25 August 2023
EMA/PRAC/337931/2023
Human Medicines Division

Pharmacovigilance Risk Assessment Committee (PRAC)

Minutes of PRAC meeting on 05-08 June 2023

Chair: Sabine Straus – Vice-Chair: Martin Huber

Health and safety information

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

Disclaimers

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

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

Note on access to documents

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

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1. Introduction

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

The Chairperson opened the meeting by welcoming all participants. 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 that no restriction in the involvement of meeting participants for agenda topics was identified. Participants were asked to declare any changes, omissions or errors to their declared interests concerning the matters for discussion. No new or additional competing interests were declared. Restrictions applicable to this meeting are captured in the List of participants included in the minutes.

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

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

1.2. Agenda of the meeting on 05-08 June 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 10-12 May 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 10-12 May 2023 were published on the EMA website on 31 August 2023 (EMA/PRAC/332783/2023).

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

2.1. Newly triggered procedures

None

2.2. Ongoing procedures

None

2.3. Procedures for finalisation

None

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

3.1. Newly triggered procedures

None

3.2. Ongoing procedures

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

Applicant(s): various

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

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

Background

A referral procedure under Article 31 of Directive 2001/83/EC is ongoing for topiramate- and topiramate/phentermine-containing medicines following the publication by *Bjørk et al.*[1] in which the authors concluded on a significant increase of neurodevelopmental disorders, in particular autism spectrum disorders and intellectual disability, in children with prenatal exposure to topiramate. Given the potential increased risk of neurodevelopmental disorders highlighted in this study with *in utero* exposure to topiramate and the known risk of congenital malformations, the matter was referred to PRAC for further evaluation. For further background, see PRAC minutes September 2022, PRAC minutes December 2022, PRAC minutes January 2023, PRAC minutes February 2023 and PRAC minutes March 2023.

Summary of recommendation(s)/conclusions

- PRAC discussed the joint assessment report issued by the Rapporteurs. .
- PRAC adopted a further list of outstanding issues (LoOI) to be addressed by the MAHs for topiramate- and topiramate/phentermine-containing medicines in accordance with a revised timetable (EMA/PRAC/702489/2022 rev.4).

3.3. Procedures for finalisation

None

3.4. Re-examination procedures[2]

None

[1] Bjørk M, Zoega H, Leinonen MK, et al. Association of prenatal exposure to antiseizure medication with risk of autism and intellectual disability. JAMA Neurol. Published online May 31, 2022. doi:10.1001/jamaneurol.2022.1269
[2] Re-examination of PRAC recommendation under Article 32 of Directive 2001/83/EC

3.5. Others

None

4. Signals assessment and prioritisation[3]

4.1. New signals detected from EU spontaneous reporting systems

See Annex I 14.1.

4.2. New signals detected from other sources

None

4.3. Signals follow-up and prioritisation

4.3.1. Ipilimumab – YERVOY (CAP) - EMEA/H/C/002213/SDA/046; nivolumab – OPDIVO (CAP) - EMEA/H/C/003985/SDA/051; pembrolizumab – KEYTRUDA (CAP) - EMEA/H/C/003820/SDA/036

Applicant(s): Bristol-Myers Squibb Pharma EEIG (Opdivo, Yervoy), Merck Sharp & Dohme B.V. (Keytruda)

PRAC Rapporteur: Menno van der Elst

Scope: Signal of capillary leak syndrome (Opdivo, Yervoy, Keytruda) and cytokine release syndrome (Opdivo)

EPITT 19880 – Follow-up to February 2023

Background

For background information, see PRAC minutes February 2023.

The MAHs replied to the request for information on the signal of capillary leak syndrome (CLS) for Opdivo (nivolumab), Yervoy (ipilimumab) and Keytruda (pembrolizumab), and on the signal of cytokine release syndrome (CRS) for Opdivo (nivolumab). The responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence concerning CLS, including additional data provided by the MAHs and the Rapporteur's assessment, PRAC agreed that no further action is deemed warranted at this stage.

In addition, having considered the available evidence concerning CRS, including additional data provided by the MAH for Opdivo (nivolumab) and the Rapporteur's assessment, PRAC agreed that there is sufficient evidence to establish a causal relationship between treatment with nivolumab and CRS.

Summary of recommendation(s)

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

- The MAH for Opdivo (nivolumab) should submit to EMA, within 60 days, a variation to amend the product information[4] in order to include CRS as an undesirable effect with a frequency 'common'.
- The MAHs for Opdivo (nivolumab), Keytruda (pembrolizumab) and Yervoy (ipilimumab) should continue to monitor cases of CLS as part of routine pharmacovigilance.

See EMA/PRAC/248309/2023 published on 03 July 2023 on the EMA website.

4.3.2. Tofacitinib – XELJANZ (CAP) - EMEA/H/C/004214/SDA/026

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Signal of acnes

EPITT 19885 – Follow-up to February 2023

Background

For background information, see PRAC minutes February 2023.

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

Discussion

Having considered the available evidence from EudraVigilance and the literature, the MAH's responses and the Rapporteur's assessment, PRAC concluded that there is sufficient evidence to establish a causal relationship between treatment with tofacitinib and acne.

Summary of recommendation(s)

- The MAH for Xeljanz (tofacitinib) should submit to EMA, within 60 days, a variation to amend the product information[5] in order to add acne as an undesirable effect with a frequency 'common'.

See EMA/PRAC/248309/2023 published on 03 July 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.

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

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. Fezolinetant - EMEA/H/C/005851

Scope: treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause

5.1.2. Dantrolene sodium, hemiheptahydrate - EMEA/H/C/006009, Orphan

Applicant: Norgine B.V.

Scope: treatment of malignant hyperthermia (including suspected cases)

5.1.3. Methylphenidate hydrochloride - EMEA/H/C/005975, PUMA6

Scope: treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children aged 6 years of age and over

5.1.4. Zilucoplan - EMEA/H/C/005450, Orphan

Applicant: UCB Pharma S.A.

Scope: treatment of generalised myasthenia gravis in adults

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

See Annex I 15.2.

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

See also Annex I 15.3.

5.3.1. Remdesivir - VEKLURY (CAP) - EMEA/H/C/005622/II/0046

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Eva Jirsová

Scope: Update of sections 4.6 and 5.1 of the SmPC in order to update information on pregnancy and breast-feeding based on final results from study IMPAACT 2032 listed as a category 3 study in the RMP; this is a phase 4, prospective, open-label, non-randomised study to address PK and safety of remdesivir in pregnant women. The package leaflet is updated accordingly. The RMP version 5.2 has also been submitted

Background

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

[6] Paediatric-use marketing authorisation(s)

CHMP is evaluating a type II variation for Veklury, a centrally authorised product containing remdesivir, to update the product information on pregnancy and breast-feeding based on final results from study IMPAACT 2032 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. For further background, see PRAC minutes March 2023.

Summary of advice

- The RMP for Veklury (remdesivir) in the context of the variation procedure under evaluation by CHMP could be considered acceptable provided that an update to RMP version 5.5 is submitted.
- PRAC considered that the MAH should continue to use modified pregnancy questionnaires and to retain them in the RMP. Moreover, the MAH should include COVID-19 pregnancy registry as a category 3 study in the RMP and to provide interim and final study reports within future PSURs. Finally, the MAH should provide comments on the wording proposal for the product information regarding contraception for women of childbearing potential and pregnancy.

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. Acalabrutinib - CALQUENCE (CAP) - PSUSA/00010887/202210

Applicant: AstraZeneca AB

PRAC Rapporteur: Željana Margan Koletić

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 Calquence, a centrally authorised medicine containing acalabrutinib 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 Calquence (acalabrutinib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add hypertension as an undesirable effect with a frequency 'common' for acalabrutinib monotherapy and 'very

common' for the combination therapy. Therefore, the current terms of the marketing authorisation(s) should be varied[7].

- In the next PSUR, the MAH should provide cumulative reviews of cases of hepatotoxicity and of myocardial infarction , including data from clinical trials. The MAH should also provide cumulative reviews of cases of pericardial disorders and of dental disorders and discuss the need for an update of the product information as warranted. Furthermore, the MAH should continue to closely monitor cases of cerebrovascular accident of cardiac failure.

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

6.1.2. Artenimol, piperaquine tetraphosphate - EURARTESIM (CAP) - PSUSA/00001069/202210

Applicant: Alfasigma S.p.A.

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 Eurartesim, a centrally authorised medicine containing artenimol/piperaquine tetraphosphate 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 Eurartesim (artenimol/piperaquine tetraphosphate) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add hepatocellular injury as an undesirable effect with a frequency 'uncommon'. Therefore, the current terms of the marketing authorisation(s) should be varied[8].
- The MAH should submit to EMA, within 6 weeks, a cumulative review of cases of autoimmune haemolytic anaemia and of delayed haemolytic anaemia.

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.

[7] 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.
[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.

6.1.3. Cefiderocol - FETCROJA (CAP) - PSUSA/00010849/202211

Applicant: Shionogi B.V.

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

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

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Fetcroja (cefiderocol) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAH should provide a cumulative review of cases of MedDRA SMQ[9] 'hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions', as well as an update on cases of cholestasis and discuss the need for an update of the product information as warranted. Moreover, the MAH should closely monitor cases of hepatocellular injury and of documented mutations of the CirA siderophore receptor during cefiderocol administration at least in cases with borderline susceptibility at start of therapy due to pre-existing betalactamases.
- The MAH should submit to EMA, within 30 days, a variation to address the issue of physical incompatibilities as stated in the publication by *Lu et al*[10].

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. Crizanlizumab - ADAKVEO (CAP) - PSUSA/00010888/202211

Applicant: Novartis Europharm Limited

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.

[9] Standardised MedDRA Queries
[10] Lu J, Liu Q, Kupiec TC, Vail H, Lynch LR, Fam DS, Vu NT. Physical Compatibility of Cefiderocol with Selected Intravenous Drugs During Simulated Y-siteAdministration. Int J Pharm Compd. 25,1, 52-61 (2021 Jan-Feb)

Based on the PRAC review of data presented in the context of this PSUR, PRAC is of the view that the product information of Adakveo, a centrally authorised medicine containing crizanlizumab, should be updated.

Summary of recommendation(s) and conclusions

- The product information should be updated to amend the existing wording on the management infusion-related reactions in order to reflect the fact that vaso-occlusive crises (VOCs) can occur concomitantly and/or as a consequence of an infusion related reaction event and give clear recommendations to healthcare professionals about the clinical management. Therefore, the current terms of the marketing authorisation(s) should be varied[11].

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.

This recommendation is without prejudice to the CHMP opinion for the referral procedure EMEA/H/A-20/1525/C/4874/0013 under Article 20 of Regulation (EC) No 726/2004 adopted on 25 May 2023, concluding on the revocation of the marketing authorisation for Adakveo.

6.1.5. Hydrocortisone[12] - EFMODY (CAP); PLENADREN (CAP) - PSUSA/00009176/202211

Applicant: Diurnal Europe BV (Efmody), Takeda Pharmaceuticals International AG Ireland Branch (Plenadren)

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 Efmody and Plenadren, centrally authorised medicines containing hydrocortisone indicated for adrenal insufficiency, congenital adrenal hyperplasia, modified-release formulations and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Efmody (hydrocortisone) and Plenadren (hydrocortisone) in the approved indication(s) remains unchanged.
- Nevertheless, the product information for Efmody (hydrocortisone) should be updated to amend the existing information about fertility and add unexpected early improvement of infertility as a warning. Therefore, the current terms of the marketing authorisation(s) should be varied[13].

[11] Update of SmPC sections 4.2, 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion.
[12] For centrally authorised products for adrenal insufficiency, congenital adrenal hyperplasia, modified-release formulations
[13] Update of SmPC sections 4.4 and 4.6. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion.

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

6.1.6. Ibrutinib - IMBRUVICA (CAP) - PSUSA/00010301/202211

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Nikica Mirošević Skvrce

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 Imbruvica, a centrally authorised medicine containing ibrutinib 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 Imbruvica (ibrutinib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add acute kidney injury and pyogenic granuloma as undesirable effects with a frequency 'common' and 'uncommon' respectively. Therefore, the current terms of the marketing authorisation(s) should be varied[14].
- In the next PSUR, the MAH should provide cumulative reviews of cases of pericardial disorders/cardiac tamponade, cardiac arrest, fractures, dental disorders and of adrenal insufficiency. The MAH should provide a review of cases of pseudolymphoma, vasculitis and of uveitis including cases with cystoid macular oedema. The MAH should also provide a review of cases of acute kidney injury, cataract, macular oedema/cystoid macular oedema, macular degeneration and retinal detachment along with a discussion to update the product information as warranted. Furthermore, the MAH should closely monitor cases of ischaemic heart disease/myocardial infarction and should include hearing impairment as an important potential risk in the list of safety concerns within 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.

6.1.7. Nintedanib[15] - VARGATEF (CAP) - PSUSA/00010318/202210

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Georgia Gkegka

[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] Oncology indications only

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 Vargatef, a centrally authorised medicine containing nintedanib 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 Vargatef (nintedanib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the existing warning regarding gastrointestinal perforations and add information about ischaemic colitis. Therefore, the current terms of the marketing authorisation(s) should be varied[16].
- In the next PSUR, the MAH should provide a cumulative review of artery dissections and aneurysms including intramural haematoma (IMHs), of proteinuria, nephrotic syndrome and thrombotic microangiopathy (TMA) including data on renal-limited thrombotic microangiopathy, of cholecystitis (with or without cholelithiasis), of angioedema, of treatment of patients receiving therapeutic anticoagulation, of adrenal insufficiency and of ischaemic colitis.

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

6.1.8. Rituximab - BLITZIMA (CAP); MABTHERA (CAP); RIXATHON (CAP); RIXIMYO (CAP); RUXIENCE (CAP); TRUXIMA (CAP) - PSUSA/00002652/202211

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

PRAC Rapporteur: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

Background

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

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Blitzima, Mabthera, Rixathon, Riximyo, Ruxience and Truxima, centrally authorised medicines containing rituximab and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

[16] 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.

