/202210

Applicant: Seqirus S.r.l

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.1.21. Parathyroid hormone - NATPAR (CAP) - PSUSA/00010591/202210

Applicant: Takeda Pharmaceuticals International AG

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

16.1.22. Ranibizumab - BYOOVIZ (CAP); LUCENTIS (CAP); RANIVISIO (CAP) - PSUSA/00002609/202210

Applicant: Samsung Bioepis NL B.V. (Byooviz), Novartis Europharm Limited (Lucentis), Midas Pharma GmbH (Ranivisio)

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.23. Sacituzumab govitecan - TRODELVY (CAP) - PSUSA/00010959/202210

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

[55] Respiratory indication(s) only

16.1.24. Selumetinib - KOSELUGO (CAP) - PSUSA/00010936/202210

Applicant: AstraZeneca AB

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.25. Somatrogon - NGENLA (CAP) - PSUSA/00010982/202210

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

16.1.26. Talazoparib - TALZENNA (CAP) - PSUSA/00010781/202210

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Inês Ribeiro-Vaz

Scope: Evaluation of a PSUSA procedure

16.1.27. Talimogene laherparepvec - IMLYGIC (CAP) - PSUSA/00010459/202210

Applicant: Amgen Europe B.V., ATMP[56]

PRAC Rapporteur: Gabriele Maurer

Scope: Evaluation of a PSUSA procedure

16.1.28. Tucatinib - TUKYSA (CAP) - PSUSA/00010918/202210

Applicant: Seagen B.V.

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

16.1.29. Vandetanib - CAPRELSA (CAP) - PSUSA/00009327/202210

Applicant: Genzyme Europe BV

PRAC Rapporteur: Tiphaine Vaillant

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. Anagrelide - ANAGRELIDE MYLAN (CAP); XAGRID (CAP); NAP - PSUSA/00000208/202209

Applicants: Mylan Pharmaceuticals Limited (Anagrelide Mylan), Takeda Pharmaceuticals

[56] Advanced therapy medicinal product

International AG Ireland Branch (Xagrid), various

PRAC Rapporteur: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

16.2.2. Posaconazole - NOXAFIL (CAP); NAP - PSUSA/00002480/202210

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

PRAC Rapporteur: Nathalie Gault

Scope: Evaluation of a PSUSA procedure

16.2.3. Sodium oxybate[57] - XYREM (CAP); NAP - PSUSA/00010612/202210

Applicants: UCB Pharma S.A. (Xyrem), various

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.2.4. Thalidomide - THALIDOMIDE BMS (CAP); THALIDOMIDE LIPOMED (CAP); NAP - PSUSA/00002919/202210

Applicants: Bristol-Myers Squibb Pharma EEIG (Thalidomide BMS), Lipomed GmbH (Thalidomide Lipomed), various

PRAC Rapporteur: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

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

16.3.1. ^{13}C-methacetin (NAP) - PSUSA/00010846/202210

Applicant(s): various

PRAC Lead: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.3.2. Ambroxol (NAP) - PSUSA/00000130/202209

Applicant(s): various

PRAC Lead: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.3.3. Ambroxol, clenbuterol (NAP) - PSUSA/00000131/202209

Applicant(s): various

PRAC Lead: Ana Sofia Diniz Martins

[57] Oral use only

Scope: Evaluation of a PSUSA procedure

16.3.4. Aminosalicylic acid (NAP) - PSUSA/00000165/202210

Applicant(s): various

PRAC Lead: Nathalie Gault

Scope: Evaluation of a PSUSA procedure

16.3.5. Artemether, lumefantrin[58] (NAP) - PSUSA/00000236/202210

Applicant(s): various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.3.6. Bromhexine (NAP) - PSUSA/00000437/202209

Applicant(s): various

PRAC Lead: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.3.7. Dinoprostone (NAP) - PSUSA/00001104/202209

Applicant(s): various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.3.8. Etidronate (NAP) - PSUSA/00001320/202209

Applicant(s): various

PRAC Lead: Rugilė Pilvinienė

Scope: Evaluation of a PSUSA procedure

16.3.9. Etomidate (NAP) - PSUSA/00001330/202209

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.3.10. Felbamate (NAP) - PSUSA/00010155/202209

Applicant(s): various

PRAC Lead: Tiphaine Vaillant

[58] All except dispersible tablet(s)

Scope: Evaluation of a PSUSA procedure

16.3.11. Lysine acetylsalicylate (NAP) - PSUSA/00001921/202209

Applicant(s): various

PRAC Lead: Melinda Palfi

Scope: Evaluation of a PSUSA procedure

16.3.12. Terbinafine (NAP) - PSUSA/00002896/202209

Applicant(s): various

PRAC Lead: Anna Mareková

Scope: Evaluation of a PSUSA procedure

16.3.13. Trifarotene (NAP) - PSUSA/00010929/202210

Applicant(s): various

PRAC Lead: Mari Thörn

Scope: Evaluation of a PSUSA procedure

16.4. Follow-up to PSUR/PSUSA procedures

None

16.5. Variation procedure(s) resulting from PSUSA evaluation

None

16.6. Expedited summary safety reviews[59]

None

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

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

[59] 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

17.1. Protocols of PASS imposed in the marketing authorisation(s)[60]

17.1.1. Chenodeoxycholic acid - CHENODEOXYCHOLIC ACID LEADIANT (CAP) - EMEA/H/C/PSA/S/0103

Applicant: Leadiant GmbH

PRAC Rapporteur: Adam Przybylkowski

Scope: Substantial amendment to a Cerebrotendinous Xanthomatosis Registry: long term non-interventional follow-up of safety and effectiveness of Chenodeoxycholic Acid Leadiant

