23 August 2024
EMA/PRAC/337971/2024
Human Medicines Division

Pharmacovigilance Risk Assessment Committee (PRAC)

Minutes of PRAC meeting on 8-11 July 2024

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 Chair opened the meeting by welcoming all participants. The meeting was held in-person.

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

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

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

The EMA Secretariat announced the names of the Committee members who delegated their vote via proxy and the Committee members who received such proxy.

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

1.2. Agenda of the meeting on 08-11 July 2024

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 10-13 June 2024

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 10-13 June 2024 were published on the EMA website on 21 August 2024 (EMA/PRAC/343192/2024).

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

2.1. Newly triggered procedures

None

2.2. Ongoing procedures

2.2.1. Metamizole (NAP); metamizole, caffeine (NAP); metamizole, caffeine, codeine (NAP); metamizole, caffeine, codeine, paracetamol (NAP); metamizole, caffeine, codeine, paracetamol, phenobarbital (NAP); metamizole, caffeine, drotaverine (NAP); metamizole, caffeine, thiamine (NAP); metamizole, hyoscine (NAP); metamizole, pitofenone (NAP); metamizole, pitofenone, fenpipramide (NAP); metamizole, pitofenone, fenpiverinium (NAP); metamizole, triacetonamine (NAP) – EMEA/H/A-107i/1537

Applicant(s): various

PRAC Rapporteur: Julia Pallos; PRAC Co-rapporteur: Barbara Kovacic Bytiqi

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

Background

A referral procedure under Article 107i of Directive 2001/83/EC is ongoing for the review of metamizole-containing products. The review was initiated following the fact that cases of agranulocytosis and related complications continue to be reported with metamizole, despite the implementation of successive and recent strengthened risk minimisation measures in Finland for the only metamizole-containing product (metamizole/pitofenone combination) authorised in this Member State. For further background, see PRAC minutes June 2024.

Summary of recommendation(s)/conclusions

- PRAC adopted a list of questions (LoQ) to the experts for the ad-hoc expert group (AHEG) meeting. As a result, PRAC adopted a revised timetable for the procedure to reflect the AHEG.

Post-meeting note: On 21 August 2024, PRAC adopted via written procedure the list of participants (LoP) for the AHEG as well as a revised timetable for the procedure to reflect the AHEG date, i.e. 26 August 2024.

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

None

3.3. Procedures for finalisation

None

3.4. Re-examination procedures[1]

None

3.5. Others

None

4. Signals assessment and prioritisation[2]

For further details and for the full PRAC recommendations, see EMA/PRAC/312286/2024 published on 12 August 2024 on the EMA website.

4.1. New signals detected from EU spontaneous reporting systems and/or other sources

See also Annex I 14.1.

4.1.1. Angiotensin II receptor blockers: azilsartan - EDARBI (CAP), NAP; irbesartan - APROVEL (CAP); IFIRMASTA (CAP); IRBESARTAN TEVA (CAP); IRBESARTAN ZENTIVA (CAP); KARVEA (CAP), NAP; irbesartan, hydrochlorothiazide - COAPROVEL (CAP); IFIRMACOMBI (CAP); IRBESARTAN HYDROCHLOROTHIAZIDE ZENTIVA (CAP); IRBESARTAN/HYDROCHLOROTHIAZIDE TEVA (CAP); KARVEZIDE (CAP), NAP; telmisartan - KINZALMONO (CAP), MICARDIS (CAP), PRITOR (CAP), TELMISARTAN ACTAVIS (CAP), TELMISARTAN TEVA PHARMA (CAP), TOLURA (CAP), NAP; telmisartan, amlodipine – TWYNSTA (CAP), NAP; telmisartan, hydrochlorothiazide - ACTELSAR HCT (CAP), KINZALKOMB (CAP), MICARDISPLUS (CAP), PRITORPLUS (CAP), TOLUCOMBI (CAP), NAP; valsartan, sacubitril – ENTRESTO (CAP), NEPARVIS (CAP); valsartan, amlodipine – COPALIA (CAP), DAFIRO (CAP), EXFORGE (CAP), NAP; valsartan, amlodipine, hydrochlorothiazide - COPALIA HCT (CAP), DAFIRO HCT (CAP), EXFORGE HCT (CAP), NAP; other fixed-dose combinations containing angiotensin II receptor blockers (NAP)

Applicant(s): Actavis Group PTC ehf. (Actelsar HCT, Telmisartan Actavis), Bayer AG (Kinzalkomb, Kinzalmono, Pritor, PritorPlus), Boehringer Ingelheim International (Micardis, MicardisPlus, Twynsta), KRKA, d.d., Novo mesto (Ifirmacombi, Ifirmasta, Tolucombi, Tolura), Novartis Europharm Limited (Copalia, Copalia HCT, Dafiro, Entresto, Exforge, Exforge HCT, Neparvis), Sanofi Winthrop Industrie (Aprovel, CoAprovel, Karvea, Karvezide), Takeda Pharma A/S (Edarbi), Teva B.V. (Irbesartan Teva, Irbesartan/Hydrochlorothiazide Teva), Teva Pharmaceuticals Europe B.V.(Telmisartan Teva Pharma), Zentiva, k.s. (Irbesartan Hydrochlorothiazide Zentiva, Irbesartan Zentiva), various

PRAC Rapporteur: Martin Huber

Scope: Signal of intestinal angioedema

EPITT 20104 – New signal

Background

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

[2] 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

Angiotensin II receptor blockers (ARB) are indicated for the treatment of hypertension, heart failure or asymptomatic left ventricular dysfunction, secondary prevention of coronary artery disease, diabetes mellitus and diabetic nephropathy, subject to certain conditions.

During routine signal detection activities, a signal of intestinal angioedema was identified by EMA, based on 45 cases retrieved from EudraVigilance for olmesartan, olmesartan/hydrochlorotiazide, olmesartan/amlodipine, candesartan, irbesartan, losartan, valsartan and valsartan/sacubitril. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by PRAC.

Discussion

Having considered the available evidence from case reports in EudraVigilance, also taking into account that intestinal angioedema is known to be associated with other renin-angiotensin acting agents such as angiotensin-converting enzymes inhibitors (ACEIs), PRAC agreed that intestinal angioedema can be considered a class-effect for angiotensin II receptor blockers and that further evaluation of the signal is warranted.

PRAC appointed Martin Huber as Rapporteur for the signal.

Summary of recommendation(s)

- The MAHs for azilsartan (Takeda), candesartan (Cheplapharm Arzneimittel), eprosartan (Viatris Healthcare), irbesartan (Sanofi Winthrop, Teva, Novo Mesto, Zentiva), losartan (Organon), olmesartan (Menarini), telmisartan (Boehringer, Bayer, Actavis Group, Krka, Novo Mesto) and valsartan (Novartis, Mylan) should submit to EMA, by 28 August 2024, their comments on the proposed updates of the product information, including the frequency calculation of this undesirable effect.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.1.2. Atezolizumab – TECENTRIQ (CAP); Avelumab – BAVENCIO (CAP); Cemiplimab – LIBTAYO (CAP); Dostarlimab – JEMPERLI (CAP); Durvalumab -IMFINZI (CAP); Ipilimumab – YERVOY (CAP); Nivolumab - OPDIVO (CAP), OPDUALAG (CAP); Pembrolizumab – KEYTRUDA (CAP); Retifanlimab - ZYNYZ (CAP); Tislelizumab – TEVIMBRA (CAP); Tremelimumab - IMJUDO (CAP)

Applicant(s): AstraZeneca AB (Imfinzi, Imjudo), Beigene Ireland Limited (Tevimbra), Bristol-Myers Squibb Pharma EEIG (Yervoy, Opdivo, Opdualag), GlaxoSmithKline (Ireland) Incyte Biosciences Distribution B.V. (Zynyz), Limited (Jemperli), Merck Europe B.V. (Bavencio), Merck Sharp & Dohme B.V. (Keytruda), Regeneron Ireland Designated Activity (Libtayo), Roche Registration GmbH (Tecentriq)

PRAC Rapporteur: Bianca Mulder

Scope: Signal of thrombotic microangiopathy

EPITT 20090 – New signal

Background

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

During routine signal detection activities, a signal of thrombotic microangiopathy was identified by EMA, based on 19 cases related to ipilimumab, pembrolizumab, atezolizumab, durvalumab, avelumab and nivolumab retrieved from EudraVigilance, literature and study reports. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by PRAC.

Discussion

Having considered the available evidence from case reports in EudraVigilance and the literature, PRAC agreed that further evaluation on the signal of thrombotic microangiopathy following administration of immune-check inhibitors is warranted.

PRAC appointed Bianca Mulder as Rapporteur for the signal.

Summary of recommendation(s)

- The MAHs for Opdivo and Opdualag (nivolumab), Keytruda (pembrolizumab), Imfinzi (durvalumab), Bavencio (avelumab), Tecentriq (atezolizumab), Libtayo (cemiplimab), Jemperli (dostarlimab), Tevimbra (tislelizumab), Yervoy (ipilimumab), Imjudo (tremelimumab) and ZYNYZ (retifanlimab) should submit by 30 September 2024 a cumulative review of cases of thrombotic microangiopathy, including data from clinical trials, post-marketing setting and literature, along with a discussion on the possible biological plausibility and mechanism of this association and on the need to update the product information and/or the RMP.
- A 90-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.1.3. Paracetamol (NAP); fixed dose combinations containing paracetamol (NAP)

Applicant: various

PRAC Rapporteur: Jean-Michel Dogné

Scope: Signal of high anion gap metabolic acidosis (HAGMA) due to pyroglutamate acidosis

EPITT 20105 – New signal

Background

Paracetamol is a non-opioid analgesic and antipyretic and it is indicated for the treatment of headache, toothache, cold-related fever, menstrual cramps, muscle and joint pain, as well as for rheumatic pain, hyperpyrexia, and also for chronic pain and other conditions that require continuous dosing.