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Blitzima, Mabthera, Rixathon, Riximyo, Ruxience and Truxima, centrally authorised medicines containing rituximab in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add enteroviral meningoencephalitis as a warning and as an undesirable effect with a frequency 'not known'. Moreover, the product information should be updated to add a warning regarding the possibility of false negative serologic testing of infections. Therefore, the current terms of the marketing authorisation(s) should be varied[17].
- In the next PSUR, the MAHs should include the acute polyneuropathy/Guillain-Barré syndrome as an important potential risk in the list of safety concerns within the PSURs.
- The MAH Roche should submit to EMA, within 6 months, a variation in order to re-evaluate the need for continuation of the additional risk minimisation measures in place for rituximab in the form of educational materials to both HCPs and patients and to align the product information with the established guidelines.

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.

6.1.9. Selpercatinib - RETSEVMO (CAP) - PSUSA/00010917/202211

Applicant: Eli Lilly Nederland 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 Retsevmo, a centrally authorised medicine containing selpercatinib 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 Retsevmo (selpercatinib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add hypothyroidism as an undesirable effect with a frequency 'very common', as well as to add a warning regarding relevant monitoring requirements. In addition, the product information should be updated to include information on drug-drug interaction with levothyroxine. Therefore, the current terms of the marketing authorisation(s) should be varied[18].

[17] 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.
[18] Update of SmPC sections 4.4, 4.5 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion.

- In the next PSUR, the MAH should continue to closely monitor cases of acute kidney injury.

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.

6.1.10. Tirzepatide - MOUNJARO (CAP) - PSUSA/00011019/202211

Applicant: Eli Lilly Nederland 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 Mounjaro, a centrally authorised medicine containing tirzepatide 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 Mounjaro (tirzepatide) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add reaction injection site pain as an undesirable effect with a frequency 'uncommon'. Therefore, the current terms of the marketing authorisation(s) should be varied[19].
- In the next PSUR, the MAH should provide a cumulative review of cases of alopecia/hair loss. In addition, the MAH should discuss the relevance of the outcome of the evaluation of the currently ongoing signal of thyroid cancer for the glucagon-like peptide-1 (GLP-1) receptor agonists (see PRAC minutes April 2023).

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.

6.1.11. Tixagevimab, cilgavimab - EVUSHELD (CAP) - PSUSA/00010992/202211

Applicant: AstraZeneca AB

PRAC Rapporteur: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

Background

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

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

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Evusheld, a centrally authorised medicine containing tixagevimab/cilgavimab 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 Evusheld (tixagevimab/cilgavimab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the exiting warning on anaphylaxis and to add anaphylaxis as an undesirable effect with a frequency 'rare'. Therefore, the current terms of the marketing authorisation(s) should be varied[20].
- In the next PSUR, the MAH should provide a cumulative review of cases of urticaria and angioedema. In addition, the MAH should discuss the publication by *Piszczek et al*[21] and provide any relevant scientific literature concerning cardiovascular safety of tixagevimab/cilgavimab.

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

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

See also Annex I 16.2.

6.2.1. Doxorubicin - CAELYX PEGYLATED LIPOSOMAL (CAP); CELDOXOME PEGYLATED LIPOSOMAL (CAP); MYOCET LIPOSOMAL (CAP); ZOLSKETIL PEGYLATED LIPOSOMAL (CAP); NAP - PSUSA/00001172/202211

Applicants: Baxter Holding B.V. (Caelyx pegylated liposomal), YES Pharmaceutical Development Services GmbH (Celdoxome pegylated liposomal), Teva B.V. (Myocet liposomal), Accord Healthcare S.L.U. (Zolsketil pegylated liposomal), various

PRAC Rapporteur: Eva Jirsová

Scope: Evaluation of a PSUSA procedure

Background

Doxorubicin is an anthracycline antineoplastic antibiotic, indicated as monotherapy for the various types of cancers, such as breast cancer, ovarian cancer, acute lymphoblastic leukaemia (ALL), acute myelogenous leukaemia (AML), chronic leukaemia, Hodgkin's disease and non-Hodgkin's lymphoma, multiple myeloma, osteosarcoma, Ewing's sarcoma, soft tissue sarcoma, neuroblastoma, rhabdomyosarcoma, Wilms' tumour, endometrial cancer,

[20] 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.
[21] Piszczek et al. Cardiac and vascular serious adverse events following tixagevimab-cilgavimab. Lancet Respir. Med. 2022, 11, e5–e6

non-seminomatous testicular cancer, prostate cancer, transitional bladder cell cancer, lung cancer, stomach (gastric) cancer, primary hepatocellular cancer, head and neck cancer, thyroid cancer, subject to certain conditions. Doxorubicin is available as conventional and liposomal formulations. The liposomal formulation is available as pegylated and non-pegylated forms.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of Caelyx Pegylated Liposomal, Celdoxome Pegylated Liposomal, Myocet Liposomal and Zolsketil Pegylated Liposomal, centrally authorised medicines containing doxorubicin, and nationally authorised medicines containing doxorubicin 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 doxorubicin-containing product(s) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisations for the non-pegylated liposomal doxorubicin (Myocet) and for the conventional doxorubicin should be maintained.
- For the pegylated liposomal doxorubicin products (Caelyx pegylated liposomal, Zolsketil pegylated liposomal, Celdoxome pegylated liposomal), the product information should be updated to add interstitial lung disease as a warning and as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisations should be varied[22].
- The MAHs for conventional and non-pegylated liposomal doxorubicin containing products should provide a cumulative review of cases of interstitial lung disease and discuss the need for an update of the product information, in the next PSUR or before, as warranted.

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

6.2.2. Tadalafil - ADCIRCA (CAP); CIALIS (CAP); TADALAFIL LILLY (CAP); NAP - PSUSA/00002841/202210

Applicants: Eli Lilly Nederland B.V. (Adcirca, Cialis, Tadalafil Lilly), various

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

Background

Tadalafil is a potent and selective phosphodiesterase (PDE) inhibitor, indicated for the treatment of erectile dysfunction (ED) and pulmonary arterial hypertension (PAH) in adults, and for the treatment of the signs and symptoms of benign prostatic hyperplasia (BPH). It is as well indicated for the treatment of ED and the signs and symptoms of BPH (ED/BPH) in men with both conditions.

[22] 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.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of Adcirca, Cialis and Tadalafil Lilly, centrally authorised medicines containing tadalafil, and nationally authorised medicines containing tadalafil 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 tadalafil-containing product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add central serous chorioretinopathy as a warning and as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisations should be varied[23].
- In the next PSUR, the MAHs should continue to closely monitor cases of acute pancreatitis. In addition, the MAHs should include hypotension/increased hypotensive effect as important identified risks, and non-arteritic anterior ischemic optic neuropathy, sudden hearing loss, retinal disorders (retinal detachment and related retinal degenerations, macular degeneration) and retinal haemorrhage as important potential risks in the list of safety concerns within 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. PSUR single assessment (PSUSA) procedures including nationally authorised products (NAPs) only

See also Annex I 16.3.

6.3.1. Ezetimibe (NAP) - PSUSA/00001346/202210

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

Ezetimibe is a lipid modifying agent indicated for the treatment of primary hypercholesterolaemia, prevention of cardiovascular disease, prevention of major cardiovascular events in patients with chronic kidney disease, homozygous familial hypercholesterolaemia (HoFH) and homozygous sitosterolaemia (phytosterolaemia).

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

Summary of recommendation(s) and conclusions

[23] 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.

- Based on the review of the data on safety and efficacy, the benefit-risk balance of ezetimibe-containing medicinal products in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAHs for ezetimibe-containing products should closely monitor cases of cutaneous vasculitis, provide a review of cases of severe cutaneous adverse reactions (SCARs) and hepatotoxicity.

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. Morphine (NAP), morphine, cyclizine (NAP) - PSUSA/00010549/202210

Applicant(s): various

PRAC Lead: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

Background

Morphine is an opioid receptor agonist indicated for the relief of severe pain or substitution therapy subject to certain conditions and cyclizine is a histamine H1 receptor antagonist of the piperazine class. The combination morphine/cyclizine is indicated for the relief of moderate to severe pain in which reduction of the nausea and vomiting associated with the administration of morphine is required.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing morphine or morphine/cyclizine 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 morphine- or morphine/cyclizine-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add acute generalised exanthematous pustulosis (AGEP), central sleep apnoea syndrome, pancreatitis and spasm of sphincter of Oddi as warnings and as undesirable effects with a frequency 'not known'; however, the product information already including these undesirable effects should maintain their calculated frequency. In addition, the product information should be updated to add drug-drug interaction with gabapentin or pregabalin and reflect the increased risk of respiratory depression following this interaction. Finally, the product information should be updated to add opioid use disorder and drug dependence as a warning and as undesirable effect. Therefore, the current terms of the marketing authorisation(s) should be varied[24].
- In the next PSUR, the MAHs for morphine-containing products should provide a cumulative review of cases of eosophageal dysfunction including opioid-induced

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

eosophageal dysfunction and discuss the need for an update of the product information as warranted. The cumulative review should include all available data from spontaneous case reports, clinical trials, literature and should include a discussion of the potential mechanism of action. In addition, the MAHs should continue to monitor cases of medication errors and are reminded that the list of safety concerns within the PSURs should not be updated without further justification.

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

None

6.5. Variation procedure(s) resulting from PSUSA evaluation

None

6.6. Expedited summary safety reviews[25]

None

7. Post-authorisation safety studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)[26]

See Annex I 17.1.

7.2. Protocols of PASS non-imposed in the marketing authorisation(s)[27]

See Annex I 17.2.

7.3. Results of PASS imposed in the marketing authorisation(s)[28]

7.3.1. Valproate[29] (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

[25] 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
[26] In accordance with Article 107n of Directive 2001/83/EC
[27] 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
[28] In accordance with Article 107p-q of Directive 2001/83/EC
[29] Valproic acid, sodium valproate, valproate pivoxil, valproate semisodium, valpriomide, valproate bismuth, calcium valproate, valproate magnesium

Background

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 required 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. See PRAC minutes May 2023.

Following the list of questions (LoQ) adopted in May 2023, the MAH Sanofi-Aventis Recherche & Développement informed EMA that only part of the questions raised by PRAC could be answered as per the adopted timetable. Moreover, the MAH informed EMA about data quality issues detected in 2 (Norway, Denmark) out of 3 databases considered for this study.

PRAC invited the MAH Sanofi-Aventis Recherche & Développement to present their position in front of the Committee.

Summary of recommendation(s) and conclusions

- Based on the PRAC rapporteur's assessment and the data provided by the MAH (also in the context of an oral explanation), PRAC adopted a revised list of questions (LoQ) and an updated timetable for this procedure.
- The MAH should provide responses on the study results and additional analyses, as per the LoQ adopted at the PRAC May 2023 plenary, as well as corrected analyses, having resolved the issue with the Norwegian/ Danish dataset.

Post-meeting note 1: In its letter to EMA and PRAC, dated 23 June 2023, the MAH's consortium confirmed that the (quality) issues detected in the Danish dataset had been investigated and confirmed as not impacting the DK (final) study results previously submitted.

Post meeting note 2: See EMA press release on data on paternal exposure to valproate published on 16 August 2023.

7.4. Results of PASS non-imposed in the marketing authorisation(s)[30]

See Annex I 17.4.

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

See also Annex I 17.5.

7.5.1. Alemtuzumab - LEMTRADA (CAP) - EMEA/H/C/003718/ANX 010.8

Applicant: Sanofi Belgium

PRAC Rapporteur: Anette Kirstine Stark

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

Scope: MAH's response to ANX 010.7 [Interim report 2 for study DUT0008: non-interventional PASS to investigate drug utilisation and safety monitoring patterns for Lemtrada (alemtuzumab)] as per the request for supplementary information (RSI) 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.

As requested in the conclusions of the referral procedure under Article 20 of Regulation (EC) No 726/2004 (EMEA/H/A-20/1483) finalised in 2019, the MAH committed to perform a drug utilisation study to assess compliance with the therapeutic indication and effectiveness of measures to minimise the risk of cardiovascular and cerebrovascular adverse events in close temporal association with Lemtrada (alemtuzumab) infusion and immune-mediated adverse reactions. Interim results of this study were assessed by the Rapporteur for PRAC review.

Summary of advice

- Based on PRAC rapporteur's assessment and the responses submitted by the MAH, PRAC considered that the withdrawal of the Belgian database from the non-interventional imposed PASS category 1 study to investigate drug utilisation and safety monitoring patterns for Lemtrada (alemtuzumab), will possibly not have a major implications on the feasibility of the study. However, PRAC considered that the consequences of this change on the investigation of the risk of mortality in patients with multiple sclerosis treated with alemtuzumab relative to comparable patients with multiple sclerosis using other disease-modifying therapies (DMTs) cannot be fully characterised and therefore, an extended feasibility analysis is needed.
- The MAH should submit to EMA, by 14 August 2023, two Article 107-o procedures (one per each PASS category 1 study) pursuant to the withdrawal of the Belgian database, as this change is considered to lead to a substantial amendment of the agreed protocols.

7.6. Others

None

7.7. New Scientific Advice

None

7.8. Ongoing Scientific Advice

None

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

None

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 also Annex I 18.2.

8.2.1. Crizanlizumab - ADAKVEO (CAP) - EMEA/H/C/004874/R/0014 (without RMP)

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Jo Robays

Scope: Conditional 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.

Adakveo, a centrally authorised product containing crizanlizumab, was authorised under a conditional marketing authorisation in 2020. Based on the fulfilment of specific obligations and safety data, the MAH submitted a request for yearly renewal of the marketing authorisation for opinion by CHMP. PRAC is responsible for providing advice to CHMP on this conditional renewal with regard to safety and risk management aspects.

Summary of advice

- Following the CHMP opinion adopted on 25 May 2023 recommending the revocation of the conditional marketing authorisation for Adakveo (crizanlizumab), as an outcome of the Article 20 referral procedure (EMEA/H/A-20/1525) for this medicinal product, the renewal procedure was put on hold.