17.1.2. Ciltacabtagene autoleucel - CARVYKTI (CAP) - EMEA/H/C/PSA/S/0104

Applicant: Janssen-Cilag International NV, ATMP[61]

PRAC Rapporteur: Jo Robays

Scope: Substantial amendment to a PASS study 68284528MMY4009 protocol to evaluate the safety of multiple myeloma patients treated with ciltacabtagene autoleucel

17.1.3. Lonafarnib - ZOKINVY (CAP) - EMEA/H/C/PSP/S/0102.1

Applicant: EigerBio Europe Limited

PRAC Rapporteur: Adam Przybylkowski

Scope: MAH's response to PSP/0102 [Prospective observational study to evaluate the long-term safety and effectiveness of lonafarnib treatment among patients with Hutchinson-Gilford Progeria Syndrome (HGPS) or a processing deficient progeroid laminopathy (PDPL) in real-world clinical care settings] as per the request to supplementary information (RSI) adopted in December 2022

17.1.4. Tisagenlecleucel - KYMRIAH (CAP) - EMEA/H/C/PSA/S/0100.1

Applicant: Novartis Europharm Limited, ATMP[62]

PRAC Rapporteur: Gabriele Maurer

Scope: Substantial amendment to a protocol for a registry study to assess the long-term safety of patients with B lymphocyte malignancies treated with tisagenlecleucel [MAH's response to PSA/S/0100]

17.2. Protocols of PASS non-imposed in the marketing authorisation(s)[63]

17.2.1. Abrocitinib - CIBINQO (CAP) - EMEA/H/C/005452/MEA 004.2

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Nikica Mirošević Skvrce

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

Scope: MAH's response to MEA 004.1 [Protocol for study B7451015: an adolescent imaging substudy to evaluate if abrocitinib has any clinically meaningful effects on bone growth and development] as per the request to supplementary information (RSI) adopted in January 2023

17.2.2. Anifrolumab - SAPHNELO (CAP) - EMEA/H/C/004975/MEA 002.1

Applicant: AstraZeneca AB

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: MAH's response to MEA 002 [Protocol for study D3461R00046: a non-interventional cohort study and meta-analysis on the risk of malignancy in systemic lupus erythematosus patients receiving anifrolumab] as per the request to supplementary information (RSI) adopted in December 2022

17.2.3. Elasomeran - SPIKEVAX (CAP) - EMEA/H/C/005791/MEA 072.1

Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: MAH's response to MEA 0072 [Protocol for study mRNA-1273-P919 (listed as category 3 study in the RMP): an observational study to assess maternal and infant outcomes following exposure to Spikevax during pregnancy and to assess whether the rate of pregnancy complications, adverse pregnancy outcomes, or adverse neonatal outcomes is associated with prenatal exposure to Spikevax] as per the request to supplementary information (RSI) adopted in January 2023

17.2.4. Eptinezumab - VYEPTI (CAP) - EMEA/H/C/005287/MEA 004.2

Applicant: H. Lundbeck A/S

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: MAH's response to MEA 004.1 [protocol for study 19756N: a long-term cardiovascular safety and real-world use of eptinezumab - an observational, historical cohort study of patients initiating eptinezumab in routine clinical practice] as per request for supplementary information (RSI) adopted in December 2022

17.2.5. Givosiran - GIVLAARI (CAP) - EMEA/H/C/004775/MEA 006.4

Applicant: Alnylam Netherlands B.V.

PRAC Rapporteur: Martin Huber

Scope: Amendment to a previously agreed protocol for study ALN-AS1-006: a global observational longitudinal prospective registry of patients with acute hepatic porphyria (AHP) [ELEVATE]]

17.2.6. Inebilizumab - UPLIZNA (CAP) - EMEA/H/C/005818/MEA 001.1

Applicant: Horizon Therapeutics Ireland DAC

PRAC Rapporteur: Amelia Cupelli

Scope: MAH's response to MEA 001 [protocol for an observational pregnancy safety study in women with neuromyelitis optica spectrum disorder (NMOSD) exposed to Uplizna (ineblizumab)] as per the request for supplementary information (RSI) adopted in November 2022

17.2.7. Inebilizumab - UPLIZNA (CAP) - EMEA/H/C/005818/MEA 003.1

Applicant: Horizon Therapeutics Ireland DAC

PRAC Rapporteur: Amelia Cupelli

Scope: MAH's response to MEA 003 [protocol for a real-world observational study of outcomes for patients with neuromyelitis optica spectrum disorder (NMOSD) treated With inebilizumab in Europe] as per the request for supplementary information (RSI) adopted in November 2022