During routine signal detection activities, a signal of high anion gap metabolic acidosis (HAGMA) due to pyroglutamate acidosis was identified by EMA, based on 71 case reports from EudraVigilance and literature. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by PRAC.

Discussion

Having considered the available evidence in the literature and in EudraVigilance, PRAC considered that there is sufficient evidence to establish a causal association between paracetamol and high anion gap metabolic acidosis (HAGMA) due to pyroglutamate acidosis

and proposed to update the product information of paracetamol-containing products (single-ingredient and fixed dose combination).

PRAC appointed Jean-Michel Dogné as Rapporteur for the signal.

Summary of recommendation(s)

- The MAH(s) for paracetamol-containing products should submit to EMA, within 60 days, their comments on the proposed amendments to the product information.

4.2. Signals follow-up and prioritisation

4.2.1. Acetazolamide (NAP)

Applicant: various

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of pulmonary oedemas

EPITT 20050 – Follow-up to March 2024

Background

For background information, see PRAC minutes March 2024.

The MAH Amdipharm Limited replied to the request for information on the signal of pulmonary oedemas and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence in EudraVigilance and in the literature, as well as the data submitted by the MAH, PRAC concluded that there is sufficient evidence to establish a causal association between acetazolamide and non-cardiogenic pulmonary oedemas. Therefore, the product information should be updated to add non-cardiogenic pulmonary oedema as a warning and as an undesirable effect with a frequency 'not known'.

Summary of recommendation(s)

- The MAHs for acetazolamide-containing products should submit to national competent authorities, within 60 days, a variation to amend the product information[3].

4.2.2. Bumetanide (NAP)

Applicant: various

PRAC Rapporteur: Mari Thorn

Scope: Signal of toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS)

EPITT 20033 – Follow-up to March 2024

Background

For background information, see PRAC minutes March 2024.

[3] Update of sections 4.4 and 4.8. The package leaflet is updated accordingly.

The MAH Karo Pharma AB replied to the request for information on the signal of toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS) and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence in EudraVigilance, including the data submitted by the MAH, PRAC concluded that there is sufficient evidence to establish a causal association between bumetanide and toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS). Therefore, the product information should be updated to add toxic epidermal necrolysis (TEN) and Stevens Johnson syndrome (SJS) as warning and as undesirable effects with a frequency 'not known'.

Summary of recommendation(s)

- The MAHs for bumetanide-containing products should submit to national competent authorities, within 60 days, a variation to amend[4] the product information.

4.2.3. Ceftriaxone (NAP)

Applicant: various

PRAC Rapporteur: Zane Neikena

Scope: Signal of precipitation when administered with calcium-containing solutions in infants between 29 days and 1 year

Action: For adoption of PRAC recommendation

EPITT 1964 – Follow-up to February 2024

Background

For background information, see PRAC minutes February 2024.

The MAH for the originator ceftriaxone-containing product (Roche) replied to the request for information on the signal of precipitation when administered with calcium-containing solutions in infants between 29 days and 1 year and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence in EudraVigilance, scientific literature, non-clinical, clinical and non-interventional studies, and the responses submitted by the MAH Roche, PRAC concluded that the current evidence is insufficient to establish a causal relationship between ceftriaxone and precipitation when administered with calcium-containing solutions in infants between 29 days and 1 year, to further warrant an update to the product information and/or risk management plan at present. No further action is deemed warranted at this stage.

Summary of recommendation(s)

- In the next PSUR, the MAHs of ceftriaxone-containing products should continue to monitor this topic (with data lock point 26/05/2028).

[4] Update of sections 4.4 and 4.8. The package leaflet is updated accordingly.

4.2.4. Dupilumab – DUPIXENT (CAP) – EMEA/H/C/004390/SDA/014

Applicant: Sanofi Winthrop Industrie

PRAC Rapporteur: Kimmo Jaakkola

Scope: Signal of thrombocytopenia

EPITT 20054 – Follow-up to March 2024

Background

For background information, see PRAC minutes March 2024.

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

Discussion

Having considered the available evidence in EudraVigilance, literature and the responses submitted by the MAH, PRAC concluded that the current evidence is insufficient to establish a causal relationship between dupilumab and thrombocytopenia to further warrant an update to the product information and/or risk management plan at present. No further action is deemed warranted at this stage.

Summary of recommendation(s)

- In the next PSUR, the MAH of Dupixent (dupilumab) should provide a review of cases of thrombocytopenia, including data primarily from clinical studies but also from other data sources. Additionally, PRAC supported the implementation of targeted follow up questionnaires in order to collect further information on thrombocytopenia.
- PRAC will assess the cumulative review within the PSUR procedure PSUSA/00010645/202503.

4.2.5. Glofitamab – COLUMVI (CAP) - EMEA/H/C/005751/SDA/006

Applicant: Roche Registration GmbH

PRAC Rapporteur: Jana Lukacisinova

Scope: Signal of immune effector cell-associated neurotoxicity syndrome

EPITT 20058 – Follow-up to March 2024

Background

For background information, see PRAC minutes March 2024.

The MAH replied to the request for information on the signal of immune effector cell-associated neurotoxicity syndrome and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence in EudraVigilance, including the responses submitted by the MAH, the available clinical trial data and the class effect of same-in-class drugs, PRAC agreed that the current evidence is sufficient to establish a causal association between glofitamab and immune effector cell-associated neurotoxicity syndrome (ICANS). Therefore, the product information should be updated to add immune effector cell-associated

neurotoxicity syndrome (ICANS) as a warning and as an undesirable effect with a frequency 'common' (for all grades) and 'uncommon' (for Grade 3-4). In addition, the product information should be updated to reflect that the patients should be monitored for ICANS following glofitamab administration and that glofitamab has major influence on the ability to drive and use machines due to symptoms related to ICANS.

Summary of recommendation(s)

- The MAH for Columvi (glotfitamab) should submit to EMA, within 60 days, a variation to amend the product information[5].

4.2.6. Glucagon-like peptide-1 (GLP-1) receptor agonists: dulaglutide – TRULICITY (CAP) - EMEA/H/C/002825/SDA/015.1; exenatide – BYDUREON (CAP) - EMEA/H/C/002020/SDA/031.1, BYETTA (CAP) - EMEA/H/C/000698/SDA/051.1; insulin degludec, liraglutide – XULTOPHY (CAP) - EMEA/H/C/002647/SDA/003.1; liraglutide – SAXENDA (CAP) - EMEA/H/C/003780/SDA/021.1, VICTOZA (CAP) – EMEA/H/C/001026/SDA/041.1; insulin glargine, lixisenatide – SULIQUA (CAP) - EMEA/H/C/004243/SDA/010.1; lixisenatide - LYXUMIA (CAP) - EMEA/H/C/002445/SDA/018.1; semaglutide – OZEMPIC (CAP) - EMEA/H/C/004174/SDA/009.1, RYBELSUS (CAP) - EMEA/H/C/004953/SDA/014.1, WEGOVY (CAP) - EMEA/H/C/005422/SDA/008.1; tirzepatide – MOUNJARO (CAP) - EMEA/H/C/005620/SDA/006.1

Applicant: AstraZeneca AB (Bydureon, Byetta), Eli Lilly Nederland B.V. (Trulicity, Mounjaro), Novo Nordisk A/S (Ozempic, Rybelsus, Saxenda, Victoza, Wegovy, Xultophy), Sanofi Winthrop Industrie (Lyxumia, Suliqua)

PRAC Rapporteur: Mari Thorn

Scope: Signal of aspiration and pneumonia aspiration

EPITT 19974 – Follow-up to March 2024

Background

For background information, see PRAC minutes March 2024.

The MAHs for semaglutide (Ozempic, Rybelsus, Wegocy), dulaglutide (Trulicity), exenatide (Bydureon, Byetta), insulin degludec, liraglutide (Xultophy), liraglutide (Saxenda, Victoza), insulin glargine, lixisenatide (Suliqua), lixisenatide (Lyxumia), tirzepatide (Mounjaro) replied to the request for information on the signal of aspiration and pneumonia aspiration and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence from case reports in EudraVigilance, literature, as well as the responses submitted by the MAHs, PRAC concluded that, although a causal association could not be established between GLP-1 receptor agonists and aspiration, the known delayed gastric emptying could increase the risk for aspiration and pneumonia aspiration in association with anaesthesia and deep sedation during concomitant administration with GLP-1 receptor agonists. Therefore, the product information of GLP-1 receptor agonists should be updated to add a warning regarding the fact that cases of pulmonary aspiration have been reported in patients receiving GLP-1 receptor agonists undergoing general anaesthesia or deep sedation.

[5] Update of sections 4.2, 4.4, 4.7 and 4.8. The package leaflet and Annex II-D are updated accordingly.