8.3. Renewals of the marketing authorisation

See Annex I 18.3.

9. Product related pharmacovigilance inspections

9.1. List of planned pharmacovigilance inspections

None

9.2. Ongoing or concluded pharmacovigilance inspections

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

9.3. Others

None

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

10.1. Safety related variations of the marketing authorisation

None

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

None

10.3. Other requests

None

10.4. Scientific Advice

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

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

11.1. Safety related variations of the marketing authorisation

None

11.2. Other requests

None

12. Organisational, regulatory and methodological matters

12.1. Mandate and organisation of PRAC

12.1.1. PRAC membership

The Chair thanked Anette Kirstine Stark for her role as member representing Denmark. The Chair announced that Marie Louise Schougaard Christiansen is the new member for Denmark.

12.1.2. Vote by proxy

None

12.2. Coordination with EMA Scientific Committees or CMDh-v

None

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

None

12.4. Cooperation within the EU regulatory network

12.4.1. Public health threats and Emergency task force (ETF) activities - update

The EMA Secretariat provided PRAC with an update regarding the safety and efficacy of medicines 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) against the new Omicron subvariants. The EMA Secretariat also updated PRAC on prevalence and characteristics of the post-COVID-19 condition, as well as on cases of symptomatic monkey pox among vaccinated patients, on cases of infection with a new variant of Echovirus 11 (E-11) - a positive-strand RNA virus belonging to the genus Enterovirus, as well as on the Novel oral poliomyelitis vaccine type 2 (nOPV2) - next-generation version of monovalent live attenuated oral polio vaccine type 2 (mOPV2) to tackle circulating vaccine-derived poliovirus type 2 outbreaks (cVDPV). Reference was also made to the common ECDC-EMA statement on updating COVID-19 vaccines composition for new variants.

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

None

12.9. Pharmacovigilance audits and inspections

12.9.1. Pharmacovigilance systems and their quality systems

None

12.9.2. Pharmacovigilance inspections

None

12.9.3. Pharmacovigilance audits

None

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

12.10.1. Periodic safety update reports

None

12.10.2. Granularity and Periodicity Advisory Group (GPAG)

PRAC lead: Menno van der Elst

The EMA Secretariat presented to PRAC the Granularity and Periodicity Advisory Group (GPAG) Best Practice Guidance (BPG). As per the GPAG 2023 workplan, the purpose of the GPAG BPG is to define clear criteria on how to handle requests to amend the EURD list ensuring consistency limiting the need for systematic consultation of GPAG. PRAC members were invited to provide their comments in writing by 14 June 2023.

Post-meeting note: The GPAG BPG was adopted by PRAC on 21 June 2023 via written procedure.

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 June 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 June 2023, the updated EURD list was adopted by CHMP and CMDh at their June 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)

12.11. 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

12.15. Post-authorisation safety studies (PASS)

12.15.1. Post-authorisation Safety Studies – imposed PASS

None

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

None

12.16. Community procedures

12.16.1. Referral procedures for safety reasons

None

12.17. Renewals, conditional renewals, annual reassessments

None

12.18. Risk communication and transparency

12.18.1. Public participation in pharmacovigilance

None

12.18.2. Safety communication

None

12.19. Continuous pharmacovigilance

12.19.1. Incident management

None

12.20. Impact of pharmacovigilance activities

None

12.21. Others

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

The PRAC Lead Liana Gross-Martirosyan and the EMA Secretariat presented to PRAC the survey to be conducted by EMA for stakeholder consultation on potential outer packaging warning regarding opioid use disorders. PRAC provided its comments on the content of the questionnaire. Further input on the content of the survey will be requested from Healthcare professionals Working Party (HCPWP) and Patient and Consumers Working Party (PCPWP) as well as from Quality Review of Documents Working Group (QRD WG). PRAC will be kept informed about the next steps.

12.21.1. EMA medical terms simplifier - plain-language description of medical terms related to medicines use

The EMA Secretariat presented to PRAC the existing resource on EMA Medical Terms Simplifier (europa.eu). This compilation provides plain-language descriptions of medical terms commonly used in information about medicines, which is used by communication specialists at EMA for materials prepared for the public and by professional medical writers. PRAC members were informed that they can provide their suggestions for further improvement and that a more user-friendly online format is provisioned for the future.

13. Any other business

None

14. Annex I – Signals assessment and prioritisation[31]

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[32].

14.1. New signals detected from EU spontaneous reporting systems

14.1.1. Amivantamab - RYBREVANT (CAP)

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Gabriele Maurer

Scope: Signal of anaphylactic reaction

EPITT 19928 – New signal

Lead Member State(s): DE

14.1.2. Dapagliflozin – EDISTRIDE (CAP), FORXIGA (CAP), EBYMECT (CAP), XIGDUO (CAP), QTERN (CAP)

Applicant: AstraZeneca AB

PRAC Rapporteur: Mari Thorn

Scope: Signal of acquired phimosis and phimosis with dapagliflozin

EPITT 19935 – New signal

Lead Member State(s): SE

14.1.3. Leuprorelin – CAMCEVI (CAP)

Applicant: Accord Healthcare S.L.U.

PRAC Rapporteur: Amelia Cupelli

Scope: Signal of severe cutaneous adverse reactions (SCARS)

EPITT 19930 – New signal

Lead Member State(s): IT

14.2. New signals detected from other sources

None

[31] 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

[32] 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

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. Latanoprost - EMEA/H/C/005933

Scope: reduction of elevated intraocular pressure (IOP)

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. Deferasirox - EXJADE (CAP) - EMEA/H/C/000670/II/0085

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Tiphaine Vaillant

Scope: Submission of an updated RMP version 21.0 in order to include the physician survey CICL670A2429 as a PASS category 3, based on the submission of a draft version of the protocol for the physician survey CICL670A2429. The Annex IID is updated to remove one sentence related to 'surveillance programme' and to introduce a minor correction

15.2.2. Dexamethasone - OZURDEX (CAP) - EMEA/H/C/001140/II/0044

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Submission of an updated Annex II and RMP version 11 in order to remove additional risk minimisation measure: Patient guide, audio CD (where required)

15.2.3. Esomeprazole - NEXIUM CONTROL (CAP) - EMEA/H/C/002618/II/0038

Applicant: GlaxoSmithKline Dungarvan Ltd

PRAC Rapporteur: Rugile Pilviniene

Scope: Submission of an updated RMP version 2.0 in order to update the list of safety concerns to meet the definition of important risk and missing information provided in GVP Module V Rev. 2

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

Applicant: UCB Pharma SA

PRAC Rapporteur: Martin Huber

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

15.2.5. 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 a Drug Utilisation Study (DUS). Furthermore, Annex II D "Conditions or restrictions with regard to the safe and effective use of the medicinal product" was revised to delete from the key elements of the physician educational material information about the utilisation study

15.2.6. Insulin lispro - HUMALOG (CAP) - EMEA/H/C/000088/WS2487/0199; LIPROLOG (CAP) - EMEA/H/C/000393/WS2487/0159

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Mari Thorn

Scope: To remove severe hypoglycemia as a result of incorrect or incomplete data provided to a compatible software application which is listed as an important potential risk for the Tempo Pen and all associated risk minimisation measures, following PRAC assessment of F3Z-MC-B030 PASS protocol (following MEA 035 concluded in October[33] 2022)

15.2.7. Laronidase - ALDURAZYME (CAP) - EMEA/H/C/000477/II/0085

Applicant: Sanofi B.V.

PRAC Rapporteur: Nathalie Gault

Scope: To update section 4.2 of the SmPC in order to modify the administration instructions following the periodic safety update single assessment (PSUSA) procedure (PSUSA/00001830/202104) adopted in December[34] 2021 based on literature review. The package leaflet is updated accordingly. The RMP version 1.0 has also been submitted

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. Aflibercept - EYLEA (CAP) - EMEA/H/C/002392/X/0084/G

Applicant: Bayer AG

PRAC Rapporteur: Nathalie Gault

[33] Held on 26-29 September 2022
[34] Held 29 November – 02 December 2021

Scope: Extension application to add a new strength of Aflibercept 114.3 mg/ml solution for injection (in a vial), to be indicated in adults for the (1) treatment of neovascular (wet) age-related macular degeneration (nAMD) and (2) visual impairment due to diabetic macular oedema (DME), grouped with a type II variation (B.II.g.2) to introduce a post-approval change management protocol to add a new presentation for Aflibercept solution 114.3 mg/ml in a single-use pre-filled syringe for intravitreal injection

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

Applicant: Les Laboratoires Servier

PRAC Rapporteur: Pernille Harg

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

15.3.3. Alirocumab - PRALUENT (CAP) - EMEA/H/C/003882/II/0078

Applicant: Sanofi Winthrop Industrie

PRAC Rapporteur: Gabriele Maurer

Scope: Extension of indication to include treatment of paediatric patients 8 years of age and older with heterozygous familial hypercholesterolemia (HeFH) as an adjunct to diet, alone or in combination with other LDL-C lowering therapies, based on final results from study EFC14643 listed as a category 3 study in the RMP; this is a randomised, double-blind, placebo-controlled study followed by an open-label treatment period to evaluate the efficacy and safety of alirocumab in children and adolescents with heterozygous familial hypercholesterolemia. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet is updated in accordance. Version 8.0 of the RMP is also submitted

15.3.4. Alpelisib - PIQRAY (CAP) - EMEA/H/C/004804/II/0018

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Menno van der Elst

Scope: Update of sections 4.5 and 5.2 of the SmPC in order to update drug-drug interaction information, based on final results from study BYL719A2111; this is a phase 1, open-label, fixed-sequence, two-period drug-drug interaction (DDI) study evaluating the PK probe substrates for CYP3A4, CYP2B6, CYP2C8, CYP2C9, and CYP2C19 when administered either alone or in combination with repeated doses of alpelisib. The Annex II and package leaflet are updated accordingly. The RMP version 6.0 has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the product information

15.3.5. Bezlotoxumab - ZINPLAVA (CAP) - EMEA/H/C/004136/II/0037

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Extension of indication to include treatment of the paediatric population (1 to 18 years of age) for ZINPLAVA, based on final results from study MK-6072-001 (MODIFY III) listed as a category 3 study in the RMP; this is a phase 3, randomised, placebo-controlled, parallel-group, multi-site, double-blind trial evaluating the safety, tolerability, pharmacokinetics (PK) and efficacy of a single infusion of bezlotoxumab in paediatric participants from 1 to <18 years of age receiving antibacterial drug treatment for Clostridioides difficile infection (CDI). As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet is updated in accordance. Version 2.3 of the RMP has also been submitted. In addition, the marketing authorisation holder (MAH) took the opportunity to introduce minor editorial changes to the product information

15.3.6. Brentuximab vedotin - ADCETRIS (CAP) - EMEA/H/C/002455/II/0107, Orphan

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication to include treatment of adult patients with previously untreated CD30+ advanced (including Stage III) Hodgkin lymphoma (HL), in combination with doxorubicin, vinblastine and dacarbazine (AVD), for ADCETRIS, based on the second interim analysis of overall survival (OS) data from ECHELON-1 study (C25003); this is a randomised, open-label, phase 3 trial of A+AVD versus ABVD as frontline therapy in patients with advanced classical HL. As a consequence, sections 4.1 and 5 of the SmPC are updated

15.3.7. Carglumic acid - CARBAGLU (CAP) - EMEA/H/C/000461/II/0045

Applicant: Recordati Rare Diseases

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Update of sections 4.2, 4.4 and 5.2 of the SmPC in order to include a proposed dose adjustment for patients with impaired renal function based on final results from study RCD-P0-027; this is a Phase I, multicenter, open-label, parallel-group adaptive pharmacokinetic single dose study of oral Carbaglu in subjects with normal and varying degrees of impaired renal function. The package leaflet is updated accordingly. The RMP version 2.2 has also been submitted. In addition, the MAH took the opportunity to implement editorial changes in Annex II and Labelling, and to bring the product information in line with the latest QRD template version 10.3

15.3.8. Concentrate of proteolytic enzymes enriched in bromelain - NEXOBRID (CAP) - EMEA/H/C/002246/II/0058

Applicant: MediWound Germany GmbH

PRAC Rapporteur: Martin Huber

Scope: Extension of current indication for removal of eschar in adults with deep partial- and

full-thickness thermal burns to the paediatric population for NexoBrid based on interim results from study MW2012-01-01 (CIDS study), listed as Study MW2012-01-01 is a 3-stage, multi-centre, multi-national, randomised, controlled, open label, 2-arm study aiming to demonstrate the superiority of NexoBrid treatment over standard of care (SOC) treatment in paediatric patients (aged 0 to 18 years) with deep partial thickness (DPT) and full thickness (FT) thermal burns of 1% to 30% of total body surface area (TBSA). As a consequence, sections 4.1, 4.2, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The package leaflet is updated accordingly. Version 9 of the RMP has also been submitted

15.3.9. Eculizumab - SOLIRIS (CAP) - EMEA/H/C/000791/II/0126, Orphan

Applicant: Alexion Europe SAS

PRAC Rapporteur: Monica Martinez Redondo

Scope: Extension of indication to include treatment of paediatric patients with refractory generalised myasthenia gravis (gMG) for Soliris, based on interim results from study ECU-MG-303; this is an open-label, multicentre, phase 3 study to evaluate the efficacy, safety, pharmacokinetics and pharmacodynamics of intravenous (IV) eculizumab in paediatric patients aged 6 to less than 18 years with acetylcholine receptor-antibody (AChR-Ab) positive (+) refractory gMG. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet is updated in accordance. Version 20.0 of the RMP has also been submitted. In addition, the MAH took the opportunity to update section 4.8 of the SmPC in order to update the frequency of the list of adverse drug reactions (ADRs) based on cumulative safety data and to introduce minor editorial changes to the product information