17.2.8. Inebilizumab - UPLIZNA (CAP) - EMEA/H/C/005818/MEA 004.1

Applicant: Horizon Therapeutics Ireland DAC

PRAC Rapporteur: Amelia Cupelli

Scope: MAH's response to MEA 004 [protocol for a safety study of patients with neuromyelitis optica spectrum disorder (NMOSD) patients receiving inebilizumab following closure of the open-label period (N-MOmentum LT)] as per the request for supplementary information (RSI) adopted in November 2022

17.2.9. Natalizumab - TYSABRI (CAP) - EMEA/H/C/000603/MEA 071.3

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Gabriele Maurer

Scope: MAH's response to MEA 071.2 [feasibility assessment report for study OXON 214-04 (listed as a category 3 study in the RMP): an observational study utilising data from EU national multiple sclerosis (MS) registries to estimate the incidence of anti-natalizumab antibody among patients who receive subcutaneous administration (SC) of natalizumab for treatment of relapsing remitting MS in order to investigate immunogenic potential of SC administration (PASS 101MS412) (from X/0116)] as per the request for supplementary information (RSI) adopted in December 2022

17.2.10. Risankizumab - SKYRIZI (CAP) - EMEA/H/C/004759/MEA 010

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Protocol for a long-term comparative cohort study in patients with Crohn's disease in a real world setting to obtain additional long-term data from the real-world experience of patients with Crohn's disease treated with risankizumab to assess product potential risks and to estimate rates of malignancy (malignancy excluding non-melanoma skin cancer (NMSC), serious infections, serious hypersensitivity reactions, and major adverse cardiovascular events (MACE) in risankizumab treated patients with Crohn's disease, relative to alternative systemic therapies (e.g., biologics)

17.2.11. Tozinameran - COMIRNATY (CAP) - EMEA/H/C/005735/MEA 010.7

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Protocol amendment to a previously agreed protocol for clinical study C4591012 to assess the occurrence of safety events of interest, including severe or atypical COVID-19 in real-world use of COVID-19 mRNA vaccine

17.2.12. Tozinameran - COMIRNATY (CAP) - EMEA/H/C/005735/MEA 064

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Protocol for a non-interventional post-approval safety study of Pfizer-BioNTech bivalent COVID-19 vaccine in the United States in order to fulfill MAH commitment within PAM MEA-011.7 based on the outcome of procedure EMEA/H/C/005735/II/0143 regarding the Agency's request related to protocol amendments for on-going PASS with Omicron BA.1 and BA.4-5

17.3. Results of PASS imposed in the marketing authorisation(s)[64]

None

17.4. Results of PASS non-imposed in the marketing authorisation(s)[65]

17.4.1. Belimumab - BENLYSTA (CAP) - EMEA/H/C/002015/II/0111

Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of the final report from year 5 Post-Treatment Follow-Up from study BEL 115467/HGS1006-C113 listed as a category 3 study in the RMP. This is a 52-week, global, multi-center, randomised, placebo-controlled, double-blind study conducted to evaluate mortality and AESI in adults with active, autoantibody-positive SLE treated with belimumab plus standard therapy vs. placebo plus standard therapy. Following the 52-week controlled treatment period (Year 1), the study included a 4-year follow-up of each participant (Year 2-5). During the follow-up period, participants no longer received study intervention. The RMP version 44 has also been submitted

17.4.2. Dimethyl fumarate - SKILARENCE (CAP) - EMEA/H/C/002157/II/0032

Applicant: Almirall S.A

PRAC Rapporteur: Mari Thorn

Scope: Submission of the final report from study M-41008-44 listed as a category 3 study in the RMP. This is a non-interventional PASS titled 'a retrospective chart review to assess the effectiveness of the Skilarence risk minimisation activities in daily practice'. The RMP

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

version 2.1 has also been submitted

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

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Martin Huber

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

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

Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

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

17.4.5. Golimumab - SIMPONI (CAP) - EMEA/H/C/000992/II/0111

Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of section 4.6 of the SmPC in order to update information on pregnancy based on final results from PASS study CNTO148ART4001 listed as a category 3 study in the RMP; this is an observational prospective cohort study to collect and analyse information pertaining to pregnancy outcomes of women exposed to golimumab during pregnancy. The RMP version 23.2 has also been submitted

17.4.6. Human papillomavirus 9-valent vaccine (recombinant, adsorbed) - GARDASIL 9 (CAP) - EMEA/H/C/003852/II/0063

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Jean-Michel Dogné

Scope: Update of section 4.6 of the SmPC in order to include additional information on

exposure during pregnancy, based on the final report of the US Pregnancy Registry, listed as a category 3 study in the RMP; the package leaflet is updated accordingly. The RMP version 5.1 has also been submitted

17.4.7. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/II/0052

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Submission of the final report from study A3921334 listed as a category 3 study in the RMP. This is a non-interventional PASS to evaluate the effectiveness of additional risk minimisation measures materials for tofacitinib in Europe via a survey of healthcare professionals

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

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Update of Annex II and RMP to version 6.0 to include the results from final clinical study report (CSR) following the completion of a non-interventional (NI) PASS A1501103: an active safety surveillance program to monitor selected events in patients with long-term voriconazole use - MEA091. In addition, MAH is also taking this opportunity to introduce editorial changes [in fulfilment of MEA 091.5]