Summary of recommendation(s)

- The MAHs for semaglutide, liraglutide, insulin degludec/liraglutide, dulaglutide, lixisenatide, insulin glargine/lixisenatide, exenatide, tirzepatide-containing products should submit to EMA, within 60 days, a variation to amend the product information[6].

4.2.7. Human Papillomavirus 9-valent Vaccine (Recombinant, adsorbed) - GARDASIL 9 (CAP) - EMEA/H/C/003852/SDA/013; human papillomavirus vaccine [types 6, 11, 16, 18] (Recombinant, adsorbed) - GARDASIL (CAP) - EMEA/H/C/003852/SDA/090

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Jean-Michel Dogné

Scope: Signal of granuloma

EPITT 20046 – Follow-up to March 2024

Background

For background information, see PRAC minutes March 2024.

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

Discussion

Having considered the available evidence from EudraVigilance and literature, as well as the responses submitted by the MAH, PRAC concluded that there is sufficient evidence to establish a causal association between Human Papillomavirus 9-valent vaccine and granuloma. Therefore, the product information should be updated to add injection site nodule as an undesirable effect with a frequency 'uncommon'.

Summary of recommendation(s)

- The MAH for Gardasil and Gardasil 9 should submit to EMA, within 60 days, a variation to amend the product information[7].

4.3. Variation procedure(s) resulting from signal evaluation

See Annex I 14.3.

5. Risk management plans (RMPs)

5.1. Medicines in the pre-authorisation phase

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

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

[6] Update of section 4.4 of the SmPC. The package is updated accordingly.
[7] Update of section 4.8. The package is updated accordingly.

See also Annex I 15.1.

5.1.1. Eplontersen - (CAP MAA) - EMEA/H/C/006295, Orphan

Applicant: AstraZeneca AB

Scope (pre D-180 phase): Indicated for the treatment of adult patients with polyneuropathy associated with hereditary transthyretin-mediated amyloidosis (ATTRv).

5.1.2. Marstacimab - (CAP MAA) - EMEA/H/C/006240, Orphan

Applicant: Pfizer Europe Ma EEIG

Scope (pre D-180 phase): Indicated for routine prophylaxis of bleeding episodes in patients with haemophilia A or haemophilia B

5.1.3. Mozafancogene autotemcel - (CAP MAA) - EMEA/H/C/005537, PRIME, Orphan

Applicant: Rocket Pharmaceuticals B.V., ATMP

Scope (pre D-120 phase): Treatment of paediatric patients with Fanconi Anaemia Type A

5.1.4. Obecabtagene autoleucel - (CAP MAA) - EMEA/H/C/005907, PRIME, Orphan

Applicant: Autolus GmbH, ATMP

Scope (pre D-120 phase): Treatment of patients with relapsed or refractory B cell precursor acute lymphoblastic leukaemia (ALL)

5.1.5. Odevixibat - (CAP MAA) - EMEA/H/C/006462

Scope (pre D-180 phase): Treatment of cholestatic pruritus in Alagille syndrome (ALGS)

5.1.6. Sargramostim - (CAP MAA) - EMEA/H/C/006411

Scope (pre D-120 phase, accelerated assessment): Treatment for exposure to myelosuppressive doses of radiation

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

See also Annex I 15.2.

5.2.1. Alpelisib - PIQRAY (CAP) - EMEA/H/C/004804/II/0024

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Bianca Mulder

Scope: Submission of an updated RMP version 8.0 in order to remove the PASS CBYL719C2404 (Cat. 3) RMP commitment (MEA 002)

Background

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

PRAC is evaluating a type II variation procedure for Piqray, a centrally authorised medicine containing alpelisib, to update the RMP to reflect the removal of the PASS CBYL719C2404 listed as category 3 study in the RMP. PRAC is responsible for adopting an outcome based on the assessment report from the PRAC Rapporteur, to be further considered at the level of CHMP, responsible for adopting an opinion on this variation.

S**ummary of advice**

- The RMP for Piqray (alpelisib) in the context of the variation procedure under evaluation by PRAC and CHMP could be considered acceptable provided that an update to RMP version 8.0 is submitted.
- PRAC agreed with the removal of the category 3 study CBYL719C2404 from the RMP, as well as with the inclusion of a specific follow-up questionnaire to address the risk of hyperglycaemia, pending the response to the request for supplementary information (RSI).

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

See also Annex I 15.3.

5.3.1. Naloxone - NYXOID (CAP) - EMEA/H/C/004325/II/0019

Applicant: Mundipharma Corporation (Ireland) Limited

PRAC Rapporteur: Liana Martirosyan

Scope: Submission of the interim report from the PAES MR903-9501 listed as an obligation in the Annex II, supported by Real World Evidence from literature and European Take-Home Naloxone programs (THN) demonstrating the effectiveness of Nyxoid in a real-world setting. Study MR903-9501 is a non-interventional multi-national, prospective, mixed methods study of the effectiveness of naloxone (including intranasal Nyxoid) administration by lay people in reversing opioid overdose. The Annex II and the RMP version 3.0 are updated accordingly. In addition, the MAH took the opportunity to introduce minor administrative changes to the package leaflet.

Background

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

CHMP is evaluating a type II variation for Nyxoid, a centrally authorised product containing naloxone, to submit an interim report for the study MR903-9501 listed as a condition to the marketing authorisation in the Annex II-D of the PI, including an updated RMP. PRAC is responsible for providing advice to CHMP on the necessary updates to the RMP to support this procedure.

Summary of advice

- The RMP for Nyxoid (naloxone) in the context of the variation procedure under evaluation by CHMP could be considered acceptable provided that an update to RMP version 3.0 is submitted.
- The MAH should provide further clarification regarding the enhanced digital access to the additional RMMs for patients/carers. PRAC considered that the package leaflet and the outer packaging should be updated to incorporate a QR code that directly links to the additional RMMs for patients/carers (including the training video). The MAH should provide a proposal for the QR code and wordings of scanning instructions. In addition, the MAH should provide the results of the data analyses for several secondary outcomes in order to draw final conclusions on the effectiveness of the RMMs in place.
- The responses should be submitted in a 60-day timetable.

6. Periodic safety update reports (PSURs)

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

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

See also Annex I 16.1.

6.1.1. Budesonide[8] - KINPEYGO (CAP) - PSUSA/00011007/202312

Applicant: STADA Arzneimittel AG

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Evaluation of a PSUSA procedure

Background

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Kinpeygo, a centrally authorised medicine containing budesonide 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 Kinpeygo (budesonide) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add hypokalaemia as an undesirable effect with a frequency 'very common'. Therefore, the current terms of the marketing authorisation(s) should be varied[9].

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.

[8] For centrally authorised products indicated for primary immunoglobulin A nephropathy only
[9] 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.

6.1.2. COVID-19 Vaccine (ChAdOx1-S [recombinant]) - VAXZEVRIA[10] - PSUSA/00010912/202312

Applicant: AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

Background

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Vaxzevria, a centrally authorised medicine containing COVID-19 Vaccine (ChAdOx1-S [recombinant]).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, PRAC agreed that the product information should be updated to add erythema multiforme and acute disseminated encephalomyelitis (ADEM) as undesirable effects with a frequency 'not known', as well as to add ADEM as a warning.

However, no PRAC recommendation was adopted due to the withdrawal of the marketing authorisation of VAXZEVRIA (COVID-19 Vaccine (ChAdOx1-S [recombinant]), recombinant). Therefore, no further PSUR should be submitted.

6.1.3. Enfortumab vedotin - PADCEV (CAP) - PSUSA/00010989/202312

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Eva Jirsová

Scope: Evaluation of a PSUSA procedure

Background

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Padcev, a centrally authorised medicine containing enfortumab vedotin 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 Padcev (enfortumab vedotin) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add a warning on serious infections, to add sepsis and adverse reaction infusion related reaction as undesirable effects with a frequency 'common', as well as diabetic ketoacidosis with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[11].
- In the next PSUR, the MAH should provide a cumulative review of urinary tract infections, pyelonephritis and pneumonia, as well as of opportunistic infections and of new onset of diabetes mellitus including cases reported from the clinical trials, the post-marketing period and the literature. The MAH should also provide separate cumulative

[10] Withdrawn Marketing Authorisation in the European Union – Commission Decision dated 27 March 2024
[11] 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.

reviews of thrombocytopenia and pancytopenia including cases reported from post marketing sources, from clinical trials and the literature, as well as to propose any update of the risk minimisation measures as warranted. In addition, the MAH should closely monitor urticaria, angioedema, acute generalized exanthematous pustulosis (AGEP) and drug reaction with eosinophilia and systemic symptoms (DRESS) as a part of the important identified risk of skin reactions, as well as to present and discuss the case reporting failure to thrive which was mentioned in the section of embryo-foetal toxicity, and to provide a review of the new fatal or life-threatening cases or of the cases with new significant safety information obtained during the follow-up reporting hyperglycaemia/diabetes mellitus/diabetic ketoacidosis in patients without medical history of diabetes mellitus. Finally, the MAH should remove infusion related-reactions from the list of safety concerns for the purposes of PSUR.