15.3.10. Elasomeran - SPIKEVAX (CAP) - EMEA/H/C/005791/II/0104/G

Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Grouped variation consisting of: 1) Extension of indication to include the use of Spikevax bivalent Original/Omicron BA.4-5 (50 micrograms/50 micrograms)/mL dispersion for injection as a two-dose primary vaccination course in children 6 months through 5 years of age, based on data from study mRNA-1273-P306 (NCT05436834), an Open-Label, Phase 3 Study to Evaluate the Safety and Immunogenicity of the mRNA-1273.214 Vaccine for SARS-CoV-2 Variants of Concern in Participants Aged 6 Months to < 6 Years; as a consequence, sections 2, 4.1, 4.2 and 6.6 of the SmPC are updated. The package leaflet and Labelling are updated in accordance. Version 6.7 of the RMP has also been submitted; 2) Extension of indication to include the use of Spikevax bivalent Original/Omicron BA.4-5 as a single-dose primary vaccination course against COVID-19 in individuals 6 years of age and older, irrespective of vaccination history, based on epidemiology and clinical data from Study P306 Part 1; as a consequence, sections 2, 4.1, 4.2 and 6.6 of the SmPC are updated. The package leaflet is updated in accordance. In addition, the Marketing authorisation holder (MAH) took the opportunity to make minor editorial changes/corrections throughout the product information

15.3.11. Faricimab - VABYSMO (CAP) - EMEA/H/C/005642/II/0002

Applicant: Roche Registration GmbH

PRAC Rapporteur: Inês Ribeiro-Vaz

Scope: Update of sections 4.2, 4.4, 4.8 and 5.1 of the SmPC in order to update efficacy and safety information and to update the warnings and the list of adverse drug reactions (ADRs), based on longer-term results from studies GR40306 (TENAYA) and GR40844 (LUCERNE); these are phase 3, multicentre, randomised, double-masked, active comparator-controlled, 112-week studies to evaluate the efficacy and safety of faricimab in patients with neovascular age-related macular degeneration (nAMD); the package leaflet is updated accordingly. The RMP version 2.0 has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the product information

15.3.12. Gilteritinib - XOSPATA (CAP) - EMEA/H/C/004752/II/0013, Orphan

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Martin Huber

Scope: Update of sections 4.2 and 5.2 in order to update the information on renal impairment based on final results from study 2215-CL-0114, listed as a category 3 study in the RMP. Study 2215-CL-0114 is a phase 1, single-dose, open-label study to investigate the effect of renal impairment on gilteritinib pharmacokinetics, safety and tolerability in 9 participants with severe renal impairment compared to 8 participants with normal renal function. The RMP version 4.0 has also been submitted. In addition, the MAH took the opportunity to introduce editorial changes

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

Applicant: Alnylam Netherlands B.V.

PRAC Rapporteur: Martin Huber

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

15.3.14. Human coagulation factor X - COAGADEX (CAP) - EMEA/H/C/003855/II/0046, Orphan

Applicant: BPL Bioproducts Laboratory GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Submission of the final report from study TEN06 - NCT03161626 (REC EMEA/H/C/003855). This is a non-interventional, multicenter, post-marketing registry study in three patients with moderate or severe hereditary FX deficiency, to assess Coagadex administered peri-operatively for haemostatic cover in major surgery during routine post-marketing use. The primary objective is to collect additional surgical data on the clinical effectiveness of Coagadex, in a post-marketing environment, for peri-operative haemostatic cover during major surgery in patients with moderate or severe hereditary factor X (FX)

deficiency. The RMP version 3.0 has also been submitted

15.3.15. Idecabtagene vicleucel - ABECMA (CAP) - EMEA/H/C/004662/II/0031, Orphan

Applicant: Bristol-Myers Squibb Pharma EEIG, ATMP[35]

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension of indication to include treatment of adult patients with relapsed and refractory multiple myeloma (RRMM) who have received at least two prior therapies, including an immunomodulatory agent, a proteasome inhibitor and an anti-CD-38 antibody and have demonstrated disease progression on the last therapy for Abecma (idecabtagene vicleucel, ide-cel), based on results from study BB2121-MM-003 (MM-003, KarMMa-3). This is a Phase 3, multicentre, randomised, open-label study to compare the efficacy and safety of ide-cel versus standard regimens in subjects with RRMM. As a consequence, sections 2.1, 2.2, 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2, 6.3, 6.4 and 6.6 of the SmPC are updated. The package leaflet and Labelling are updated in accordance. Version 3.0 of the RMP has also been submitted. Furthermore, the product information is brought in line with the Guideline on core SmPC, Labelling and package leaflet for advanced therapy medicinal products (ATMPs) containing genetically modified cells

and CHMP

15.3.16. Influenza vaccine (live attenuated, nasal) - FLUENZ TETRA (CAP) - EMEA/H/C/002617/II/0130

Applicant: AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

Scope: Submission of the final report from study MA-VA-MEDI3250-1116 (A Case Control Study of the Effectiveness of quadrivalent live attenuated influenza vaccine (Q/LAIV) Versus Inactivated Influenza Vaccine and No Vaccine in Subjects 2 to 17 Years of Age) listed as a category 3 study in the RMP. This was an observational study. The objective of this study was to evaluate the effectiveness of Q/LAIV compared to IIV or no vaccine in community-dwelling subjects 2 to 17 years of age against laboratory-confirmed influenza. The RMP version 11.0 has also been submitted

15.3.17. Lenalidomide - REVLIMID (CAP) - EMEA/H/C/000717/II/0123

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Tiphaine Vaillant

Scope: Update of section 4.4 of the SmPC, Annex IID and Article 127a and the tools/documents included in the Educational Healthcare Professional Kit, in order to harmonise the terminology utilised in the RMP and product information documents relating to the safety concern of teratogenicity and its risk minimisation measure of the Pregnancy Prevention Plan (PPP) across the 3 immunomodulatory imide drugs (IMiDs). These proposed changes will only have a limited impact on the National Competent Authority (NCA)-approved content/text of the educational materials, and the key messages to the HCP and patients. Furthermore, the regulatory obligations regarding the PPP will not be impacted.

[35] Advanced therapy medicinal product

The MAH is also taking the opportunity to update the RMP with PASS Protocol milestones. The updated RMP version 38 was provided

15.3.18. Letermovir - PREVYMIS (CAP) - EMEA/H/C/004536/II/0033/G, Orphan

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Kirsti Villikka

Scope: Grouped application consisting of 1) Extension of indication to include treatment of prophylaxis of cytomegalovirus in kidney transplant recipients (KTR) for PREVYMIS, based on final results from study P002MK8228; this is a Phase III, randomised, double-blind, active comparator-controlled study to evaluate the efficacy and safety letermovir versus valganciclovir for the prevention of Human Cytomegalovirus (CMV) Disease in adult kidney transplant recipients. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The package leaflet is updated in accordance. Version 4.1 of the RMP has also been submitted. In addition, the MAH took the opportunity to implement editorial changes; 2) Update of section 4.2 of the SmPC in order to update duration of treatment recommendation based on final results from study P040MK8228; this is a Phase III randomised, double-blind, placebo-controlled clinical trial to evaluate the safety and efficacy of letermovir (LET) prophylaxis when extended from 100 days to 200 days post-transplant in cytomegalovirus (CMV) seropositive recipients (R+) of an allogeneic hematopoietic stem cell transplant (HSCT)

15.3.19. Luspatercept - REBLOZYL (CAP) - EMEA/H/C/004444/II/0021, Orphan

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Jo Robays

Scope: Extension of indication to include treatment of adult patients with anaemia due to very low, low and intermediate-risk myelodysplastic syndromes (MDS), who may require RBC transfusions for Reblozyl, based on results from study ACE-536-MDS-002 (COMMANDS), an active-controlled, open-label, randomised Phase 3 study comparing the efficacy and safety of luspatercept vs epoetin alfa in adult subjects with anemia due to IPSS-R very low, low or intermediate risk MDS, who are ESA naïve and require RBC transfusions, and studies ACE-536-MDS-001(MEDALIST), ACE-536-MDS-004 , A536-03, A536-05 and ACE-536-LTFU-001. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet is updated in accordance. Version 2.0 of the RMP has also been submitted

15.3.20. Melphalan flufenamide - PEPAXTI (CAP) - EMEA/H/C/005681/II/0002

Applicant: Oncopeptides AB

PRAC Rapporteur: Martin Huber

Scope: Extension of indication to include treatment of patients with multiple myeloma who have received at least two prior lines of therapies before PEPAXTI, based on final results from study OP-103 OCEAN; this is a randomised, open-label phase III study in patients with relapsed or refractory multiple myeloma following two to four lines of prior therapies and who were refractory to lenalidomide and the last line of therapy. As a consequence, sections 4.1, 4.4, 4.8 and 5.1 of the SmPC are updated. The package leaflet is updated in

accordance. Version 1.1 of the RMP has also been submitted. In addition, the MAH took the opportunity to implement editorial changes in the SmPC

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

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Grouped application consisting of: 1) Extension application to add a new strength of 25 mg soft capsule; 2) Addition of a new indication of treatment of fibrosing interstitial lung diseases (ILDs) in children and adolescents from 6 to 17 years of age, based on results from study 1199 0337 (InPedILD); a randomised, placebo-controlled, double-blind, multicentre, multinational, phase III clinical trial undertaken to evaluate dose-exposure and safety of nintedanib on top of standard of care in children and adolescents (6 to 17 years old) with clinically significant fibrosing ILD. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The package leaflet is updated in accordance. In addition, the MAH took the opportunity to implement minor editorial changes to the list of local representatives in the package leaflet. The updated RMP version 12.0 is also submitted

15.3.22. Nonacog beta pegol - REFIXIA (CAP) - EMEA/H/C/004178/II/0032

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Gabriele Maurer

Scope: Extension of indication to include treatment and prophylaxis of bleeding in children below 12 years of age with haemophilia B including previously untreated patients for REFIXIA, based on interim results from studies NN7999-3774 and NN7999-3895. NN7999-3774 is a multicentre, open-label, non-controlled study evaluating the safety, efficacy and pharmacokinetics of nonacog beta pegol in previously treated children with haemophilia B, while NN7999-3895 is a multicentre, open-label, single-arm, non-controlled trial evaluating the safety and efficacy of nonacog beta pegol in previously untreated patients with haemophilia B. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The package leaflet is updated accordingly. Version 5.0 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the product information

15.3.23. Odevixibat - BYLVAY (CAP) - EMEA/H/C/004691/II/0011, Orphan

Applicant: Albireo

PRAC Rapporteur: Adam Przybylkowski

Scope: Extension of indication to include treatment of cholestasis and pruritus in Alagille syndrome (ALGS) in patients from birth and older for BYLVAY, based on final results from Study A4250-012 and interim results from Study A4250-015. Study A4250-012 is a 24-week, randomised, double-blind, placebo-controlled Phase III study conducted in 52 patients with a genetically confirmed diagnosis of ALGS and presence of pruritus and high serum bile acid levels at baseline. Study A4250-015 is an ongoing 72-week open-label extension trial for patients who completed Study A4250-012 and evaluates the long-term safety and efficacy of Bylvay in patients with ALGS. As a consequence, sections 4.1, 4.2,

4.8, 5.1, and 5.2 of the SmPC are updated. The package leaflet is updated in accordance. Version 2.1 of the RMP has also been submitted

15.3.24. Omalizumab - XOLAIR (CAP) - EMEA/H/C/000606/X/0115/G

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Mari Thorn

Scope: Extension application to add a new strength of 300 mg (150 mg/ml) for Xolair solution for injection grouped with quality type II, IB and IAIN variations. The RMP (version 17.0) is updated in accordance.

15.3.25. Pembrolizumab - KEYTRUDA (CAP) - EMEA/H/C/003820/II/0134

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication to include pembrolizumab in combination with platinum-containing chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant, treatment of resectable Stage II, IIIA, or IIIB (T3 4N2) non-small cell lung carcinoma in adults for Keytruda based on study KEYNOTE-671, a phase III, randomised, double-blind trial of platinum doublet chemotherapy +/- pembrolizumab as neoadjuvant/adjuvant therapy for participants with resectable stage II, IIIA, and resectable IIIB (T3-4N2) non-small cell lung cancer. As a consequence, sections 4.1, 4.2 and 5.1 of the SmPC are updated. The package leaflet is updated in accordance. Version 41.1 of the RMP has also been submitted

15.3.26. Pembrolizumab - KEYTRUDA (CAP) - EMEA/H/C/003820/II/0135

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication to include pembrolizumab in combination with chemotherapy the first-line treatment of locally advanced unresectable or metastatic HER2-negative gastric or gastrooesophageal junction adenocarcinoma in adults based on study KEYNOTE-859, a randomised, double-blind phase 3 trial, evaluating KEYTRUDA in combination with chemotherapy compared to placebo in combination with chemotherapy for the first-line treatment of patients with HER2-negative locally advanced unresectable or metastatic gastric or esophagogastric junction (GEJ) adenocarcinoma. As a consequence sections 4.1 and 5.1 of the SmPC are updated. The package leaflet and Annex II are updated in accordance. Version 42.1 of the RMP has also been submitted

15.3.27. Pomalidomide - IMNOVID (CAP) - EMEA/H/C/002682/II/0047, Orphan

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Monica Martinez Redondo

Scope: Update of section 4.4 of the SmPC, Annex IID and Article 127a and the tools/documents included in the Educational Healthcare Professional Kit, in order to harmonise the terminology utilised in the RMP and product information documents relating

to the safety concern of teratogenicity and its risk minimisation measure of the Pregnancy Prevention Plan across the 3 immunomodulatory imide drugs (IMiDs). These proposed changes will only have a limited impact on the National Competent Authority (NCA)-approved content/text of the educational materials, and the key messages to the HCP and patients. Furthermore, the regulatory obligations regarding the pregnancy prevention plan (PPP) will not be impacted. The updated RMP version 16 was provided