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

17.5.1. Abatacept - ORENCIA (CAP) - EMEA/H/C/000701/MEA 048.11

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Kimmo Jaakkola

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

17.5.2. Belimumab - BENLYSTA (CAP) - EMEA/H/C/002015/MEA 003.18

Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Ninth annual interim report for study BEL116543/HGS1006-C1124 (SABLE): a long-term controlled safety registry evaluating the incidence of all-cause mortality and adverse events of special interest (AESIs) in patients with systemic lupus erythematosus followed for a minimum of 5 years

17.5.3. Elasomeran - SPIKEVAX (CAP) - EMEA/H/C/005791/MEA 003.10

Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Eighth interim report for study P903 (listed as a category 3 study in the RMP): a PASS 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

17.5.4. Erenumab - AIMOVIG (CAP) - EMEA/H/C/004447/MEA 001.2

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Kirsti Villikka

Scope: Interim report for study CAMG334A2023: a non-interventional study to examine patient characteristics and drug utilisation patterns in migraine patients treated with prophylactic drugs in the Nordic registries [final clinical study report (CSR) expected end of data collection + 1 year]

17.5.5. Inotersen - TEGSEDI (CAP) - EMEA/H/C/004782/MEA 001.8

Applicant: Akcea Therapeutics Ireland Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Annual progress report for study TEG4001: a prospective, non-interventional, long-term, multinational cohort safety study of patients with hereditary transthyretin amyloidosis with polyneuropathy (hATTR-PN)

17.5.6. Lenvatinib - LENVIMA (CAP) - EMEA/H/C/003727/MEA 014.5

Applicant: Eisai GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Second annual study progress report for study E7080-M000-508: an observational study to characterise hepatic related toxicity and overall safety profile in real-life conditions in the EU (Western population) in hepatocellular carcinoma (HCC) patients, including patients with Child-Pugh B

17.5.7. Patisiran - ONPATTRO (CAP) - EMEA/H/C/004699/MEA 003.5

Applicant: Alnylam Netherlands B.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: MAH's response to MEA 003.4 to second interim study report for ALN-TTR02-010: patisiran- lipid nanoparticle (LNP) pregnancy surveillance programme (PSP) to collect primary data on pregnant women from the US, the United Kingdom (UK), France, Spain, Italy, Portugal and Germany, and other potential countries, who have been exposed to patisiran during the exposure window, defined as 12 weeks prior to their last menstrual period (LMP), or at any time during pregnancy as well as to collect and analyse information pertaining to pregnancy complications and birth outcomes in women exposed to patisiran

during pregnancy, as per the request for supplementary information (RSI) as adopted in January 2023

17.5.8. Tozinameran - COMIRNATY (CAP) - EMEA/H/C/005735/MEA 054.1

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]

17.6. Others

17.6.1. Alemtuzumab - LEMTRADA (CAP) - EMEA/H/C/003718/ANX 009.2

Applicant: Sanofi Belgium

PRAC Rapporteur: Anette Kirstine Stark

Scope: The provision of answers to questions about the feasibility report of the non-interventional PASS to investigate the risk of mortality in multiple sclerosis (MS) patients treated with alemtuzumab (Lemtrada) relative to comparable MS patients using other disease modifying treatments (DMTs) as requested in the new EMEA/H/C/003718/ANX/0009.1

17.6.2. Darolutamide - NUBEQA (CAP) - EMEA/H/C/004790/REC 004.2

Applicant: Bayer AG

PRAC Rapporteur: Jan Neuhauser

Scope: MAH's response to REC 004.1 [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)] as per request for supplementary information (RSI) adopted in December 2022

17.6.3. Venetoclax - VENCLYXTO (CAP) - EMEA/H/C/004106/LEG 017.1

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Eva Jirsová

Scope: From II-0031: Commitment to provide targeted tumour lysis syndrome (TLS) assessment reports on a biannual basis (submitted annually within the PSUR, and 6 months after the PSUR submission in a separate report) through 2023, and annually thereafter, as per the RMP v8.0. These biannual assessment reports ensure close monitoring of the important identified risk of TLS, and the evaluation of the impact of newly implemented risk minimisation measures for TLS, on adherence to both already existing and updated recommendation added to the SmPC, the impact of the DHPC distributed to hematologists, and the patient card

17.7. New Scientific Advice

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

17.8. Ongoing Scientific Advice

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

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

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

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

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

18.1. Annual reassessments of the marketing authorisation

18.1.1. Glucarpidase - VORAXAZE (CAP) - EMEA/H/C/005467/S/0013 (without RMP)

Applicant: SERB S.A.S.

PRAC Rapporteur: Martin Huber

Scope: Annual reassessment of the marketing authorisation

18.1.2. Tecovirimat - TECOVIRIMAT SIGA (CAP) - EMEA/H/C/005248/S/0004 (without RMP)

Applicant: SIGA Technologies Netherlands B.V.