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. Mosunetuzumab - LUNSUMIO (CAP) - PSUSA/00010999/202312

Applicant: Roche Registration GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

Background

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Lunsumio, a centrally authorised medicine containing mosunetuzumab 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 Lunsumio (mosunetuzumab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add immune effector cell-associated neurotoxicity syndrome (ICANs) as a warning and as an undesirable effect with a frequency 'uncommon', to provide guidance on treatment of ICANS, and dose adaptations for Lunsumio (mosunetuzumab), should they occur, as well as to reflect appropriate risk minimisation measures regarding the driving and use of heavy or potentially dangerous machines. Therefore, the current terms of the marketing authorisation(s) should be varied[12].
- In the next PSUR, the MAH should continue to closely monitor ICANS, including all available cumulative and new data from clinical trials, post-marketing and literature on Grade 3 ICANS, ICANS and related events that started outside of the medical facility, as well as actions taken and outcomes, and provide an evaluation on clinical symptoms and a proposal on an update of the PI as warranted.

[12] Update of SmPC sections 4.2, 4.4, 4.7 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion.

- The MAH should also update the RMP to add ICANS as important identified risk, as well as the pharmacovigilance plan and risk minimisation measures accordingly, including an update on the patient card in Annex II.

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

6.1.5. Roxadustat - EVRENZO (CAP) - PSUSA/00010955/202312

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Anna Mareková

Scope: Evaluation of a PSUSA procedure

Background

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Evrenzo (roxadustat) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the warning on thrombotic vascular events and add blood copper increased as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[13].
- In the next PSUR, the MAH should closely monitor and provide review of cases of ischemic central nervous system vascular conditions, with detailed description of the cases including information on Hb levels and time to onset.

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

6.1.6. Ustekinumab - STELARA (CAP) - PSUSA/00003085/202312

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

Background

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

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Stelara (ustekinumab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to revise a warning on administration of live vaccines in infants exposed to ustekinumab in utero. Therefore, the current terms of the marketing authorisation(s) should be varied[14].
- In the next PSUR, the MAH should provide a cumulative review of non-melanoma skin cancer including cutaneous squamous cell cancer, basal cell cancer and merkel cell carcinoma and discuss the need to update the product information to strengthen the information and warnings concerning NMSC as warranted. In addition, the MAH should provide a cumulative review of autoimmune hepatitis, of demyelinating events, of dilated cardiomyopathy, of endometrial cancer, and of small for gestational age including a discussion to update the product information as warranted, of serious hypersensitivity reactions including anaphylaxis and angioedema as well as serious infusions related reactions, with a particular focus on the effectiveness of the current risk minimisation measures.
- The MAH should also submit within 6 months as part of a post-authorisation measure (LEG), an updated cumulative review of severe depression/suicidal ideation cases, using an appropriate SMQ (Depression and suicide/self-injury) including data from clinical trial, registry, post-marketing, literature and other sources.

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

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

See Annex I 16.2.

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

See also Annex I 16.3.

6.3.1. Atomoxetine (NAP) - PSUSA/00000262/202311

Applicant(s): various

PRAC Lead: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

Background

[14] Update of SmPC sections 4.4, 4.5 and 4.6. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion

Atomoxetine is a selective norepinephrine reuptake inhibitor and is indicated for the treatment of attention-deficit/hyperactivity disorder (ADHD) in children 6 years of age and older, adolescents, and adults.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing atomoxetine 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 atomoxetine-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add a warning about serotonin syndrome, amend the warning about aggressive behaviour, hostility or emotional lability to include information from post-marketing about homicidal ideation in paediatric patients, and to add bruxism as an undesirable effect with the frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[15].
- In the next PSUR, the MAHs should provide a cumulative review of cases of atomoxetine overdose alone separating the fatal from the non-fatal cases and discussing the need to update the PI as warranted, as well as cumulative reviews of cases of seizures in which no other medicine than atomoxetine was being received concomitantly, of cases related to tonic-clonic seizures or terms related (as tonic-seizures), of cases regarding the preferred terms (PTs) related to cerebrovascular accidents in paediatric patients, and of tinnitus cases. In addition, the MAHs should closely monitor cases of pancreatitis and cases resembling potential pancreatitis like amylase increased reports, cases of ptosis and Bell's palsy, of events related to suicide analysing also the events of suicide attempts and completed suicide separately from the event of suicidal ideation, and to provide an in-detail assessment of cardiovascular events, others than the ones already described in the product information, as specific types of arrhythmias, differentiating amongst paediatric patients and adult patients. The off-label use and the fatalities should be detailed in the next PSURs as well, the exposure information should be presented differentiating between adults and paediatric patients (children and adolescents), and the number of cases associated to ADRs as well as the pattern of ADRs most frequently associated with medication errors.

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. Cefpodoxim (NAP) - PSUSA/00000604/202312

Applicant(s): various

PRAC Lead: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

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

Background

Cefpodoxim is a third-generation cephalosporin with a confirmed activity against the several causative pathogens of respiratory tract, indicated for the treatment of infections caused by bacterial organisms sensitive to cefpodoxime in adults and children, including upper respiratory tract infections of the ear nose throat (ENT) like tonsillitis, pharyngitis, acute sinusitis, acute otitis media (in children only), lower respiratory tract infections (LRTIs) like acute bronchitis, pneumonia, superinfection of chronic obstructive airways disease (COAD), urinary tract infections (UTIs) like uncomplicated lower and/or upper UTI, uncomplicated gonococcal urethritis, and skin and soft tissue infections (SSTIs).

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing cefpodoxim 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 cefpodoxim-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add a warning regarding severe cutaneous adverse reactions (SCARs) and to add acute generalized exanthematous pustulosis (AGEP) and drug reaction with eosinophilia and systemic symptoms (DRESS) as undesirable effects with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[16].
- In the next PSUR, all MAHs should continue to closely monitor cases of rhabdomyolysis, while the MAHs Sandoz and Daiichi Sankyo should also closely monitor cases of seizures and perform a critical review of data from all sources to further explore the potential role of cefpodoxim in seizures.

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

6.3.3. Codeine, ibuprofen (NAP) - PSUSA/00000850/202312

Applicant(s): various

PRAC Lead: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

Background

Codeine is a centrally acting weak narcotic analgesic. Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID) with analgesic, antipyretic and anti-inflammatory properties. Codeine/ibuprofen is a fixed dose combination indicated for the symptomatic treatment of mild to moderate pain in adults and in patients over 12 years of age as warranted of the product, as well as for the treatment of acute moderate pain which cannot be relieved by other analgesics such as paracetamol or ibuprofen alone.

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

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing codeine/ibuprofen 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 codeine/ibuprofen-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the existing warning on the risk of drug dependency/drug abuse, to add a warning about central sleep apnoea (CSA), hyperalgesia, Kounis syndrome and hepatobiliary disorders. In addition, the product information should be amended to add drug dependence, as well as Kounis syndrome, pancreatitis and sphincter of Oddi dysfunction as undesirable effects with frequency 'not known'. The product information should also be amended to highlight the need to store the fixed dose combination in a safe and secure place and to add the interactions with gabapentinoids. Therefore, the current terms of the marketing authorisation(s) should be varied[17].
- In the next PSUR, all MAHs should provide cumulative reviews including a discussion on the need to update the product information as warranted on haemorrhage or bleeding (except gastro-intestinal) including cases resulting from drug interaction between ibuprofen and other drugs known for their haemorrhagic effect (including SSRIs), on intestinal diaphragm-like strictures, fixed drug eruption, tubulointerstitial nephritis, symmetrical drug related intertrigous and flexural exanthema, NSAIDs and hormonal contraception, hallucinations (excluding sleep-related), complications of streptococcal infections including those with short-term treatment of codeine/ibuprofen, hypothermia, serotonin syndrome when codeine is combined with drugs known to induce serotonin syndrome, myasthenia gravis and the risk of exacerbated respiratory depression.

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

6.3.4. Dydrogesterone, estradiol (NAP) - PSUSA/00001276/202312

Applicant(s): various

PRAC Lead: Nathalie Gault

Scope: Evaluation of a PSUSA procedure

Background

17β-estradiol (E2) is chemically and biologically identical to endogenous human estradiol. Dydrogesterone is an orally active progestogen having an activity comparable to parenterally administered progesterone. Estradiol/dydrogesterone combination is a fixed dose combination with active ingredients 17β-estradiol (as hemihydrate) and dydrogesterone, indicated for the treatment of hormone replacement therapy (HRT) for estrogen deficiency symptoms in postmenopausal women at least 6 or 12 months since last menses and as prevention of osteoporosis in postmenopausal women at high risk of future fractures who are

[17] 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.

intolerant of, or contraindicated for, other medicinal products approved for the prevention of osteoporosis, as warranted.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing dydrogesterone/estradiol 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 dydrogesterone/estradiol-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add a contraindication and a warning regarding meningioma. Therefore, the current terms of the marketing authorisation(s) should be varied[18].
- In the next PSUR, the MAH should add the risk of meningioma as an important identified risk to the list of the safety concerns.

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

6.3.5. Glatiramer (NAP) - PSUSA/00001529/202311

Applicant(s): various

PRAC Lead: Karin Erneholm

Scope: Evaluation of a PSUSA procedure

Background

Glatiramer acetate is a polypeptide (a random polymer of L-alanine, L-glutamic acid, L-lysine, and L-tyrosine) that has some structural resemblance to myelin basic protein, indicated for the treatment of patients with relapsing forms of multiple sclerosis (MS).