15.3.28. Pralsetinib - GAVRETO (CAP) - EMEA/H/C/005413/II/0012

Applicant: Roche Registration GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of sections 4.2, 4.4 and 4.5 of the SmPC in order to amend posology recommendations, warnings and drug-drug interaction information regarding the co-administration with CYP3A4 inhibitors, P-gp inhibitors and CYP3A4 inducers based on final results from the DDI study GP43162, listed as a category 3 study in the RMP, as well as results from the physiologically based pharmacokinetic (PBPK) analyses summarised in the PBPK Report 1120689. Study GP43162 is a phase 1, open-label, fixed-sequence study to evaluate the effect of a single dose of cyclosporine on the single dose pharmacokinetics of pralsetinib in healthy subjects. The RMP version 1.6 has also been submitted

15.3.29. Remdesivir - VEKLURY (CAP) - EMEA/H/C/005622/II/0050

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Eva Jirsová

Scope: Update of sections 4.2, 4.4, 4.8 and 5.2 of the SmPC in order to address the safety of remdesivir and its metabolites in patients with hepatic impairment and to update information on hepatic and coagulation laboratory abnormalities based on final results from study GS US 540 9014 (listed as category 3 study in the RMP): a phase 1 open-label, adaptive, single-dose study to evaluate the pharmacokinetics of remdesivir and its metabolite(s) in subjects with normal hepatic function and hepatic impairment, and on safety data from post-marketing and clinical trials experience. The package leaflet is updated accordingly. The RMP version 5.4 has also been submitted. In addition, the MAH took the opportunity submit Minor Linguistic Amendments (MLA) for Veklury

15.3.30. Selexipag - UPTRAVI (CAP) - EMEA/H/C/003774/X/0038

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Nathalie Gault

Scope: Extension application to add a new strength of 100 µg film-coated tablets in HDPE bottle. The RMP (version 10.1) is updated in accordance

15.3.31. Talazoparib - TALZENNA (CAP) - EMEA/H/C/004674/X/0015/G

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Inês Ribeiro-Vaz

Scope: Grouped application consisting of: 1) Addition of a new strength of 0.1 mg hard

capsules; 2)Extension of indication to add talazoparibin combination with enzalutamide for the treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC), based on final results from study C3441021 (TALAPRO-2) as well as supplemental data from study C3441006 (TALAPRO-1). Study C3441021 (TALAPRO-2) is a randomised, double-blind, placebo-controlled, phase 3 study of talazoparib in combination with enzalutamide in mCRPC, while study C3441006 (TALAPRO-1) is a phase 2, open-label, response rate study of talazoparib in men with DNA repair defects and mCRPC who previously received taxane-based chemotherapy and progressed on at least one novel hormonal agent. As a consequence, sections 1, 2, 3, 4.1, 4.2, 4.5, 4.7, 4.8, 5.1, 5.2, 6.1, 6.5, 8 of the SmPC are updated. The package leaflet and Labelling are updated in accordance. Version 1.1 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the product information

15.3.32. Thalidomide - THALIDOMIDE BMS (CAP) - EMEA/H/C/000823/II/0076

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Tiphaine Vaillant

Scope: Update of section 4.4 of the SmPC, Annex IID and Article 127a and the tools/documents included in the Educational Healthcare Professional Kit, in order to harmonise the terminology utilised in the RMP and product information documents relating to the safety concern of teratogenicity and its risk minimisation measure of the Pregnancy Prevention Plan (PPP) across the 3 immunomodulatory imide drugs (IMiDs). These proposed changes will only have a limited impact on the National Competent Authority (NCA)-approved content/text of the educational materials, and the key messages to the HCP and patients. Furthermore, the regulatory obligations regarding the PPP will not be impacted. The MAH is also taking the opportunity to update the RMP with PASS Protocol milestones, and to make some editorial changes in the labelling. The updated RMP version 20 was provided

15.3.33. Tirzepatide - MOUNJARO (CAP) - EMEA/H/C/005620/II/0007

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication to include chronic weight management, including weight loss and weight maintenance, as an adjunct to a reduced-calorie diet and increased physical activity in adults with an initial body mass index (BMI) of ≥ 30 kg/m2 (obesity), or ≥ 27 kg/m2 to < 30 kg/m2 (overweight) in the presence of at least one weight-related comorbid condition, based on a global, pivotal phase 3 study I8F-MC-GPHK (SURMOUNT-1) and five supportive phase 3 studies (SURPASS-1 to -5) in participants with T2DM and BMI ≥ 27 kg/m2. SURMOUNT-1 is a phase 3, randomised, double-blind, placebo-controlled trial to investigate the efficacy and safety of tirzepatide once weekly in participants without type 2 diabetes who have obesity or are overweight with weight related comorbidities. As a consequence, sections 4.1, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet is updated in accordance. Version 2.1 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the product information

15.3.34. Tozinameran - COMIRNATY (CAP) - EMEA/H/C/005735/II/0177/G

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Grouped application consisting of: 1) Extension of indication to include Comirnaty Original/Omicron BA.4-5 (5/5 micrograms)/dose concentrate for dispersion for injection and Comirnaty Original/Omicron BA.4-5 (15/15 micrograms)/dose dispersion for injection for use as primary vaccination course against COVID-19 in children aged 5 to 11 years and in individuals 12 years of age and older, respectively, based on interim results from studies C4591044 and C4591048. Study C4591044 is an interventional, randomised, active-controlled, phase 2/3 study to investigate the safety, tolerability, and immunogenicity of bivalent BNT162b RNA-based vaccine candidates as a booster dose in COVID-19 vaccine–experienced healthy individuals, while study C4591048 is a phase 1/2/3 master study to investigate the safety, tolerability, and immunogenicity of a bivalent BNT162b2 RNA-based vaccine candidate. 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 9.1 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the product information; 2) To change the ATC Code of tozinameran, riltozinameran and famtozinameran from J07BX03 to J07BN01

15.3.35. Tozinameran - COMIRNATY (CAP) - EMEA/H/C/005735/X/0176

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Extension application to add a new strength of 1.5/1.5 µg (tozinameran, famtozinameran) for active immunisation in infants and children between 6 months to 4 years of age

15.3.36. Tozinameran - COMIRNATY (CAP) - EMEA/H/C/005735/X/0180

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Extension application to add a new strength of 5/5 µg (tozinameran, famtozinameran) dispersion for injection for active immunisation for children aged 5 to 11 years of age

15.3.37. Trastuzumab deruxtecan - ENHERTU (CAP) - EMEA/H/C/005124/II/0031

Applicant: Daiichi Sankyo Europe GmbH

PRAC Rapporteur: Inês Ribeiro-Vaz

Scope: Update of sections 4.8, 5.1 and 5.2 of the SmPC in order to update safety, efficacy and pharmacokinetic information based on data from study DS8201-A-U301 and study DS8201-A-U302. Study U301 was a Phase 3, randomised, 2-arm, open-label, multicenter study designed to compare the safety and efficacy of T-DXd vs TPC in HER2-positive, unresectable and/or metastatic BC subjects who were resistant or refractory to T-DM1. Study U302 was a Phase 3, multicenter, randomised, open-label, 2-arm, active-controlled

study in subjects with unresectable and/or metastatic HER2-positive (IHC 3+ or ISH-positive) BC previously treated with trastuzumab plus taxane in the advanced/metastatic setting or who had progressed within 6 months after neoadjuvant or adjuvant treatment involving a regimen including trastuzumab plus taxane. The package leaflet and Annex II are updated accordingly. The updated RMP version 4.1 has also been submitted

15.3.38. Vonicog alfa - VEYVONDI (CAP) - EMEA/H/C/004454/II/0030

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Mari Thorn

Scope: Extension of indication to include prophylactic treatment to prevent or reduce the frequency of bleeding episodes based on final results from study 071301 and interim results from study SHP677-304. Study 071301 is a prospective, phase 3, open-label, international multicenter study on efficacy and safety of prophylaxis with rVWF in severe von Willebrand disease; while study SHP677-304 is a phase 3B, prospective, open-label, uncontrolled, multicenter study on long term safety and efficacy of rVWF in paediatric and adult subjects with severe von Willebrand disease. As a consequence, sections 4.1, 4.2, 4.4, 5.1, 5.2, 6.2 and 6.6 of the SmPC are updated. The package leaflet is updated in accordance. Version 4.0 of the RMP has also been submitted

15.3.39. Zanubrutinib - BRUKINSA (CAP) - EMEA/H/C/004978/II/0014

Applicant: BeiGene Ireland Ltd

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication to include zanubrutinib in combination with obinutuzumab treatment of adult patients with relapsed or refractory follicular lymphoma who have received at least two prior systemic treatments for BRUKINSA, based on results from studies BGB-3111-212 and BGB-3111-GA101-001. BGB-3111-212 is an ongoing international, Phase 2, open-label, randomised (2:1), active control study of zanubrutinib plus obinutuzumab (Arm A) versus obinutuzumab monotherapy (Arm B) in patients with R/R FL. The primary efficacy endpoint is overall response rate (ORR); while BGB-3111-GA101-001 is a Phase 1b Study to Assess Safety, Tolerability and Antitumor Activity of the Combination of BGB-3111 with Obinutuzumab in Subjects with B-Cell Lymphoid Malignanciesa. As a consequence, sections 4.1, 4.4, 4.8 and 5.1 of the SmPC are updated. The package leaflet is updated in accordance. Version 3.1 of the RMP has also been submitted. In addition, the MAH took the opportunity to implement editorial changes to the SmPC

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. Aclidinium bromide, formoterol fumarate dihydrate - BRIMICA GENUAIR (CAP); DUAKLIR GENUAIR (CAP) - PSUSA/00010307/202211

Applicant: Covis Pharma Europe B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.2. Alpelisib - PIQRAY (CAP) - PSUSA/00010871/202211

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.3. Amivantamab - RYBREVANT (CAP) - PSUSA/00010977/202211

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Gabriele Maurer

Scope: Evaluation of a PSUSA procedure

16.1.4. Benralizumab - FASENRA (CAP) - PSUSA/00010661/202211

Applicant: AstraZeneca AB

PRAC Rapporteur: David Olsen

Scope: Evaluation of a PSUSA procedure

16.1.5. Capmatinib - TABRECTA (CAP) - PSUSA/00011022/202211

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Inês Ribeiro-Vaz

Scope: Evaluation of a PSUSA procedure

16.1.6. Ceritinib - ZYKADIA (CAP) - PSUSA/00010372/202210

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.7. Cobicistat, elvitegravir, emtricitabine, tenofovir alafenamide - GENVOYA (CAP) - PSUSA/00010449/202211

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Valentina Di Giovanni

Scope: Evaluation of a PSUSA procedure

16.1.8. Daratumumab - DARZALEX (CAP) - PSUSA/00010498/202211

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Inês Ribeiro-Vaz

Scope: Evaluation of a PSUSA procedure

16.1.9. Dinutuximab beta - QARZIBA (CAP) - PSUSA/00010597/202211

Applicant: EUSA Pharma (Netherlands) B.V.

PRAC Rapporteur: Gabriele Maurer

Scope: Evaluation of a PSUSA procedure

16.1.10. Drospirenone, estetrol - DROVELIS (CAP); LYDISILKA (CAP) - PSUSA/00010938/202211

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

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.11. Emicizumab - HEMLIBRA (CAP) - PSUSA/00010668/202211

Applicant: Roche Registration GmbH

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.1.12. Givosiran - GIVLAARI (CAP) - PSUSA/00010839/202211

Applicant: Alnylam Netherlands B.V.

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.13. Glasdegib - DAURISMO (CAP) - PSUSA/00010859/202211

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.14. Hepatitis B surface antigen, CpG 1018 adjuvant - HEPLISAV B (CAP) - PSUSA/00010919/202211

Applicant: Dynavax GmbH

PRAC Rapporteur: Gabriele Maurer

Scope: Evaluation of a PSUSA procedure

16.1.15. Insulin glargine, lixisenatide - SULIQUA (CAP) - PSUSA/00010577/202211

Applicant: Sanofi Winthrop Industrie

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.16. Ixazomib - NINLARO (CAP) - PSUSA/00010535/202211

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.17. Linzagolix choline - YSELTY (CAP) - PSUSA/00010998/202211

Applicant: Theramex Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.18. Lonafarnib - ZOKINVY (CAP) - PSUSA/00011005/202211

Applicant: EigerBio Europe Limited

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.19. Lumasiran - OXLUMO (CAP) - PSUSA/00010884/202211

Applicant: Alnylam Netherlands B.V.

PRAC Rapporteur: Mari Thorn

Scope: Evaluation of a PSUSA procedure

16.1.20. Ocriplasmin - JETREA (CAP) - PSUSA/00010122/202210

Applicant: Inceptua AB

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.21. Ozanimod - ZEPOSIA (CAP) - PSUSA/00010852/202211

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

16.1.22. Padeliporfin - TOOKAD (CAP) - PSUSA/00010654/202211

Applicant: STEBA Biotech S.A

PRAC Rapporteur: Maia Uusküla

Scope: Evaluation of a PSUSA procedure

16.1.23. Pandemic influenza vaccine (H5N1) (live attenuated, nasal) - PANDEMIC INFLUENZA VACCINE H5N1 ASTRAZENECA (CAP) - PSUSA/00010501/202211

Applicant: AstraZeneca AB

PRAC Rapporteur: Sonja Hrabcik

Scope: Evaluation of a PSUSA procedure

16.1.24. Pegcetacoplan - ASPAVELI (CAP) - PSUSA/00010974/202211

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

16.1.25. Potassium citrate, potassium hydrogen carbonate - SIBNAYAL (CAP) - PSUSA/00010932/202210

Applicant: Advicenne

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.26. Remdesivir - VEKLURY (CAP) - PSUSA/00010840/202211

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Eva Jirsová

Scope: Evaluation of a PSUSA procedure

16.1.27. Ripretinib - QINLOCK (CAP) - PSUSA/00010962/202211

Applicant: Deciphera Pharmaceuticals (Netherlands) B.V.