PRAC Rapporteur: Martin Huber

Scope: Annual reassessment of the marketing authorisation

18.2. Conditional renewals of the marketing authorisation

18.2.1. Ataluren - TRANSLARNA (CAP) - EMEA/H/C/002720/R/0071 (without RMP)

Applicant: PTC Therapeutics International Limited

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Conditional renewal of the marketing authorisation

18.2.2. Avapritinib - AYVAKYT (CAP) - EMEA/H/C/005208/R/0025 (without RMP)

Applicant: Blueprint Medicines (Netherlands) B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Conditional renewal of the marketing authorisation

18.2.3. Budesonide - KINPEYGO (CAP) - EMEA/H/C/005653/R/0003 (without RMP)

Applicant: STADA Arzneimittel AG

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Conditional renewal of the marketing authorisation

18.2.4. Larotrectinib - VITRAKVI (CAP) - EMEA/H/C/004919/R/0031 (without RMP)

Applicant: Bayer AG

PRAC Rapporteur: Rugile Pilviniene

Scope: Conditional renewal of the marketing authorisation

18.2.5. Tafasitamab - MINJUVI (CAP) - EMEA/H/C/005436/R/0009 (without RMP)

Applicant: Incyte Biosciences Distribution B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Conditional renewal of the marketing authorisation

18.2.6. Teclistamab - TECVAYLI (CAP) - EMEA/H/C/005865/R/0002 (without RMP)

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Jana Lukacisinova

Scope: Conditional renewal of the marketing authorisation

18.3. Renewals of the marketing authorisation

18.3.1. Adalimumab - HULIO (CAP) - EMEA/H/C/004429/R/0041 (without RMP)

Applicant: Viatris Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: 5-year renewal of the marketing authorisation

18.3.2. Brigatinib - ALUNBRIG (CAP) - EMEA/H/C/004248/R/0049 (without RMP)

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Inês Ribeiro-Vaz

Scope: 5-year renewal of the marketing authorisation

18.3.3. Buprenorphine - BUVIDAL (CAP) - EMEA/H/C/004651/R/0021 (with RMP)

Applicant: Camurus AB

PRAC Rapporteur: Tiphaine Vaillant

Scope: 5-year renewal of the marketing authorisation

18.3.4. Galcanezumab - EMGALITY (CAP) - EMEA/H/C/004648/R/0023 (with RMP)

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Kirsti Villikka

Scope: 5-year renewal of the marketing authorisation

18.3.5. Imlifidase - IDEFIRIX (CAP) - EMEA/H/C/004849/R/0014 (without RMP)

Applicant: Hansa Biopharma AB

PRAC Rapporteur: Menno van der Elst

Scope: 5-year renewal of the marketing authorisation

18.3.6. Lanadelumab - TAKHZYRO (CAP) - EMEA/H/C/004806/R/0035 (without RMP)

Applicant: Takeda Pharmaceuticals International AG Ireland Branch

PRAC Rapporteur: Kirsti Villikka

Scope: 5-year renewal of the marketing authorisation

18.3.7. Meropenem, vaborbactam - VABOREM (CAP) - EMEA/H/C/004669/R/0019 (without RMP)

Applicant: Menarini International Operations Luxembourg S.A.

PRAC Rapporteur: Maria del Pilar Rayon

Scope: 5-year renewal of the marketing authorisation

18.3.8. Paclitaxel - APEALEA (CAP) - EMEA/H/C/004154/R/0017 (with RMP)

Applicant: Inceptua AB

PRAC Rapporteur: Inês Ribeiro-Vaz

Scope: 5-year renewal of the marketing authorisation

18.3.9. Pegfilgrastim - FULPHILA (CAP) - EMEA/H/C/004915/R/0042 (without RMP)

Applicant: Viatris Limited

PRAC Rapporteur: Menno van der Elst

Scope: 5-year renewal of the marketing authorisation

18.3.10. Radium (Ra^{223}) - XOFIGO (CAP) - EMEA/H/C/002653/R/0049 (with RMP)

Applicant: Bayer AG

PRAC Rapporteur: Rugile Pilviniene

Scope: 5-year renewal of the marketing authorisation

18.3.11. Tildrakizumab - ILUMETRI (CAP) - EMEA/H/C/004514/R/0042 (with RMP)

Applicant: Almirall S.A

PRAC Rapporteur: Adam Przybylkowski

Scope: 5-year renewal of the marketing authorisation

18.3.12. Vestronidase alfa - MEPSEVII (CAP) - EMEA/H/C/004438/R/0033 (without RMP)

Applicant: Ultragenyx Germany GmbH

PRAC Rapporteur: Maria del Pilar Rayon

Scope: 5-year renewal of the marketing authorisation

18.3.13. Valoctocogene roxaparvovec - ROCTAVIAN (CAP) - EMEA/H/C/005830/R/0003 (without RMP)

Applicant: BioMarin International Limited, ATMP[66]

PRAC Rapporteur: Menno van der Elst

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 10-12 May 2023 meeting. Participants marked with "a" attended the plenary session while those marked with "b" attended ORGAM.