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing glatiramer 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 glatiramer-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add a warning regarding long latency anaphylactic reactions and to add anaphylactic reaction as an undesirable effect with a frequency 'uncommon'. Therefore, the current terms of the marketing authorisation(s) should be varied[19]. Moreover, PRAC agreed on the distribution of a direct healthcare professional communication (DHPC) together with a communication

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

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

plan in order to increase awareness on the fact that anaphylactic reactions may occur months and years after treatment initiation and that symptoms of post injection reactions may overlap with anaphylactic reactions.

- In the next PSUR, all MAHs should provide a cumulative review of cases of meningitis aseptic, an updated characterisation of post-injection reactions, along with discussions on the need to update the PI as warranted. Furthermore, all MAHs should provide an analysis and evaluation of anaphylactic reactions and anaphylactic reactions occurring with a long latency (>31 days) after administration/initiation of treatment with the aim of identifying a potential subpopulation at certain risk and/or risk factors of developing anaphylactic reactions including a discussion on the possible mechanism of action and any proposal for an update of the product information and further risk minimisation measures as warranted. Finally, all MAHs should add long latency anaphylaxis as an important identified risk in the PSUR list of safety concerns.

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.

6.3.6. Hydroxycarbamide[20] (NAP) - PSUSA/00009182/202312

Applicant(s): various

PRAC Lead: Petar Mas

Scope: Evaluation of a PSUSA procedure

Background

Hydroxycarbamide is classified as other antineoplastic agent due to its cytotoxic properties indicated for the treatment of chronic myeloid leukaemia (CML), essential thrombocythemia (ET), polycythaemia vera (PV), primary squamous cell (epidermoid) carcinomas of the head and neck (excluding the lip) and carcinoma of the cervix, concomitantly with irradiation therapy, sickle cell anaemia (SCA), idiopathic myelofibrosis, as warranted.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing hydroxycarbamide 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 hydroxycarbamide-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add a warning regarding interference with continuous glucose monitoring systems. Therefore, the current terms of the marketing authorisation(s) should be varied[21].
- In the next PSUR, all MAHs should provide a review of cases of splenomegaly and splenectomy and of myelodysplastic syndrome from all available sources including but not limited to clinical trials data, post-marketing data and literature sources for

[20] Except for centrally authorised product
[21] Update of SmPC section 4.4. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position.

myeloproliferative indications, as well as of interval cases reporting amenorrhea including data from the MAHs' internal database, literature sources, clinical trials and any other source. All MAHs should also closely monitor cases reporting seizures and hyponatremia.

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

6.3.7. Methylprednisolone (NAP) - PSUSA/00002026/202311

Applicant(s): various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

Background

Methylprednisolone is a glucocorticoid with potent anti-inflammatory and immunosuppressive effects, indicated in many clinical conditions among which severe erythema multiforme (Stevens-Johnson syndrome), rheumatoid arthritis, allergic states, bronchial asthma, angioneurotic oedema, anaphylaxis, ulcerative colitis, Crohn's disease, aspiration of gastric contents, fulminating or disseminated tuberculosis (with appropriate anti-tuberculous chemotherapy), cerebral oedema secondary to cerebral tumour, acute exacerbations of multiple sclerosis superimposed on a relapsing-remitting background, as warranted.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing methylprednisolone 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 methylprednisolone-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add a warning regarding thyrotoxic periodic paralysis. Therefore, the current terms of the marketing authorisation(s) should be varied[22].
- In the next PSUR, all MAHs should provide cumulative reviews of rhabdomyolysis cases including a discussion on the need to update the product information as warranted, and of fistula including a literature review. In addition, the MAH Leo Pharma should provide a cumulative review of cases of steroid withdrawal syndrome for topical use products. Finally, the MAHs Dermapharma, Fidia Farmaceutici, Hikma farmaceutica and Pfizer should closely monitor and provide a cumulative review of cases of reversible cerebral vasoconstriction syndrome related to infusions and tablets.

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

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

6.3.8. Salicylic acid[23] (NAP) - PSUSA/00002680/202312

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

Salicylic acid is a keratolytic agent indicated for local treatment of psoriasis capitis, seborrheic dermatitis capitis, pityriasis sicca, for the removal of corns, calluses, warts and partridge's eye, as well as in the symptomatic treatment in case of blepharitis, non-specific conjunctivitis, ocular irritations due to dust, smog or sun and in ocular irrigation in case of conjunctival irritation, as warranted.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing salicylic acid 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 salicylic acid-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add/amend a warning regarding the use in pregnancy for salicylic acid-containing medicinal products for topical and ophthalmic use, if similar or stricter information regarding use in pregnancy is not already included. For products for cutaneous use as 10% solution or gel on the scalp, the PI should also be amended to add a contraindication for use during the third trimester of pregnancy. Therefore, the current terms of the marketing authorisation(s) should be varied[24].
- In the next PSUR, all MAHs should include a brief statement whether cases of overdose, abuse, misuse, off-label use or use in paediatric or elderly population were identified, as well as to discuss the relevance of the wording on fertility for oral and intravenous acetylsalicylic acid products for topical salicylic acid products, taking into account potential systemic exposure after treatment in the intended indication, the recommended dose and duration of treatment.

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.

6.3.9. Terazosin (NAP) - PSUSA/00002895/202311

Applicant(s): various

PRAC Lead: Liana Martirosyan

Scope: Evaluation of a PSUSA procedure

[23] Topical use only

[24] Update of SmPC sections 4.4 and 4.6. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position.

Background

Terazosin is an alpha-1-adrenoceptor antagonists indicated for symptoms with benign prostatic hyperplasia and/or hypertension.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing terazosin 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 terazosin-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add nasal congestion as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[25].
- In the next PSUR, all MAHs should remove all risks from the PSUR safety concerns as this are now well-described and routine pharmacovigilance will apply.

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

6.4. Follow-up to PSUR/PSUSA procedures

None

6.5. Variation procedure(s) resulting from PSUSA evaluation

See also Annex I 16.5.

6.5.1. Naltrexone hydrochloride, bupropion hydrochloride - MYSIMBA (CAP) - EMEA/H/C/003687/II/0063

Applicant: Orexigen Therapeutics Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: To update sections 4.3, 4.4 and 4.5 of the SmPC and streamline the relevant wording on opioids following the assessment of PSUSA/00010366/202209 procedure. The package leaflet is updated accordingly. The RMP version 12.9 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.

Following the evaluation of the most recently submitted PSUR(s) for the above-mentioned medicine(s), PRAC requested the MAH to submit a variation to update the product information to streamline the wording on opioids. PRAC is responsible for adopting an

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

outcome based on the assessment report from the PRAC Rapporteur, to be further considered at the level of CHMP, responsible for adopting an opinion on this variation. For further background, see PRAC minutes February 2024 and PRAC minutes May 2024.

Summary of recommendation(s)

- Based on the totality of the available evidence and having considered the totality of information provided by the MAH in writing and during the oral explanation (held on 14 May 2024), PRAC maintained its position to strengthen risk minimisation measures related to the important identified risk of interactions with opioids.
- PRAC also considered that there is a risk of insufficient effects of opioid analgesia, including use as part of anaesthesia in patients treated with Mysimba.
- Due to the potential for clinically relevant effects of this interaction, PRAC recommended changes to the product information including the extension of the contraindications to all patients receiving opioid-containing medication and a warning about the insufficient effects of opioid analgesia, including use as part of anaesthesia, in patients treated with Mysimba. PRAC also recommended amendments to the key elements for the prescriber checklist included in Annex IID.
- In addition, PRAC considered it necessary that a patient card is implemented to inform patients of the need to stop taking Mysimba at least 3 days prior to surgery and for the event of emergency care, and that a DHPC should be disseminated in order to ensure that the new advice on how to minimise the risk of concomitant use of Mysimba with opioids and the respective clinical actions to be taken are timely conveyed to healthcare professionals.
- PRAC considered the proposals for changes to the product information submitted by the MAH. As these proposals were considered insufficient to address the risks identified with the concomitant use of Mysimba with opioid containing products and no agreement could be reached with the MAH on appropriate risk minimisation measures to ensure the safe and effective use of Mysimba, PRAC recommended the refusal of the variation to the terms of the Marketing Authorisation.

6.6. Expedited summary safety reviews[26]

None

7. Post-authorisation safety studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)[27]

See Annex I 17.1.

[26] 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
[27] In accordance with Article 107n of Directive 2001/83/EC

7.2. Protocols of PASS non-imposed in the marketing authorisation(s)[28]

See Annex I 17.2.

7.3. Results of PASS imposed in the marketing authorisation(s)[29]

None

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

See also Annex I 17.4.

7.4.1. Vonicog alfa - VEYVONDI (CAP) - EMEA/H/C/004454/II/0033

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Mari Thorn

Scope: Submission of the final report from study TAK-577-4005 listed as a category 3 PASS in the RMP. This is a non-interventional retrospective cohort study that evaluated the safety of VEYVONDI in real-world clinical practice. The RMP version 5.0 has also been submitted

Background

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

As stated in the RMP of Veyvondi (vonicog alfa), the MAH conducted a non-imposed non-interventional PASS (TAK-577-4005) to estimate the risk of hypersensitivity reactions, thromboembolic events and von Willebrand factor (VWF) inhibitor or FVIII inhibitor formation after treatment with Veyvondi (vonicog alfa), as well as to describe the association of thromboembolic events with use of FVIII concomitantly with Veyvondi (vonicog alfa). The Rapporteur assessed the MAH's final study report in addition to the MAH's answers to the request for supplementary information (RSI). For further background, see PRAC minutes April 2024.