PRAC Rapporteur: Željana Margan Koletić

Scope: Evaluation of a PSUSA procedure

16.1.28. Rurioctocog alfa pegol - ADYNOVI (CAP) - PSUSA/00010663/202211

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.29. Setmelanotide - IMCIVREE (CAP) - PSUSA/00010941/202211

Applicant: Rhythm Pharmaceuticals Netherlands B.V.,

PRAC Rapporteur: Anna Mareková

Scope: Evaluation of a PSUSA procedure

16.1.30. Stiripentol - DIACOMIT (CAP) - PSUSA/00002789/202211

Applicant: BIOCODEX

PRAC Rapporteur: Maia Uusküla

Scope: Evaluation of a PSUSA procedure

16.1.31. Susoctocog alfa - OBIZUR (CAP) - PSUSA/00010458/202211

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Gabriele Maurer

Scope: Evaluation of a PSUSA procedure

16.1.32. Tofacitinib - XELJANZ (CAP) - PSUSA/00010588/202211

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

16.1.33. Vestronidase alfa - MEPSEVII (CAP) - PSUSA/00010709/202211

Applicant: Ultragenyx Germany GmbH

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

16.1.34. Volanesorsen - WAYLIVRA (CAP) - PSUSA/00010762/202211

Applicant: Akcea Therapeutics Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.35. Zanubrutinib - BRUKINSA (CAP) - PSUSA/00010960/202211

Applicant: BeiGene Ireland Ltd

PRAC Rapporteur: Menno van der Elst

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. Deferasirox - DEFERASIROX ACCORD (CAP); DEFERASIROX MYLAN (CAP); EXJADE (CAP); NAP - PSUSA/00000939/202210

Applicants: Accord Healthcare S.L.U. (Deferasirox Accord), Mylan Pharmaceuticals Limited (Deferasirox Mylan), Novartis Europharm Limited (EXJADE), 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. Acitretin (NAP) - PSUSA/00000051/202210

Applicant(s): various

PRAC Lead: Marie Louise Schougaard Christiansen

Scope: Evaluation of a PSUSA procedure

16.3.2. Atovaquone, proguanil (NAP) - PSUSA/00000266/202210

Applicant(s): various

PRAC Lead: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.3.3. Clevidipine (NAP) - PSUSA/00010288/202211

Applicant(s): various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.3.4. Drospirenone (NAP) - PSUSA/00010853/202211

Applicant(s): various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.3.5. Epinastine (NAP) - PSUSA/00001231/202210

Applicant(s): various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.3.6. Human coagulation factor VII (NAP) - PSUSA/00001619/202210

Applicant(s): various

PRAC Lead: Sonja Hrabcik

Scope: Evaluation of a PSUSA procedure

16.3.7. Isoflurane (NAP) - PSUSA/00001786/202210

Applicant(s): various

PRAC Lead: Melinda Palfi

Scope: Evaluation of a PSUSA procedure

16.3.8. Lenograstim (NAP) - PSUSA/00001839/202210

Applicant(s): various

PRAC Lead: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

16.3.9. Rubidium (^{82}Rb) chloride (NAP) - PSUSA/00010806/202210

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.3.10. Tixocortol (NAP), chlorhexidine gluconate, tixocortol pivalate (NAP) - PSUSA/00010333/202211

Applicant(s): various

PRAC Lead: Nathalie Gault

Scope: Evaluation of a PSUSA procedure

16.3.11. Valsartan, rosuvastatin (NAP) - PSUSA/00010735/202210

Applicant(s): various

PRAC Lead: Polona Golmajer

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[36]

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.

17.1. Protocols of PASS imposed in the marketing authorisation(s)[37]

17.1.1. Axicabtagene ciloleucel - Yescarta (CAP) - EMEA/H/C/PSA/S/0102.1

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

PRAC Rapporteur: Anette Kirstine Stark

Scope: Substantial amendment to a protocol for a long-term, non-interventional study of recipients of Yescarta for treatment of relapsed or refractory Diffuse Large B-cell Lymphoma and Primary Mediastinal B-cell Lymphoma [MAH's response to PSA/S/0102]

17.1.2. Valproate[39] (NAP) - EMEA/H/N/PSP/J/0075.11

Applicant: Sanofi-Aventis Recherche & Développement

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Responses to the request to supplementary information (RSI) of the third interim report and updated protocol (version 11) for drug utilisation study (DUS) extension (DUS ext.) to assess the effectiveness of the new risk minimisation measures and to further characterise the prescribing patterns for valproate and related substances [MAH's response to PSP/J/0075.10]

[36] 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
[37] In accordance with Article 107n of Directive 2001/83/EC
[38] Advanced therapy medicinal product
[39] Valproic acid, sodium valproate, valproate pivoxil, valproate semisodium, valpriomide, valproate bismuth, calcium valproate, valproate magnesium

17.1.3. Valproate[40] (NAP) - EMEA/H/N/PSP/J/0075.12

Applicant: Sanofi-Aventis Recherche & Développement

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Responses to the request to supplementary information (RSI) of the fourth interim report and Statistical Analysis Plan for drug utilisation study (DUS) extension (DUS ext.) to assess the effectiveness of the new risk minimisation measures and to further characterise the prescribing patterns for valproate and related substances [MAH's response to PSP/J/0075.9]

17.2. Protocols of PASS non-imposed in the marketing authorisation(s)[41]

17.2.1. Abaloparatide - ELADYNOS (CAP) - EMEA/H/C/005928/MEA 001

Applicant: Radius Health (Ireland) Limited

PRAC Rapporteur: Anette Kirstine Stark

Scope: Submission of a protocol for an European non-interventional PASS to assess serious cardiovascular events of MI, stroke, all-cause and cardiovascular mortality, and arrhythmias for abaloparatide

17.2.2. Abrocitinib - CIBINQO (CAP) - EMEA/H/C/005452/MEA 002.2

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: MAH’s response to MEA 002.1[protocol for study B7451084: an active surveillance study to monitor the real-world safety of abrocitinib among patients with atopic dermatitis (AD) in the EU. The objective of the study is to estimate the incidence rates of safety endpoints of interest among AD patients receiving abrocitinib and AD patients receiving appropriate systemic treatments including dupilumab for AD in a real-world setting] as per the request to supplementary information (RSI) as adopted in January 2023

17.2.3. Abrocitinib - CIBINQO (CAP) - EMEA/H/C/005452/MEA 003.2

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: MAH’s response to MEA 003.1 [protocol for study B7451085: a drug utilisation study to evaluate the effectiveness of risk minimisation measures (RMMs) for abrocitinib in the EU using electronic healthcare data. The study objectives will be to evaluate indicators of HCP’s adherence to the risk minimisation measures in accordance with the abrocitinib SmPC and prescriber brochure] as per the request to supplementary information (RSI) adopted in January 2023

[40] Valproic acid, sodium valproate, valproate pivoxil, valproate semisodium, valpriomide, valproate bismuth, calcium valproate, valproate magnesium
[41] In accordance with Article 107m of Directive 2001/83/EC, supervised by PRAC in accordance with Article 61a (6) of Regulation (EC) No 726/2004

17.2.4. Acalabrutinib - CALQUENCE (CAP) - EMEA/H/C/005299/MEA 002.7

Applicant: AstraZeneca AB

PRAC Rapporteur: Željana Margan Koletić

Scope: MAH's response to MEA 002.6 [protocol amendment to include a cohort to Study D8220C00008: phase 3b, multicentre, open-label, single-arm in subjects with chronic lymphocytic leukaemia (ASSURE) to address missing information around moderate to severe cardiac impaired patients in subjects treated with Calquence(acalabrutinib)] as per the request for supplementary information (RSI) adopted in February 2023

17.2.5. Anifrolumab - SAPHNELO (CAP) - EMEA/H/C/004975/MEA 001.1

Applicant: AstraZeneca AB

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Protocol for study D3461R00028: a multiple database study of the use (and safety) of anifrolumab in women with systemic lupus erythemathosus (SLE) during pregnancy

17.2.6. Avalglucosidase alfa - NEXVIADYME (CAP) - EMEA/H/C/005501/MEA 007.1

Applicant: Sanofi B.V.

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: MAH's response to MEA 007 [Protocol for study OBS17445 (listed as category 3 study in the RMP): a PASS to assess long term safety in patients with Pompe disease treated with avalglucosidase alfa in the commercial setting] as per request for supplementary information (RSI) adopted in January 2023

17.2.7. Avatrombopag - DOPTELET (CAP) - EMEA/H/C/004722/MEA 003.3

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Monica Martinez Redondo

Scope: MAH's response to MEA 003.2 [feasibility assessment for a study to further characterise the long-term safety profile of avatrombopag in patients with primary chronic immune thrombocytopenia in European patient registers and electronic healthcare databases as requested in the conclusions of variation II/0004/G finalised in December 2020] as per the request for supplementary information (RSI) adopted October 2022

17.2.8. Cipaglucosidase alfa - POMBILITI (CAP) - EMEA/H/C/005703/MEA 001

Applicant: Amicus Therapeutics Europe Limited

PRAC Rapporteur: Mari Thorn

Scope: Submission of a protocol for study POM-005 (non-imposed/non-interventional, listed as category 3 in the RMP): a global prospective observational registry of patients with pompe disease

17.2.9. Cladribine - MAVENCLAD (CAP) - EMEA/H/C/004230/MEA 003.3

Applicant: Merck Europe B.V.

PRAC Rapporteur: Inês Ribeiro-Vaz

Scope: MAH's responses to MEA 003.2 [Amendment to a previously agreed protocol for study MS700568-0004: Pregnancy outcomes in women exposed to oral cladribine: a multi-country cohort database study – CLEAR] as per the request for supplementary information (RSI) adopted in February 2023

17.2.10. Coronavirus (COVID-19) vaccine (B.1.351 variant, prefusion Spike delta TM protein, recombinant) - VIDPREVTYN BETA (CAP) - EMEA/H/C/005754/MEA 002.1

Applicant: Sanofi Pasteur

PRAC Rapporteur: Jana Lukacisinova

Scope: MAH's response to MEA 002 [Submission of a protocol for study VAT 00007: Post-authorisation, observational study to assess the safety of VidPrevtyn Beta using routinely collected secondary data in Europe through VAC4EU. A non-interventional PASS to assess the occurrence of pre-specified AESIs and safety concerns following administration of VidPrevtyn Beta as a booster dose in a real-world setting as per the request for supplementary information (RSI) adopted in February 2023

17.2.11. Lenalidomide - REVLIMID (CAP) - EMEA/H/C/000717/MEA 046.7

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Tiphaine Vaillant

Scope: MAH's response to MEA 046.6 [Substantial amendment to a protocol previously endorsed in November 2017 for study CC-5013-MCL-005 to further investigate and characterise the association of lenalidomide and tumour flare reaction (TFR)/high tumour burden following the extension of indication for the treatment of adult patients with relapsed and/or refractory mantle cell lymphoma (RRMCL)] as per the request for supplementary information (RSI) adopted in February 2032

17.2.12. Odevixibat - BYLVAY (CAP) - EMEA/H/C/004691/MEA 003.3

Applicant: Albireo

PRAC Rapporteur: Adam Przybylkowski

Scope: MAH's response to MEA 003.2[Submission of an updated study protocol (version 1.0) for study A4250-019 (listed as a category 3 study in the RMP): prospective registry-based study of the long-term safety of odevixibat in patients with progressive familial intrahepatic cholestasis (PFIC) to collect safety data on hepatotoxicity, diarrhoea, fat-soluble vitamins and fat-soluble nutrients in patients treated with odevixibat] as per request for supplementary information (RSI) adopted in February 2023

17.2.13. Ozanimod - ZEPOSIA (CAP) - EMEA/H/C/004835/MEA 005.1

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Maria del Pilar Rayon

Scope: MAH's response to MEA 005 [protocol for study IM0471037: a PASS titled 'Long-term real-world safety of ozanimod – A PASS in patients diagnosed with ulcerative colitis'. This study is a category 3 study (required additional pharmacovigilance activity - UC indication) listed in the RMP version 3.0] as per the request for supplementary information (RSI) adopted in September 2022

17.2.14. Risankizumab - SKYRIZI (CAP) - EMEA/H/C/004759/MEA 009

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Protocol for study P23-653 (non-imposed/non-interventional): Pregnancy Exposure and Outcomes for Women with Crohn's Disease Treated with Risankizumab. A comparative cohort study to describe risankizumab exposure in pregnant patients with Crohn's disease, and compare pregnancy and infant outcomes to pregnant patients with Crohn's disease who were treated with alternative therapies (e.g., biologics). In addition, descriptive analyses of pregnancy outcomes in patients with Crohn's disease without exposure to any treatments under investigation will also be conducted

17.2.15. Spesolimab - SPEVIGO (CAP) - EMEA/H/C/005874/MEA 003

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Nathalie Gault

Scope: Protocol for study 1368-0128 (Non-imposed/Non-interventional): a 5-year active surveillance, PASS to characterise the safety of spesolimab for flare treatment in patients with generalized pustular psoriasis (GPP). Objectives: To evaluate the risks serious or opportunistic infections, systemic hypersensitivity reaction, malignancy, and peripheral neuropathy in adult patients (aged ≥18 years) experiencing a GPP flare who are treated with spesolimab or other treatments in the routine clinical care setting

17.2.16. Tezepelumab - TEZSPIRE (CAP) - EMEA/H/C/005588/MEA 001

Applicant: AstraZeneca AB

PRAC Rapporteur: Eva Jirsová

Scope: Protocol for study D5180R00010 (TREATY): A Non-Interventional Multi-Database PASS to Assess Pregnancy-Related Safety Data from Women with Severe Asthma Exposed to Tezepelumab

17.2.17. Upadacitinib - RINVOQ (CAP) - EMEA/H/C/004760/MEA 003.4

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: MAH's response to MEA 003.2 [Amendment to a previously agreed protocol for study P19-150: a long-term PASS of upadacitinib use in rheumatoid arthritis (RA) patients in Europe to evaluate the safety of upadacitinib among patients with RA receiving routine clinical care to include additional study outcomes of bone fractures and add further

clarification that the malignancy outcomes will be stratified for malignancies excluding non-melanoma skin cancer (NMSC) and NMSC, separately (RMP version 6.2)] as per request for supplementary information (RSI) adopted in January 2023