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

[66] Advanced medicinal therapy product

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Jo Robays [a]	Alternate	Belgium	No interests declared	
Maria Popova-Kiradjieva [a,b]	Member	Bulgaria	No interests declared	
Nikica Mirošević Skvrce [a,b]	Member	Croatia	No interests declared	
Željana Margan Koletić [a,b]	Alternate	Croatia	No interests declared	
Elena Kaisis [a,b]	Member	Cyprus	No interests declared	
Panagiotis Psaras [a,b]	Alternate	Cyprus	No interests declared	
Eva Jirsová [a,b]	Member	Czechia	No interests declared	
Jana Lukacisinova [a,b]	Alternate	Czechia	No interests declared	
Anette Kirstine Stark [a,b]	Member	Denmark	No interests declared	
Marie Louise Schougaard Christiansen [b]	Alternate	Denmark	No interests declared	
Maia Uusküla [a]	Member	Estonia	No interests declared	
Kroot Aab [a]	Alternate	Estonia	No interests declared	
Kirsti Villikka [a,b]	Member	Finland	No interests declared	
Kimmo Jaakkola [a,b]	Alternate	Finland	No interests declared	
Tiphaine Vaillant [a,b]	Member	France	No interests declared	
Nathalie Gault [a,b]	Alternate	France	No interests declared	
Martin Huber [a,b]	Member (Vice-Chair)	Germany	No interests declared	
Gabriele Maurer [a,b]	Alternate	Germany	No participation in final deliberations and voting on:	15.3.19. Nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/II/0130
Sofia Trantza [a]	Member	Greece	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Georgia Gkegka [a,b]	Alternate	Greece	No interests declared	
Julia Pallos [b]	Member	Hungary	No participation in final deliberations and voting on:	14.1.1. Azacitidine – AZACITIDINE ACCORD (CAP), AZACITIDINE BETAPHARM (CAP), AZACITIDINE MYLAN (CAP), ONUREG (CAP), VIDAZA (CAP) 15.3.19. Nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/II/0130 16.2.4. Thalidomide - THALIDOMIDE BMS (CAP); THALIDOMIDE LIPOMED (CAP); NAP - PSUSA/00002919/202210 17.5.1. Abatacept - ORENCIA (CAP) - EMEA/H/C/000701/MEA 048.11
Melinda Palfi [a,b]	Alternate	Hungary	No interests declared	
Guðrún Stefánsdóttir [a,b]	Member	Iceland	No participation in final deliberations and voting on:	15.3.9. Denosumab - PROLIA (CAP) - EMEA/H/C/001120/II/0098 15.3.27. Sotorasib - LUMYKRAS (CAP) - EMEA/H/C/005522/II/0010/G 16.1.27. Talimogene laherparepvec - IMLYGIC (CAP) -

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				PSUSA/00010459 /202210
Eamon O Murchu [a,b]	Alternate	Ireland	No interests declared	
Amelia Cupelli [a,b]	Member	Italy	No interests declared	
Valentina Di Giovanni [a,b]	Alternate	Italy	No interests declared	
Zane Neikena [a]	Member	Latvia	No interests declared	
Lina Seibokiene [a]	Alternate	Lithuania	No participation in discussion, final deliberations and voting on:	6.1.6. Rivaroxaban - XARELTO (CAP) - PSUSA/00002653 /202209
Nadine Petitpain [a]	Member	Luxembourg	No participation in final deliberations and voting on:	3.2.1. Pseudoephedrine (NAP); pseudoephedrine, acetylsalicylic acid (NAP); pseudoephedrine, acetylcysteine, paracetamol (NAP); pseudoephedrine, acrivastine (NAP); pseudoephedrine, ascorbic acid, paracetamol (NAP); pseudoephedrine, cetirizine (NAP); pseudoephedrine, ebastine (NAP); pseudoephedrine, guaifenesin (NAP); pseudoephedrine, ibuprofen (NAP); pseudoephedrine, chlorphenamine (NAP); pseudoephedrine, chlorphenamine, codeine (NAP); pseudoephedrine,

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				chlorphenamine, dextromethorphan (NAP); pseudoephedrine, chlorphenamine, paracetamol (NAP); pseudoephedrine, chlorphenamine, dextromethorphan, paracetamol (NAP); pseudoephedrine, dextromethorphan (NAP); pseudoephedrine, dextromethorphan, paracetamol (NAP); pseudoephedrine, dextromethorphan, ascorbic acid, paracetamol (NAP); pseudoephedrine, dextromethorphan, guaifenesin, paracetamol (NAP); pseudoephedrine, dextromethorphan, guaifenesin, triprolidine (NAP); pseudoephedrine, dextromethorphan, triprolidine (NAP); pseudoephedrine, diphenhydramine, paracetamol (NAP); pseudoephedrine, doxylamine, paracetamol (NAP); pseudoephedrine, loratadine (NAP); pseudoephedrine, paracetamol (NAP); pseudoephedrine, paracetamol, pholcodine (NAP); pseudoephedrine,

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				triprolidine (NAP); pseudoephedrine, triprolidine, guaifenesin (NAP); pseudoephedrine, triprolidine, paracetamol (NAP); pseudoephedrine, desloratadine - AERINAZE (CAP) – EMA/H/A-31/1526
Benjamin Micallef [a]	Alternate	Malta	No interests declared	
Menno van der Elst [a,b]	Member	Netherlands	No interests declared	
Liana Gross-Martirosyan [a,b]	Alternate	Netherlands	No interests declared	
David Olsen [a,b]	Member	Norway	No participation in final deliberations and voting on:	3.1.1. Hydroxyprogesterone (NAP) - EMEA/H/A-31/1528 3.2.1. Pseudoephedrine (NAP); pseudoephedrine, acetylsalicylic acid (NAP); pseudoephedrine, acetylcysteine, paracetamol (NAP); pseudoephedrine, acrivastine (NAP); pseudoephedrine, ascorbic acid, paracetamol (NAP); pseudoephedrine, cetirizine (NAP); pseudoephedrine, ebastine (NAP); pseudoephedrine, guaifenesin (NAP); pseudoephedrine, ibuprofen (NAP); pseudoephedrine,