Summary of advice

- Based on the available data, the MAH's responses to the RSI and the Rapporteur's review, PRAC considered that the ongoing variation assessing the final study report could be recommended for approval.
- PRAC agreed to update the product information in order to remove the description of two cases of asymptomatic deep vein thrombosis single as the text no longer reflects the number of reported cases, as well as to update the RMP to remove the completed study TAK-577-4005, while no changes in the safety concerns is needed at the moment since they are continuously followed in an ongoing category 3 study based on the EUHASS registry.

[28] 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
[29] In accordance with Article 107p-q of Directive 2001/83/EC
[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

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

See Annex I 17.5. 17.4.

7.6. Others

See also Annex I 17.6.

7.6.1. Dengue tetravalent vaccine (live, attenuated) - DENGVAXIA (CAP) - EMEA/H/C/004171/MEA 014

Applicant: Sanofi Pasteur

PRAC Rapporteur: Sonja Hrabcik

Scope: From Initial MAA:
Non-Feasibility Assessment PASS DNG00043 (Cat. 3)
Cross-sectional survey to evaluate vaccinator's knowledge and understanding of the restricted indication to only individuals previously infected will be used to measure the effectiveness of risk minimization measures (HCP guide) in Europe

Background

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

As stated in the RMP of Dengvaxia (Dengue tetravalent vaccine (live, attenuated)), as part of measuring the effectiveness of risk minimization measures in Europe, the MAH was required to conduct a non-interventional post-authorisation safety study (DNG00043) to evaluate vaccinator's knowledge and understanding of the safety messages following Dengvaxia (Dengue tetravalent vaccine (live, attenuated)) product information updates on the restricted indication to only individuals previously infected. The Rapporteur assessed the MAH's feasibility assessment of the study.

Summary of advice

- Based on the current available data and the feasibility assessment for the DNG00043 study, PRAC agreed to discontinue the study DNG00043 as it is not considered feasible to achieve its objectives in view of the limited exposure and the limited participating healthcare professionals. However, PRAC noted that the feasibility should be reassessed if any of the parameters such as the marketing status or exposure change.

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 Annex I 18.2.

8.3. Renewals of the marketing authorisation

See also Annex I 18.3.

8.3.1. Solriamfetol - SUNOSI (CAP) - EMEA/H/C/004893/R/0023 (with RMP)

Applicant: Atnahs Pharma Netherlands B.V.

PRAC Rapporteur: Julia Pallos

Scope: 5-year renewal of the marketing authorisation

Background

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

Sunosi (solriamfetol), a centrally authorised medicine containing solriamfetol, was authorised in 2020.

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

Summary of advice

- Based on the review of the available pharmacovigilance data for Sunosi (solriamfetol) and the CHMP Rapporteur's assessment report, PRAC agreed that an additional five-year renewal of the marketing authorisation should be considered if satisfactory responses to the request for supplementary information are provided.
- PRAC considered that the MAH should provide an updated Addendum to Clinical Overview since the following information is missing as required by the Annex II: overview of signals, signal evaluation, and relevant information on patterns of medication errors and potential medication errors (even when not associated with adverse outcomes) during the period covered by the renewal. In addition, the MAH should provide clarification on the status of JZP110-405 study, on the implementation of results from lactation study (JZP110-401) in the product information and to elucidate on

the outcome of studies 15-004 and 15-005. Finally, the MAH should provide the updated RMP.

9. Product related pharmacovigilance inspections

9.1. List of planned pharmacovigilance inspections

None

9.2. Ongoing or concluded pharmacovigilance inspections

None

9.3. Others

None

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

10.1. Safety related variations of the marketing authorisation

None

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

None

10.3. Other requests

None

10.4. Scientific Advice

None

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

11.1. Safety related variations of the marketing authorisation

None

11.1.1. Oral retinoids (acitretin, alitretinoin, isotretinoin) (NAP) - PT/H/xxxx/WS/069

Applicant(s): various

PRAC Lead: Ana Sofia Martins

Scope: PRAC consultation on a worksharing procedure to assess the protocol of a category 3 qualitative study among healthcare professionals (HCPs) and patients to investigate barriers and reasons why certain measures parts of the oral retinoid therapy Pregnancy Prevention Programme (PPP) are not always followed in clinical practice and the preferred ways of HCPs and patients to receive information on the PPP, submitted following PRAC conclusions on the assessment of the final results of the category 1 PASS (EMEA/H/N/PSR/J/0040)

Background

Retinoids are vitamin A-derivatives indicated for the treatment of several conditions mainly affecting the skin, including severe acne and psoriasis. Some retinoids are also used to treat certain forms of cancer.

In the context of the evaluation of a work sharing procedure to assess the protocol of a category 3 qualitative study among HCPs and patients to investigate barriers and reasons why certain measures parts of the oral retinoid therapy PPP are not always followed in clinical practice and the preferred ways of HCPs and patients to receive information on the PPP, Portugal requested PRAC advice on its assessment. For further background information, see PRAC minutes October 2023.

Summary of advice

- Based on the review of the available information, PRAC agreed with the evaluation of the reference member state (RMS) with few suggestions, recommending amendments to the study protocol regarding the selected countries to ensure an adequate representation of all European regions, the study objectives which should focus on the reasons of the non-adherence to the measures and potential improvements, the individual interviews, the sample size, the data analysis and the inclusion criteria.

11.2. Other requests

None

12. Organisational, regulatory and methodological matters

12.1. Mandate and organisation of PRAC

12.1.1. Election of PRAC Chairperson

The mandate of the PRAC Chair, Sabine Straus, will expire on 01 September 2024. The election of the new Chair took place in accordance with the PRAC rules of procedure.

The nomination received was presented to the Committee.

PRAC elected Ulla Wändel Liminga as PRAC Chair for a three-year mandate starting on 02 September 2024.

PRAC and the Agency congratulated Ulla Wändel Liminga on her election and wished her all the best in her new role as Chair of the Committee.

The newly elected Chair thanked Sabine Straus, the PRAC Chair, for her contributions to PRAC over the last 6 years.

12.1.2. PRAC membership

The Chair thanked Kirsti Villikka for their contribution as the member for Finland.

The Chair welcomed Anette Kirstine Stark as a member appointed as Independent Scientific Expert (ISE) by the European Commission (EC), as well as Hedvig Marie Egeland Nordeng, Annalisa Capuano, Milou-Daniel Drici, Maria Teresa Herdeiro and Patricia McGettigan re-appointed as ISEs by the EC as of 03 July 2024.

12.1.3. Vote by proxy

Annalisa Capuano gave a proxy to Amelia Cupelli to vote on behalf of Annalisa Capuano during the entire meeting.

Jan Neuhauser gave a proxy to Martin Huber to vote on behalf of Jan Neuhauser during the entire meeting.

Roxana Dondera gave a proxy to Julia Pallos to vote on behalf of Roxana Dondera during 08 and 09 July 2024.

Hedvig Marie Egeland Nordeng gave a proxy to Maria Teresa Herdeiro to vote on behalf of Hedvig Marie Egeland Nordeng for the election of the PRAC Chair.

12.2. Coordination with EMA Scientific Committees or CMDh-v

12.2.1. EMA Scientific Co-ordination Board (SciCoBo) - update

Following the Scientific Coordination Board meeting of February 2024 where the Chairs of all EMA Committees agreed to sign a Joint Resolution (JR), which seeks to extend the ethical and behavioural principles that apply to EMA staff also to all Members and Alternates in the EMA Committees (incl. CMDh, CMDv and CTCG), the EMA Secretariat presented to PRAC those principles. PRAC noted the information and was informed that the JR would be filed alongside each Committee's Rules of Procedure (RoP), and subsequently incorporated in each Committee's RoP at the next update.

The <CXMP> members were informed that on 02 February 2024, during the Scientific Coordination Board meeting, the Chairs of all EMA Committees, agreed to sign a Joint Resolution, seeking to extend the ethical and behavioural principles that apply to EMA staff, also to all Members and Alternates who are members of the EMA Committees (incl. CMDh, CMDv and CTCG) and a presentation was given explaining what those ethical and behavioural principles are. The Joint Resolution would be filed alongside each Committee's Rules of Procedure (RoP) and subsequently incorporated in each Committee's RoP at the next update.

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

None

12.4. Cooperation within the EU regulatory network

12.4.1. Health threats and EMA Emergency Task Force (ETF) activities - update

The EMA Secretariat provided to PRAC an update on the COVID-19 vaccines and treatments, including data on the effectiveness of the booster vaccines on the new SARS Cov-2 variants. An update on the post-acute sequelae of SARS-CoV-2 infection was provided, as well as an update on monkeypox and its vaccine effectiveness. In addition, the EMA Secretariat provided an update on the EMA recommendation to update the antigenic composition of authorised COVID-19 vaccines for 2024- 2025 and on the EMA guidance document related to medicinal products use for treatment and prophylaxis in case of exposure to chemical agents used as weapons of terrorism, crime or warfare. PRAC noted the information.

12.5. Cooperation with International Regulators

None

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

None

12.7. PRAC work plan

None

12.8. Planning and reporting

12.8.1. Marketing authorisation applications (MAA) forecast for 2024 – planning update dated Q2 2024

The EMA Secretariat presented for information to PRAC a quarterly updated report on marketing authorisation applications (MAA) planned for submission (the business 'pipeline') in 2024 highlighting the applications without appointed Rapporteur(s).