17.2.18. Upadacitinib - RINVOQ (CAP) - EMEA/H/C/004760/MEA 004.4

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: MAH's response to MEA 004.2 [Amendment to a previously agreed protocol for study P19-141: a long-term PASS of upadacitinib use in rheumatoid arthritis (RA) patients in the US in order to: 1) compare the incidence of malignancy, non-melanoma skin cancer (NMSC), major adverse cardiovascular events (MACE), venous thromboembolism (VTE) and serious infection events in adults with RA who receive upadacitinib in the course of routine clinical care relative to those who receive biologic therapy for the treatment of RA; 2) describe the incidence rates of herpes zoster, opportunistic infections and evidence of drug-induced liver injury (DILI); 3) describe the incidence of the above outcomes in very elderly patients (aged $\geqslant$ 75 years); 4) characterise VTE clinical risk factors and baseline biomarkers in a sub-study of new initiators of upadacitinib and comparator biologic therapies] as per request for supplementary information (RSI) adopted in January 2023

17.2.19. Upadacitinib - RINVOQ (CAP) - EMEA/H/C/004760/MEA 012.3

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: MAH's response to MEA 012.2 [protocol for study P21-825: an evaluation of the effectiveness of additional risk minimisation measures for upadacitinib in the treatment of atopic dermatitis] as per the request for supplementary information (RSI) adopted in January 2023

17.2.20. Upadacitinib - RINVOQ (CAP) - EMEA/H/C/004760/MEA 013.3

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: MAH's response to MEA 013.2 [revised protocol for study P20-390: a cohort study of long-term safety of upadacitinib in the treatment of atopic dermatitis in Denmark and Sweden] as per request for supplementary information (RSI) adopted in December 2022

17.2.21. Upadacitinib - RINVOQ (CAP) - EMEA/H/C/004760/MEA 016.1

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: MAH's response to MEA 016 [Protocol for study P23-479: a drug utilisation study for evaluation of the effectiveness of additional risk minimisation measures for upadacitinib in the treatment of ulcerative colitis in Sweden and Denmark] as per request for supplementary information (RSI) adopted in January 2023

17.2.22. Valoctocogene roxaparvovec - ROCTAVIAN (CAP) - EMEA/H/C/005830/MEA 005

Applicant: BioMarin International Limited, ATMP[42]

PRAC Rapporteur: Menno van der Elst

Scope: Protocol of a survey of haematologists to assess the effectiveness of the additional risk minimisation measures (aRMMs) for ROCTAVIAN (valoctocogene roxaparvovec)

17.2.23. Voclosporin - LUPKYNIS (CAP) - EMEA/H/C/005256/MEA 002

Applicant: Otsuka Pharmaceutical Netherlands B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Protocol for study 348-201-00021 (Non-imposed/Non-interventional, listed as category 3 study in the RMP): Observational PASS in Europe to further characterise and quantify long-term safety profile with respect to neurotoxicity, chronic nephrotoxicity, and malignancy with use of voclosporin

17.3. Results of PASS imposed in the marketing authorisation(s)[43]

None

17.4. Results of PASS non-imposed in the marketing authorisation(s)[44]

17.4.1. Baricitinib - OLUMIANT (CAP) - EMEA/H/C/004085/II/0039/G

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Submission of the final reports from studies I4V-MC-B016 and I4V-MC-B011 listed as category 3 non-interventional PASS studies in the RMP. B016 is a drug utilisation study for the assessment of off-label use of baricitinib in the paediatric population in the United Kingdom. B011 is a retrospective cohort study to assess the safety of baricitinib compared with other therapies used in the treatment of rheumatoid arthritis in Nordic countries. The RMP version 19.1 has also been submitted

17.4.2. Cabozantinib - CABOMETYX (CAP) - EMEA/H/C/004163/II/0033

Applicant: Ipsen Pharma

PRAC Rapporteur: Menno van der Elst

Scope: Submission of the final report from study F-FR-60000-001 (CASSIOPE) listed as a category 3 study in the RMP. This is a prospective, non-imposed and non-interventional study of Cabozantinib tablets in adults with advanced renal cell carcinoma (RCC) following prior vascular endothelial growth factor (VEGF)-targeted therapy. The RMP version 7.0 has also been submitted

[42] Advanced therapy medicinal product
[43] In accordance with Article 107p-q of Directive 2001/83/EC
[44] In accordance with Article 61a (6) of Regulation (EC) No 726/2004, in line with the revised variations regulation for any submission as of 4 August 2013

17.4.3. Coronavirus (COVID-19) vaccine (Ad26.COV2-S, recombinant) - JCOVDEN (CAP) - EMEA/H/C/005737/II/0071/G

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Grouped application consisting of: 1) Submission of the final study report of a clinical TTS characterization study listed as a category 3 study in the RMP. This is a Test Pre- and Post-Vaccination Serum Across All Populations Using Clinical Samples From Ad26-based Company Vaccine Studies Other Than Ad26.COV2.S; 2) Submission of the Addendum to final CSR of the study VAC31518COV2001 listed as a category 3 study in the RMP. This is a randomised, double-blind, placebo-controlled Phase 2a study to evaluate a range of dose levels and vaccination intervals of Ad26.COV2.S in healthy adults aged 18 to 55 years, and adults aged 65 years and older. The RMP version 6.1 has also been submitted

17.4.4. Coronavirus (COVID-19) vaccine (ChAdOx1-S [recombinant]) - VAXZEVRIA (CAP) - EMEA/H/C/005675/II/0091

Applicant: AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

Scope: Submission of the final report from study D8111R00020 listed as a category 3 study in the RMP. This is a systematic literature review for studies evaluating adverse events of Vaxzervria in patients taking immunosuppressant medications and/or with primary immunodeficiency

17.4.5. Dabigatran etexilate - PRADAXA (CAP) - EMEA/H/C/000829/II/0144

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Anette Kirstine Stark

Scope: Submission of the final report from the Human Factors Study (007-HFE-009035), listed as a category 3 study in the RMP; this is a non-interventional study to assess the effectiveness of a training video to mitigate potential medication errors during the reconstitution and dosing of the dabigatran etexilate paediatric oral solution.

17.4.6. Edoxaban - LIXIANA (CAP) - EMEA/H/C/002629/WS2483/0045; ROTEAS (CAP) - EMEA/H/C/004339/WS2483/0032

Applicant: Daiichi Sankyo Europe GmbH

PRAC Rapporteur: Nathalie Gault

Scope: Submission of the final report from DSE-EDO-04-14-EU (Non-Interventional Study on Edoxaban Treatment in Routine Clinical Practice for Patients with Non-Valvular Atrial Fibrillation, ETNA-AF Europe), listed as a category 3 study in the RMP (MEA 006). This is a multicentre, prospective, non-interventional, observational PASS. The RMP version 15.1 has also been submitted

17.4.7. Lenalidomide - REVLIMID (CAP) - EMEA/H/C/000717/II/0126

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Tiphaine Vaillant

Scope: Submission of the final report from study CC-5013-MDS-010 listed as an obligation in the Annex II of the product information. This is a prospective non-interventional PASS, designed as a disease registry of patients with transfusion dependent IPSS low or intermediate-1-risk myelodysplastic syndromes (MDS) and isolated del(5q). Section D of the Annex II and the RMP (version 39) are updated accordingly

17.4.8. Piperaquine tetraphosphate, artenimol - EURARTESIM (CAP) - EMEA/H/C/001199/II/0040/G

Applicant: Alfasigma S.p.A.

PRAC Rapporteur: Martin Huber

Scope: Grouped variation consisting of: 1) Submission of the final report from the effectiveness evaluation survey for Eurartesim (protocol no. 3366) (listed as a category 3 study in the RMP): an European multi-centre online survey to assess physician understanding of the revised edition of the educational material. Consequential changes to RMP version 16.1 have been implemented; 2) Submission of an updated RMP version 16.1 in order to delete "severe malaria" as missing information from the list of safety specifications

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

17.5.1. Alemtuzumab - LEMTRADA (CAP) - EMEA/H/C/003718/MEA 007.15

Applicant: Sanofi Belgium

PRAC Rapporteur: Anette Kirstine Stark

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

17.5.2. Arsenic trioxide - TRISENOX (CAP) - EMEA/H/C/000388/MEA 050.5

Applicant: Teva B.V.

PRAC Rapporteur: Tiphaine Vaillant

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

17.5.3. Autologous CD34+ enriched cell fraction that contains CD34+ cells transduced with retroviral vector that encodes for the human ADA cDNA sequence - STRIMVELIS (CAP) - EMEA/H/C/003854/ANX 004.4

Applicant: Orchard Therapeutics (Netherlands) B.V., ATMP[45]

PRAC Rapporteur: Menno van der Elst

Scope: Third interim report for study GSK2696273 – an adenosine deaminase severe combined immunodeficiency (ADA-SCID) registry for patients treated with Strimvelis gene therapy: a long-term prospective, non-interventional follow-up of safety and effectiveness

17.5.4. Avelumab - BAVENCIO (CAP) - EMEA/H/C/004338/MEA 002.5

Applicant: Merck Europe B.V.

PRAC Rapporteur: Anette Kirstine Stark

Scope: Fourth yearly progress update report for study MS100070-0031 (listed as a category 3 study in the RMP): a non-interventional cohort study to assess characteristics and management of patients with Merkel cell carcinoma (MCC) in Germany

17.5.5. Cabotegravir - VOCABRIA (CAP) - EMEA/H/C/004976/MEA 004.3

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Martin Huber

Scope: Interim report for study 215162 (listed as a category 3 study in the RMP): a prospective observational cohort study to monitor for hepatotoxicity and regimen discontinuation due to liver related adverse events among patients initiating cabotegravir-containing antiretroviral regimen

17.5.6. Cabotegravir - VOCABRIA (CAP) - EMEA/H/C/004976/ANX 002

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Martin Huber

Scope: Interim report for a drug utilisation study (DUS): Drug Utilisation, Adherence, Effectiveness and Resistance: A Prospective Observational Cohort Study in People Living with HIV (PLWH) initiating ARV regimen CAB+RPV LA in Collaboration with EuroSIDA

17.5.7. Coronavirus (COVID-19) vaccine (ChAdOx1-S [recombinant]) - VAXZEVRIA (CAP) - EMEA/H/C/005675/MEA 114

Applicant: AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

Scope: First progress report for study No. D8111R00010; ATTEST (Association of the risk for Thrombotic Thrombocytopenia Syndrome and Exposure To COVID-19 vaccines) is a category 3 PASS study with the objective to evaluate an association between COVID-19 vaccine exposure and thromboembolic events occurring with thrombocytopenia (thrombotic

[45] Advanced therapy medicinal product

thrombocytopenia syndrome; TTS)

17.5.8. Filgrastim - FILGRASTIM HEXAL (CAP) - EMEA/H/C/000918/MEA 007.14

Applicant: Hexal AG

PRAC Rapporteur: Menno van der Elst

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

17.5.9. Filgrastim - ZARZIO (CAP) - EMEA/H/C/000917/MEA 007.14

Applicant: Sandoz GmbH

PRAC Rapporteur: Menno van der Elst

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

17.5.10. Inotersen - TEGSEDI (CAP) - EMEA/H/C/004782/MEA 007.4

Applicant: Akcea Therapeutics Ireland Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: MAH's response to MEA 007.3 [Second interim report for study TEG4005: a pregnancy surveillance programme of infants and women exposed to Tegsedi (inotersen) during pregnancy] as per request for supplementary information (RSI) adopted in February 2023

17.5.11. Mogamulizumab - POTELIGEO (CAP) - EMEA/H/C/004232/MEA 001.3

Applicant: Kyowa Kirin Holdings B.V.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: MAH's response to MEA 001.2 [Interim report for a PASS to characterise the safety of allogeneic haematopoietic stem cell transplantation (HSCT) in patients with cutaneous T-cell lymphoma (CTCL) treated with mogamulizumab] as per request for supplementary information (RSI) adopted in February 2023

17.5.12. Ofatumumab - KESIMPTA (CAP) - EMEA/H/C/005410/MEA 003.2

Applicant: Novartis Ireland Limited

PRAC Rapporteur: Amelia Cupelli

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

relapsing multiple sclerosis

17.5.13. Rilpivirine - REKAMBYS (CAP) - EMEA/H/C/005060/ANX 002

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: First annual interim report for the non-interventional PASS drug utilisation study (DUS) (listed as category 1 study in the RMP): 'Drug Utilization, Adherence, Effectiveness and Resistance: A Prospective Observational Cohort Study in People living with HIV (PLWH) initiating ARV regimen CAB+RPV LA in Collaboration with EuroSIDA'

17.5.14. Selexipag - UPTRAVI (CAP) - EMEA/H/C/003774/MEA 001.9

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Nathalie Gault

Scope: Interim report for study EXPOSURE: an observational cohort study of pulmonary arterial hypertension (PAH) patients newly treated with either Uptravi (selexipag) or any other PAH-specific therapy, in clinical practice

17.5.15. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/MEA 008.6

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Second interim report for study A3921312 (listed as a category 3 study in the RMP): a prospective non-interventional comparative active surveillance PASS of serious infection, malignancy, cardiovascular and other adverse event rates among patients treated with Xeljanz (tofacitinib) for moderately to severely active rheumatoid arthritis (RA) within the British Society for Rheumatology Biologics Register-Rheumatoid Arthritis (BSRBR-RA)

17.5.16. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/MEA 009.6

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Second interim report for study A3921314: (listed as a category 3 study in the RMP): a prospective non-interventional comparative active surveillance PASS of serious infection, malignancy, cardiovascular and other adverse event rates among patients treated with Xeljanz (tofacitinib) for moderately to severely active rheumatoid arthritis (RA) within the Swedish (ARTIS) register

17.5.17. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/MEA 010.6

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Second interim report for study A3921316 (listed as a category 3 study in the RMP): a prospective non-interventional comparative active surveillance PASS of serious infection,

malignancy, cardiovascular and other adverse event rates among patients treated with Xeljanz (tofacitinib) for moderately to severely active rheumatoid arthritis (RA) within the Spanish registry of adverse events of biological therapies and biosimilars in rheumatoid diseases (BIOBADASER)