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				chlorphenamine (NAP); pseudoephedrine, chlorphenamine, codeine (NAP); pseudoephedrine, chlorphenamine, dextromethorphan (NAP); pseudoephedrine, chlorphenamine, paracetamol (NAP); pseudoephedrine, chlorphenamine, dextromethorphan, paracetamol (NAP); pseudoephedrine, dextromethorphan (NAP); pseudoephedrine, dextromethorphan, paracetamol (NAP); pseudoephedrine, dextromethorphan, ascorbic acid, paracetamol (NAP); pseudoephedrine, dextromethorphan, guaifenesin, paracetamol (NAP); pseudoephedrine, dextromethorphan, guaifenesin, triprolidine (NAP); pseudoephedrine, dextromethorphan, triprolidine (NAP); pseudoephedrine, diphenhydramine, paracetamol (NAP); pseudoephedrine, doxylamine, paracetamol (NAP); pseudoephedrine, loratadine (NAP); pseudoephedrine, paracetamol

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				(NAP); pseudoephedrine, paracetamol, pholcodine (NAP); pseudoephedrine, triprolidine (NAP); pseudoephedrine, triprolidine, guaifenesin (NAP); pseudoephedrine, triprolidine, paracetamol (NAP); pseudoephedrine, desloratadine - AERINAZE (CAP) – EMA/H/A-31/1526 6.1.6. Rivaroxaban - XARELTO (CAP) - PSUSA/00002653/202209 16.3.11. Lysine acetylsalicylate (NAP) - PSUSA/00001921/202209 17.6.2. Darolutamide - NUBEQA (CAP) - EMEA/H/C/004790/REC 004.2 18.2.4. Larotrectinib - VITRAKVI (CAP) - EMEA/H/C/004919/R/0031 (without RMP) 18.3.10. Radium (Ra223) - XOFIGO (CAP) - EMEA/H/C/002653/R/0049 (with RMP)
Pernille Harg [a],[b]	Alternate	Norway	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Adam Przybylkowski [a]	Member	Poland	No interests declared	
Katarzyna Ziolkowska [a,b]	Alternate	Poland	No interests declared	
Ana Sofia Diniz Martins [a,b]	Member	Portugal	No interests declared	
Ines Ribeiro-Vaz [a,b]	Alternate	Portugal	No interests declared	
Roxana Dondera [a,b]	Member	Romania	No interests declared	
Irina Sandu [a,b]	Alternate	Romania	No interests declared	
Anna Mareková [a,b]	Member	Slovakia	No interests declared	
Miroslava Gocova [a]	Alternate	Slovakia	No interests declared	
Polona Golmajer [a,b]	Member	Slovenia	No interests declared	
Milena Radoha-Bergoc [b]	Alternate	Slovenia	No participation in final deliberations and voting on:	3.2.1. Pseudoephedrine (NAP); pseudoephedrine, acetylsalicylic acid (NAP); pseudoephedrine, acetylcysteine, paracetamol (NAP); pseudoephedrine, acrivastine (NAP); pseudoephedrine, ascorbic acid, paracetamol (NAP); pseudoephedrine, cetirizine (NAP); pseudoephedrine, ebastine (NAP); pseudoephedrine, guaifenesin (NAP); pseudoephedrine, ibuprofen (NAP); pseudoephedrine, chlorphenamine (NAP); pseudoephedrine, chlorphenamine, codeine (NAP); pseudoephedrine,

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				chlorphenamine, dextromethorphan (NAP); pseudoephedrine, chlorphenamine, paracetamol (NAP); pseudoephedrine, chlorphenamine, dextromethorphan, paracetamol (NAP); pseudoephedrine, dextromethorphan (NAP); pseudoephedrine, dextromethorphan, paracetamol (NAP); pseudoephedrine, dextromethorphan, ascorbic acid, paracetamol (NAP); pseudoephedrine, dextromethorphan, guaifenesin, paracetamol (NAP); pseudoephedrine, dextromethorphan, guaifenesin, triprolidine (NAP); pseudoephedrine, dextromethorphan, triprolidine (NAP); pseudoephedrine, diphenhydramine, paracetamol (NAP); pseudoephedrine, doxylamine, paracetamol (NAP); pseudoephedrine, loratadine (NAP); pseudoephedrine, paracetamol (NAP); pseudoephedrine, paracetamol, pholcodine (NAP); pseudoephedrine,