12.9. Pharmacovigilance audits and inspections

12.9.1. Pharmacovigilance systems and their quality systems

None

12.9.2. Pharmacovigilance inspections

None

12.9.3. Pharmacovigilance audits

None

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

12.10.1. Periodic safety update reports

None

12.10.2. Granularity and Periodicity Advisory Group (GPAG)

None

12.10.3. PSURs repository

None

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

In line with the criteria for plenary presentation of updates to the EURD List adopted by PRAC in December 2021, PRAC endorsed the draft revised EURD list, version July 2024, 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 July 2024, the updated EURD list was adopted by CHMP and CMDh at their July 2024 meetings and published on the EMA website, see: Home> Human Regulatory>Post-authorisation>Pharmacovigilance>Periodic safety update reports>> List of Union reference dates and frequency of submission of periodic safety update reports (PSURs)

12.10.5. Periodic safety update reports single assessment (PSUSA) – review of 'other considerations' section in the assessment report – proposed approach post pilot phase

PRAC lead: Sabine Straus, Martin Huber

Following the discussion during the organisational, regulatory and methodological matters (ORGAM) on 27 June 2024, and after further discussions at the level of CMDh SOS Working Group, the PRAC Vice-chair Martin Huber reported back to the committee on the discussion outcome with the CMDh SOS WG (for further background see PRAC minutes March 2023, PRAC minutes May 2023, PRAC minutes November 2023 and PRAC minutes June 2024). Following the pilot phase and further refinements, PRAC endorsed the proposal to permanently remove the 'other considerations' section (section 6) from the PSUSA assessment report (AR) for all PSUSA types (CAP only, mix CAP/NAP and NAPs only) in order to streamline the PSUSA AR, and supported the proposals regarding the alternative options, presented by CMDh on the topics of extrapolation of the PSUSA outcomes and drug-drug interactions (DDI). As for the next steps, the CMDh will be updated on PRAC's endorsement and proposed next steps and the PSUSA AR templates will then be updated accordingly, and if necessary, this update might be considered for a future topic during an upcoming webinar training session for the assessors.

12.11. Signal management

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

PRAC lead: Martin Huber

The EMA Secretariat presented an update of the work of the SMART Methods stream, including an update on on ongoing projects, on the adverse drug reaction (ADR) representation learning with a cluster analysis, on sources of signals, as well as on the Health Data Lab pilot. PRAC noted the information.

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

12.15.3. Good pharmacovigilance practices (GVP) module VIII on 'Post-authorisation safety studies (PASS)' Revision 4 - update

The EMA Secretariat presented to PRAC an update on the fourth revision of GVP module VIII on PASS, regarding its alignment with the current legislation, the feasibility assessment, the data sources and the policy for publishing of articles. PRAC members were invited to send their comments by 6 September 2024, as the document will be prepared next for release for public consultation.

12.16. Community procedures

12.16.1. Referral procedures for safety reasons

None

12.17. Renewals, conditional renewals, annual reassessments

None

12.18. Risk communication and transparency

12.18.1. Public participation in pharmacovigilance

None

12.18.2. Safety communication

None

12.19. Continuous pharmacovigilance

12.19.1. Incident management

None

12.20. Impact of pharmacovigilance activities

12.20.1. Good Pharmacovigilance Practice (GVP) – mid-year update 2024

PRAC lead: Sabine Straus

PRAC was provided with an overview of the status of the activities on GVP updates included in the PRAC workplan for 2024. In addition, the EMA Secretariat presented a list of ongoing and planned activities on various GVP modules updates, together with their proposed timelines. PRAC also confirmed to start the update of the GVP 'Product- or Population-Specific Considerations I: Vaccines for prophylaxis' and a call to establish an author's team will follow. The EMA secretariat will keep PRAC informed about the status on GVP updates.

PRAC noted the information.

12.21. Others

12.21.1. IRIS - update on transfer of procedures to IRIS by the end of 2024

The EMA Secretariat presented to PRAC an update on the IRIS implementation and upcoming transfer of procedures, as well as an update on the key changes that will impact the work of the network, including rapporteurs and Committee members. The EMA Secretariat also provided a short demo session on the IRIS platform. Further training will be provided by the end of 2024. The EMA Secretariat launched a call for volunteers among Committee members to act as 'early adopters' so that they are the first ones to learn the IRIS functionalities and to support other Committee members during the transition period. Interested members should express their interest for this role in writing by 31 July 2024.

12.21.2. PRAC drafting group on the risks of dependence and addiction of opioids – update

PRAC lead: Liana Martirosyan

The PRAC Lead presented to PRAC the updated report on the activity of the drafting group (DG) on the risks of dependence and addiction of opioids. For background information see PRAC minutes April 2024. PRAC considered the report of the DG where it was highlighted that opioid use disorder (OUD) is a known risk and included in the product information of concerned opioid-containing medicinal products. Furthermore, the Task Force on Opioid Monitoring and Crisis Prevention at EMA has established that all Member States (MSs) have taken various actions to address OUD in their local situations. The DG report consolidates views on the possible introduction of an outer packaging warning on the OUD risk from the EU MSs' competent authorities, the EMA Working Party on Quality Review of Documents (QRD), the eligible organisations representing patients and healthcare professionals to EMA, identified expert organisations and the Multilingual Packages Working Group of the Co-ordination Group for Mutual Recognition and Decentralised Procedures – human (CMDh MLP WG), and analyses the input from these stakeholders. PRAC considered the DG report in the context of the current OUD situations in MSs and noted differences in the requirements and preferences of MSs regarding a possible introduction of an outer packaging warning. Given all considerations, introducing an outer packaging warning is currently not further pursued by PRAC. However, PRAC agreed to continue keeping the product information of the concerned medicinal products updated and consistent across products by means of the PSUSA procedures, monitoring the situation through the assessments of the PSURs and evidence from real-world data, and exchanging information with the Task Force on Opioid Monitoring and Crisis Prevention at EMA which involves collaboration with the European Union Drugs Agency (EUDA). If appropriate, PRAC agreed that it may consider further actions in the future, taking into account the DG report.

12.21.3. PRAC Assessors trainings - update

PRAC Lead(s): Martin Huber, Sabine Straus

The EMA Secretariat presented to PRAC the upcoming scheduled trainings aimed to increase capacity building of the pharmacovigilance network. PRAC noted the information.

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. Azathioprine – JAYEMPI (CAP); NAP

Applicant(s): Nova Laboratories Ireland Limited, various

PRAC Rapporteur: Karin Erneholm

Scope: Signal of non-cirrhotic portal hypertension/Portosinusoidal vascular disease

EPITT 20091 – New signal

14.1.2. Esketamine – SPRAVATO (CAP)

Applicant(s): Janssen-Cilag International N.V.

PRAC Rapporteur: Kirsti Villikka

Scope: Signal of bradycardia

EPITT 20103 – New signal

14.1.3. Montelukast (NAP)

Applicants: various

PRAC Rapporteur: Kimmo Jaakkola

Scope: Signal of persistent neuropsychiatric events

EPITT 20100 – New signal

14.1.4. Nitric oxide – INOMAX (CAP); NAP

Applicant(s): Linde Healthcare AB, various

PRAC Rapporteur: Jo Robays

Scope: Signal of pulmonary oedema in patients with veno-occlusive disease

[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

EPITT 20086 – New signal

14.1.5. Risperidone[33] (NAP)

Applicant: various

PRAC Rapporteur: Martin Huber

Scope: Signal of medication errors associated with accidental overdoses in children and adolescents treated with risperidone 1 mg/mL oral solution

EPITT 20085 – New signal

14.1.6. Rosuvastatin (NAP)

Applicant: various

PRAC Rapporteur: Bianca Mulder

Scope: Signal of tubulointerstitial nephritis

EPITT 20084 – New signal

14.1.7. Semaglutide - OZEMPIC, RYBELSUS, WEGOVY (CAP)

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Mari Thorn

Scope: Signal of tubulointerstitial nephritis

EPITT 20092 – New signal

14.1.8. Semaglutide - OZEMPIC, RYBELSUS, WEGOVY (CAP)

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Mari Thorn

Scope: Signal of appendicitis

EPITT 20095 – New signal

14.2. New signals detected from other sources

None

14.3. Variation procedure(s) resulting from signal evaluation

14.3.1. Brolucizumab - BEOVU (CAP) - EMEA/H/C/004913/II/0028

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Gabriele Maurer

Scope: Update of section 4.8 of the SmPC in order to add 'scleritis' to the list of adverse

[33] Oral solution only

drug reactions (ADRs) with frequency 'not known', following the recommendation by PRAC in the outcome for the signal assessment of Scleritis. The package leaflet is updated accordingly

15. Annex I – Risk management plans

15.1. Medicines in the pre-authorisation phase

As per the agreed criteria, PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of the RMP for the 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. Apremilast - (CAP MAA) - EMEA/H/C/006193

Scope (pre D-180 phase): Treatment of psoriatic arthritis, psoriasis, Behçet's disease

15.1.2. Levetiracetam - (CAP MAA) - EMEA/H/C/006186

Scope (pre D-180 phase): Treatment of partial onset seizures

15.1.3. Pomalidomide - (CAP MAA) - EMEA/H/C/006302

Scope (pre D-180 phase): In combination with dexamethasone is indicated in the treatment of adult patients with relapsed and refractory multiple myeloma (MM)

15.1.4. Ranibizumab - (CAP MAA) - EMEA/H/C/006528

Scope: Treatment of neovascular (wet) age-related macular degeneration (AMD), visual impairment due to diabetic macular oedema (DME), proliferative diabetic retinopathy (PDR), visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO) and visual impairment due to choroidal neovascularisation (CNV)

15.1.5. Ustekinumab - (CAP MAA) - EMEA/H/C/006448

Scope: Treatment of Crohn's disease, Ulcerative colitis, Plaque psoriasis, Paediatric plaque psoriasis and Psoriatic arthritis (PsA)

15.1.6. Vorasidenib - (CAP MAA) - EMEA/H/C/006284, Orphan

Applicant: Les Laboratoires Servier

Scope (pre D-180 phase): Treatment of predominantly non-enhancing astrocytoma or oligodendroglioma with a IDH1 R132 mutation or IDH2 R172 mutation

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. Avelumab - BAVENCIO (CAP) - EMEA/H/C/004338/II/0044/G

Applicant: Merck Europe B.V.