17.5.18. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/MEA 011.6

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Second interim report for study A3921317: (listed as a category 3 study in the RMP): a prospective non-interventional comparative active surveillance PASS of serious infection, malignancy, cardiovascular and other adverse event rates among patients treated with Xeljanz (tofacitinib) for moderately to severely active rheumatoid arthritis (RA) within the German registry Rheumatoide Arthritis: Beobachtung der Biologika-Therapie (RABBIT)

17.5.19. Tozinameran - COMIRNATY (CAP) - EMEA/H/C/005735/MEA 011.9

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

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

17.5.20. Upadacitinib - RINVOQ (CAP) - EMEA/H/C/004760/MEA 003.3

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Annual progress report for study P19-150 (EUPAS39217): a long-term PASS of upadacitinib use in rheumatoid arthritis (RA) patients in Europe to evaluate the safety of upadacitinib among patients with RA receiving routine clinical care

17.5.21. Upadacitinib - RINVOQ (CAP) - EMEA/H/C/004760/MEA 004.3

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Annual progress report for study P19-141 (EUPAS39194): a long-term PASS of upadacitinib use in rheumatoid arthritis (RA) patients in the US in order to: 1) compare the incidence of malignancy, non-melanoma skin cancer (NMSC), major adverse cardiovascular events (MACE), venous thromboembolism (VTE) and serious infection events in adults with RA who receive upadacitinib in the course of routine clinical care relative to those who receive biologic therapy for the treatment of RA; 2) describe the incidence rates of herpes zoster, opportunistic infections and evidence of drug-induced liver injury (DILI); 3) describe the incidence of the above outcomes in very elderly patients (aged $\geqslant$ 75 years); 4) characterise VTE clinical risk factors and baseline biomarkers in a sub-study of new initiators of upadacitinib and comparator biologic therapies

17.5.22. Upadacitinib - RINVOQ (CAP) - EMEA/H/C/004760/MEA 005.2

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Annual progress report for study P20-199 (EUPAS39211): a drug utilisation study (DUS) to evaluate the effectiveness of the additional risk minimisation measures (aRMM) in place to describe the baseline characteristics of new users of upadacitinib, and in a similar manner, to describe new users of a biological disease-modifying antirheumatic drugs (bDMARD) for comparison

17.5.23. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/MEA 044.16

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Rhea Fitzgerald

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

17.6. Others

None

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. Afamelanotide - SCENESSE (CAP) - EMEA/H/C/002548/S/0045 (without RMP)

Applicant: Clinuvel Europe Limited

PRAC Rapporteur: Martin Huber

Scope: Annual reassessment of the marketing authorisation

18.1.2. Clofarabine - EVOLTRA (CAP) - EMEA/H/C/000613/S/0078 (without RMP)

Applicant: Sanofi B.V.

PRAC Rapporteur: Tiphaine Vaillant

Scope: Annual reassessment of the marketing authorisation

18.1.3. Velmanase alfa - LAMZEDE (CAP) - EMEA/H/C/003922/S/0031 (without RMP)

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Jan Neuhauser

Scope: Annual reassessment of the marketing authorisation

18.2. Conditional renewals of the marketing authorisation

18.2.1. Belantamab mafodotin - BLENREP (CAP) - EMEA/H/C/004935/R/0017 (with RMP)

Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Conditional renewal of the marketing authorisation

18.3. Renewals of the marketing authorisation

18.3.1. Dengue tetravalent vaccine (live, attenuated) - DENGVAXIA (CAP) - EMEA/H/C/004171/R/0027 (without RMP)

Applicant: Sanofi Pasteur

PRAC Rapporteur: Sonja Hrabcik

Scope: 5-year renewal of the marketing authorisation

18.3.2. 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

18.3.3. Lenalidomide - LENALIDOMIDE ACCORD (CAP) - EMEA/H/C/004857/R/0021 (without RMP)

Applicant: Accord Healthcare S.L.U.

PRAC Rapporteur: Tiphaine Vaillant

Scope: 5-year renewal of the marketing authorisation

18.3.4. Lidocaine, prilocaine - FORTACIN (CAP) - EMEA/H/C/002693/R/0038 (without RMP)

Applicant: Recordati Ireland Ltd

PRAC Rapporteur: Maria del Pilar Rayon

Scope: 5-year renewal of the marketing authorisation

18.3.5. Mexiletine - NAMUSCLA (CAP) - EMEA/H/C/004584/R/0014 (without RMP)

Applicant: Lupin Europe GmbH

PRAC Rapporteur: Eva Jirsová

Scope: 5-year renewal of the marketing authorisation

18.3.6. Mogamulizumab - POTELIGEO (CAP) - EMEA/H/C/004232/R/0021 (without RMP)

Applicant: Kyowa Kirin Holdings B.V.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: 5-year renewal of the marketing authorisation

18.3.7. Pegfilgrastim - PELMEG (CAP) - EMEA/H/C/004700/R/0025 (without RMP)

Applicant: Mundipharma Corporation (Ireland) Limited

PRAC Rapporteur: Menno van der Elst

Scope: 5-year renewal of the marketing authorisation

18.3.8. Tezacaftor, ivacaftor - SYMKEVI (CAP) - EMEA/H/C/004682/R/0038 (with RMP)

Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: 5-year renewal of the marketing authorisation

18.3.9. Trastuzumab - OGIVRI (CAP) - EMEA/H/C/004916/R/0054 (without RMP)

Applicant: Viatris Limited

PRAC Rapporteur: Gabriele Maurer

Scope: 5-year renewal of the marketing authorisation

18.3.10. Venetoclax - VENCLYXTO (CAP) - EMEA/H/C/004106/R/0046 (without RMP)

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Eva Jirsová

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 5-8 June 2023 meeting.

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Sabine Straus	Chair	The Netherlands	No interests declared	
Jan Neuhauser	Member	Austria	No interests declared	
Sonja Hrabcik	Alternate	Austria	No interests declared	
Jean-Michel Dogné	Member	Belgium	No interests declared	
Jo Robays	Alternate	Belgium	No interests declared	
Maria Popova-Kiradjieva	Member	Bulgaria	No interests declared	
Nikica Mirošević Skvrce	Member	Croatia	No interests declared	
Željana Margan Koletić	Alternate	Croatia	No interests declared	
Panagiotis Psaras	Alternate	Cyprus	No interests declared	
Eva Jirsová	Member	Czechia	No interests declared	
Jana Lukacisinova	Alternate	Czechia	No interests declared	
Anette Kirstine Stark	Member	Denmark	No interests declared	
Marie Louise Schougaard Christiansen	Alternate	Denmark	No interests declared	
Maia Uusküla	Member	Estonia	No interests declared	
Kroot Aab	Alternate	Estonia	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Kirsti Villikka	Member	Finland	No interests declared	
Kimmo Jaakkola	Alternate	Finland	No interests declared	
Tiphaine Vaillant	Member	France	No interests declared	
Nathalie Gault	Alternate	France	No interests declared	
Martin Huber	Member (Vice-Chair)	Germany	No interests declared	
Gabriele Maurer	Alternate	Germany	No participation in final deliberations and voting on:	4.3.1. Ipilimumab – YERVOY (CAP) - EMEA/H/C/002213/SDA/046; nivolumab – OPDIVO (CAP) - EMEA/H/C/003985/SDA/051; pembrolizumab – KEYTRUDA (CAP) - EMEA/H/C/003820/SDA/036
Sofia Trantza	Member	Greece	No interests declared	
Georgia Gkegka	Alternate	Greece	No interests declared	
Julia Pallos	Member	Hungary	No participation in final deliberations and voting on:	4.3.1. Ipilimumab – YERVOY (CAP) - EMEA/H/C/002213/SDA/046; nivolumab – OPDIVO (CAP) - EMEA/H/C/003985/SDA/051; pembrolizumab – KEYTRUDA (CAP) - EMEA/H/C/003820/SDA/036 15.3.15. Idecabtagene vicleucel - ABECMA (CAP)

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				- EMEA/H/C/004662/II/0031, Orphan 15.3.17. Lenalidomide - REVLIMID (CAP) - EMEA/H/C/000717/II/0123 15.3.19. Luspatercept - REBLOZYL (CAP) - EMEA/H/C/004444/II/0021, Orphan 15.3.27. Pomalidomide - IMNOVID (CAP) - EMEA/H/C/002682/II/0047, Orphan 15.3.32. Thalidomide - THALIDOMIDE BMS (CAP) - EMEA/H/C/000823/II/0076 16.1.21. Ozanimod - ZEPOSIA (CAP) - PSUSA/00010852/202211 17.2.11. Lenalidomide - REVLIMID (CAP) - EMEA/H/C/000717/MEA 046.7 17.2.13. Ozanimod - ZEPOSIA (CAP) - EMEA/H/C/004835/MEA 005.1

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				17.4.7. Lenalidomide - REVLIMID (CAP) - EMEA/H/C/000717/II/0126
Melinda Palfi	Alternate	Hungary	No interests declared	
Guðrún Stefánsdóttir	Member	Iceland	No restrictions applicable to this meeting	
Eamon O Murchu	Alternate	Ireland	No interests declared	
Amelia Cupelli	Member	Italy	No interests declared	
Valentina Di Giovanni	Alternate	Italy	No interests declared	
Zane Neikena	Member	Latvia	No interests declared	
Lina Seibokiene	Alternate	Lithuania	No restrictions applicable to this meeting	
Nadine Petitpain	Member	Luxembourg	No restrictions applicable to this meeting	
Benjamin Micallef	Alternate	Malta	No interests declared	
Menno van der Elst	Member	Netherlands	No interests declared	
Liana Gross-Martirosyan	Alternate	Netherlands	No interests declared	
David Olsen	Member	Norway	No participation in final deliberations and voting on:	15.3.1. Aflibercept - EYLEA (CAP) - EMEA/H/C/002392/X/0084/G
Pernille Harg	Alternate	Norway	No interests declared	
Adam Przybylkowski	Member	Poland	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Ana Sofia Diniz Martins	Member	Portugal	No interests declared	
Ines Ribeiro-Vaz	Alternate	Portugal	No interests declared	
Roxana Dondera	Member	Romania	No interests declared	
Irina Sandu	Alternate	Romania	No interests declared	
Miroslava Gocova	Alternate	Slovakia	No interests declared	
Polona Golmajer	Member	Slovenia	No interests declared	
Maria del Pilar Rayon	Member	Spain	No interests declared	
Monica Martinez Redondo	Alternate	Spain	No interests declared	
Ulla Wändel Liminga	Member	Sweden	No interests declared	
Mari Thorn	Alternate	Sweden	No interests declared	
Annalisa Capuano	Member	Independent scientific expert	No interests declared	
Milou Daniel Drici	Member	Independent scientific expert	No interests declared	
Maria Teresa Herdeiro	Member	Independent scientific expert	No interests declared	
Patricia McGettigan	Member	Independent scientific expert	No interests declared	
Tania Schink	Member	Independent scientific expert	No participation in final deliberations and voting on:	16.1.1. Aclidinium bromide, formoterol fumarate dihydrate - BRIMICA GENUAIR (CAP); DUAKLIR GENUAIR (CAP) - PSUSA/00010307/202211 17.4.6. Edoxaban - LIXIANA (CAP) -

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				EMEA/H/C/002629/WS2483/0045; ROTEAS (CAP) - EMEA/H/C/004339/WS2483/0032
Hedvig Nordeng	Member	Independent scientific expert	No interests declared	
Roberto Frontini	Member	Healthcare Professionals' Representative	No restrictions applicable to this meeting	
Salvatore Messana	Alternate	Healthcare Professionals' Representative	No interests declared	
Jamila Hamdani	Expert	Belgium	No interests declared	
Fabrice Moore	Expert	Belgium	No interests declared	
Melita Dumančić	Expert	Croatia	No restrictions applicable to this meeting	
Ivana Kosier	Expert	Croatia	No interests declared	
Ivana Ljubičić	Expert	Croatia	No interests declared	
Petar Mas	Expert	Croatia	No interests declared	
Petra Vacková	Expert	Czechia	No interests declared	
Marian Hjortlund Allon	Expert	Denmark	No interests declared	
Annette Cleveland Nielsen	Expert	Denmark	No interests declared	
Helle Gerda Olsen	Expert	Denmark	No interests declared	
Moritz Sander	Expert	Denmark	No interests declared	
Ane Blicher Schelde	Expert	Denmark	No restrictions applicable to this meeting	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Aynur Sert	Expert	Denmark	No interests declared	
Emma Stadsbjerg	Expert	Denmark	No interests declared	
Thomas Berbain	Expert	France	No interests declared	
Camille De-Kervasdoue	Expert	France	No interests declared	
Vincent Gazin	Expert	France	No interests declared	
Marie-Caroline Pesquidous	Expert	France	No restrictions applicable to this meeting	
Anne Kleinau	Expert	Germany	No interests declared	
Dennis Lex	Expert	Germany	No interests declared	
Vivien Molitor	Expert	Germany	No interests declared	
Natalie Welter	Expert	Germany	No participation in final deliberations and voting on:	
Ronan Grimes	Expert	Ireland	No interests declared	
Diana Litenboka	Expert	Latvia	No interests declared	
Diāna Inga Paegle	Expert	Latvia	No interests declared	
André Elferink	Expert	Netherlands	No interests declared	
Hester Peltenburg	Expert	Netherlands	No interests declared	
Inge Zomerdijk	Expert	Netherlands	No interests declared	
Nina Malvik	Expert	Norway	No interests declared	
Carla Torre	Expert	Portugal	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Natividad Galiana	Expert	Spain	No restrictions applicable to this meeting	
Consuelo Mejías	Expert	Spain	No interests declared	
Charlotte Backman	Expert	Sweden	No interests declared	
Sara Brandel	Expert	Sweden	No restrictions applicable to this meeting	
Oscar Ljungberg	Expert	Sweden	No interests declared	
Karin Nylén	Expert	Sweden	No interests declared	
Anna Schölin	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