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				triprolidine (NAP); pseudoephedrine, triprolidine, guaifenesin (NAP); pseudoephedrine, triprolidine, paracetamol (NAP); pseudoephedrine, desloratadine - AERINAZE (CAP) – EMA/H/A-31/1526
Maria del Pilar Rayon [a,b]	Member	Spain	No interests declared	
Monica Martinez Redondo [a,b]	Alternate	Spain	No interests declared	
Ulla Wändel Liminga [a,b]	Member	Sweden	No interests declared	
Mari Thorn [a,b]	Alternate	Sweden	No interests declared	
Annalisa Capuano [a]	Member	Independent scientific expert	No interests declared	
Milou Daniel Drici [a,b]	Member	Independent scientific expert	No interests declared	
Maria Teresa Herdeiro [a,b]	Member	Independent scientific expert	No interests declared	
Patricia McGettigan [a]	Member	Independent scientific expert	No interests declared	
Tania Schink [a]	Member	Independent scientific expert	No participation in final deliberations and voting on:	6.1.3. Edoxaban - LIXIANA (CAP); ROTEAS (CAP) - PSUSA/00010387/202210 6.1.6. Rivaroxaban - XARELTO (CAP) - PSUSA/00002653/202209
Hedvig Nordeng [a]	Member	Independent scientific expert	No interests declared	
Roberto Frontini [a,b]	Member	Healthcare Professionals' Representative	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
Salvatore Messana [a]	Alternate	Healthcare Professionals' Representative	No interests declared	
Declan Noone [a]	Member	Patients' Organisation Representative	No interests declared	
Daniela Philadelphy [b]	Expert	Austria	No restrictions applicable to this meeting	
Laurence de Fays [a]	Expert	Belgium	No restrictions applicable to this meeting	
Fabrice Moore [a]	Expert	Belgium	No interests declared	
Flora Musuamba Tshinanu [a]	Expert	Belgium	No interests declared	
Martine Sabbe [a]	Expert	Belgium	No interests declared	
Ivana Kosier [a]	Expert	Croatia	No interests declared	
Nina Lalić [a]	Expert	Croatia	No restrictions applicable to this meeting	
Veronika Deščíková [a]	Expert	Czechia	No interests declared	
Michaela Dlouhá [a]	Expert	Czechia	No interests declared	
Lucie Skálová [a]	Expert	Czechia	No interests declared	
Alexander Braathen [a]	Expert	Denmark	No interests declared	
Kirsten Egebjerg Juul [a]	Expert	Denmark	No interests declared	
Helle Gerda Olsen [a]	Expert	Denmark	No interests declared	
Moritz Sander [a]	Expert	Denmark	No interests declared	
Ane Blicher Schelde [a]	Expert	Denmark	No restrictions	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			applicable to this meeting	
Andreas James Schaeffer Senders [a]	Expert	Denmark	No interests declared	
Aynur Sert [a]	Expert	Denmark	No interests declared	
Per Sindahl [a]	Expert	Denmark	No interests declared	
Emma Stadsbjerg [a]	Expert	Denmark	No interests declared	
Barbara Blicher Thomsen [a]	Expert	Denmark	No interests declared	
Chau Minh Tran [a]	Expert	Denmark	No interests declared	
Katrin Kurvits [a]	Expert	Estonia	No interests declared	
Julia Maslovskaja [a]	Expert	Estonia	No interests declared	
Helve Vestman [a]	Expert	Estonia	No interests declared	
Pauline Dayani [a]	Expert	France	No interests declared	
Vincent Gazin [a]	Expert	France	No interests declared	
Marie-Caroline Pesquidous [a]	Expert	France	No restrictions applicable to this meeting	
Nicole Bethge [a]	Expert	Germany	No interests declared	
Dennis Lex [a],[b]	Expert	Germany	No interests declared	
Ronan Grimes [a]	Expert	Ireland	No interests declared	
Aine McKenna [a]	Expert	Ireland	No interests declared	
David O Riordan [a]	Expert	Ireland	No interests declared	
Ruchika Sharma [a]	Expert	Ireland	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
Patrizia Felicetti [a]	Expert	Italy	No interests declared	
Carmela Macchiarulo [a]	Expert	Italy	No interests declared	
Pasquale Marchione	Expert	Italy	No interests declared	
Elena Matarangolo [a]	Expert	Italy	No interests declared	
Fiorella Petronzelli [a]	Expert	Italy	No restrictions applicable to this meeting	
Diana Paegle [a]	Expert	Latvia	No interests declared	
Michal Pirozynski [a]	Expert	Malta		
Marianne Klanker [a]	Expert	Netherlands	No interests declared	
Marcel Kwa [a]	Expert	Netherlands	No interests declared	
Peter Mol [a]	Expert	Netherlands	No restrictions applicable to this meeting	
Evelyn Olthof [a]	Expert	Netherlands	No interests declared	
Carla Torre [a]	Expert	Portugal	No interests declared	
Natividad Galiana [a]	Expert	Spain	No restrictions applicable to this meeting	
María Martínez [b]	Expert	Spain	No interests declared	
Luz Medrano [a]	Expert	Spain	No interests declared	
Charlotte Backman [a,b]	Expert	Sweden	No interests declared	
Johanna Henriksnäs [a]	Expert	Sweden	No interests declared	
Jenny Jönsson [a]	Expert	Sweden	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
Miriam Taekema [a]	Expert	Sweden	No interests declared	
A representative from the European Commission attended the meeting				
Meeting run with support from relevant EMA staff				

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

20. Annex III - List of acronyms and abbreviations

For a list of acronyms and abbreviations, see:

List of abbreviations used in EMA human medicines scientific committees and CMDh documents, and in relation to EMA's regulatory activities

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