PRAC Rapporteur: Karin Erneholm

Scope: Grouped application comprising four variations as follows:
Type II (C.I.11.b): To update Annex II and the RMP version 7.1 for Bavencio to change the classification of "safety in patients with autoimmune disease" to the important identified risk "other immune mediated adverse reactions" along with removal of the patient information brochure from the educational material, following the PRAC assessment report PSUSA/00010635/202303.
Type IA (A.6): To change ATC level name from Other antineoplastic agents, monoclonal antibodies to Antineoplastic agents, monoclonal antibodies, PD-1/PDL-1 (Programmed cell death protein 1/death ligand 1) inhibitors in Section 5.1 of the Summary of Product Characteristics (SmPC). The ATC code remains unchanged.
Type IA (C.I.z): To update the statement for "infusion-related reactions" in section 4.4 of the SmPC and to align terminology with the RMP for the term "immune-related" versus "immune-mediated".
Type IAIN (C.I.12): To remove from the product information the black symbol and explanatory statements for medicinal products subject to additional monitoring.
In addition, the MAH took this opportunity to introduce editorial changes and to bring the PI in line with the latest QRD template version 10.3

15.2.2. Epoetin beta - NEORECORMON (CAP) - EMEA/H/C/000116/II/0126

Applicant: Roche Registration GmbH

PRAC Rapporteur: Martin Huber

Scope: Submission of an updated RMP version 4.0 in order to align with GVP Module V (Rev. 2)

15.2.3. Larotrectinib - VITRAKVI (CAP) - EMEA/H/C/004919/II/0036

Applicant: Bayer AG

PRAC Rapporteur: Rugile Pilviniene

Scope: Submission of an updated RMP version 2.1 in order to adjust the sample size for the non-interventional PASS ON-TRK as well as to update epidemiological, clinical trial and post-marketing data

15.2.4. Voxelotor - OXBRYTA (CAP) - EMEA/H/C/004869/II/0011, Orphan

Applicant: Pfizer Europe Ma EEIG

PRAC Rapporteur: Jo Robays

Scope: Submission of an updated RMP version 1.2 in order to include the current data for the main existing treatment options and to extend the submission deadline for Study GBT440-0122 (C5341029) and for Study GBT440-034 (C5341022)

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. Apremilast - OTEZLA (CAP) - EMEA/H/C/003746/II/0044/G

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Monica Martinez Redondo

Scope: A grouped application of a Type II Variation with two Type IA Variations, as follows:

Type II (C.I.6.a): Extension of indication to include the treatment of moderate to severe chronic plaque psoriasis in children and adolescents from the age of 6 years who have a contraindication, have an inadequate response, or are intolerant to at least one other systemic therapy or phototherapy for OTEZLA, based on final results from study CC-10004-PPSO-003 as well as results from studies CC-10004-PPSO-001 and CC-10004-PPSO-004. CC-10004-PPSO-003 is a phase 3, multi-center, randomised, double-blind, placebo-controlled study to assess the efficacy and safety of apremilast (CC-10004) in paediatric subjects from 6 through 17 years of age with moderate to severe plaque psoriasis. As a consequence, sections 4.1, 4.2, 4.4 ,4.8, 5.1, 5.2, 5.3 and 6.6 of the SmPC are updated. The package leaflet and Labelling are updated in accordance. Version 15.0 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to introduce minor editorial and formatting changes to the PI and to update the list of local representatives in the package leaflet.

2 Type IA (B.II.e.5.a.1)

15.3.2. Encorafenib - BRAFTOVI (CAP) - EMEA/H/C/004580/WS2538/0034; Binimetinib - MEKTOVI (CAP) - EMEA/H/C/004579/WS2538/0030

Applicant: Pierre Fabre Medicament

PRAC Rapporteur: Rugile Pilviniene

Scope: Extension of indication to include binimetinib in combination with encorafenib for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with a BRAF V600 mutation for MEKTOVI and BRAFTOVI based on results from study PHAROS (Study ARRAY-818-202) at the primary completion date; this is a Phase II, open-label, multicentre, non-comparative study (interventional). As a consequence, sections 4.1, 4.4, 4.8, 5.1, 5.2, 9 and 10 of the SmPC are updated. The package leaflet is updated in accordance. Version 2.1 of the RMP has also been submitted. As part of the application the MAH is requesting a 1-year extension of the market protection for MEKTOVI

15.3.3. Bosutinib - BOSULIF (CAP) - EMEA/H/C/002373/X/0058/G

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Martin Huber

Scope: Extension application to introduce a new pharmaceutical form (hard capsules) associated with two new strengths (50 mg and 100 mg) grouped with an extension of indication (C.I.6.a) to include treatment of paediatric patients greater than or equal to 1 year of age with newly-diagnosed (ND) chronic phase (CP) Philadelphia chromosome-positive chronic myelogenous leukaemia (Ph+ CML) for BOSULIF, based on interim results from study ITCC-054/AAML1921 (BCHILD); this is a phase 1/2, multicenter, international, single-arm, open-label study of bosutinib in pediatric patients with newly diagnosed chronic phase or resistant/intolerant Ph+ chronic myeloid leukemia. 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 accordingly. Version 7.0 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the product information

15.3.4. Brentuximab vedotin - ADCETRIS (CAP) - EMEA/H/C/002455/II/0111, Orphan

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Bianca Mulder

Scope: Extension of indication for ADCETRIS to include treatment for adult patients with previously untreated CD30+ Stage IIB with risk factors, Stage III or Stage IV HL in combination with etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone (BrECADD), based on final results from phase 3 study HD21 (NCT02661503). This study is titled Treatment Optimization Trial in the First-Line Treatment of Advanced-Stage Hodgkin Lymphoma; Comparison of 4-6 Cycles of Escalated BEACOPP With 4-6 Cycles of BrECADD. 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 Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the package leaflet and to implement editorial changes to the SmPC

15.3.5. Canakinumab - ILARIS (CAP) - EMEA/H/C/001109/II/0085

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Gabriele Maurer

Scope: 1. Type II (B.II.e.1.b.2)
The updated RMP version 14.0 has also been submitted to introduce changes related to the addition of the presentation

15.3.6. COVID-19 Vaccine Janssen (Ad26.COV2.S) - JCOVDEN (CAP) - EMEA/H/C/005737/II/0076

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of sections 4.5, 4.8 and 5.1 of the SmPC in order to update information regarding the co-administration of JCOVDEN with influenza vaccine based on the final report from study VAC31518COV3005 listed as a category 3 study in the RMP; this is a randomised, double-blind, Phase 3 study to evaluate safety, reactogenicity, and immunogenicity of co-administration of Ad26.COV2.S and influenza vaccines in healthy adults 18 years of age and older. The package leaflet is updated accordingly. Version 8.1 of the RMP has also been submitted

15.3.7. Dapivirine - DAPIVIRINE VAGINAL RING 25 MG (Art 58[34]) - EMEA/H/W/002168/II/0025/G

Applicant: International Partnership for Microbicides Belgium AISBL

PRAC Rapporteur: Jan Neuhauser

Scope: A grouped application consisting of:
Type II (C.I.4): Update of section 4.6 of the SmPC in order to update information on breastfeeding based on final results from study MTN-043 (B-PROTECTED) listed as a category 3 study in the RMP (MEA/009). MTN-043 is a Phase 3b, randomized, open-label, safety, and drug detection study of dapivirine vaginal ring and oral Truvada in breastfeeding mother-infant pairs. The Package Leaflet is updated accordingly. The RMP version 1.4 has also been submitted. In addition, the MAH took the opportunity to update Annex II of the PI.
Type IB (C.I.11.z): Submission of an updated RMP version 1.4 in order to request a change on the due date for the MTN-034 (REACH) study

15.3.8. Darvadstrocel - ALOFISEL (CAP) - EMEA/H/C/004258/II/0051/G, Orphan

Applicant: Takeda Pharma A/S, ATMP

PRAC Rapporteur: Gabriele Maurer

Scope: A grouped application comprised of 4 Type II Variations, as follows:
(C.I.4): Update of sections 4.8 and 5.1 of the SmPC in order to update the safety information, based on pooled safety data from the two phase 3 controlled studies (ADMIRE-CD & ADMIRE-CD II) and to update efficacy information based on final results from study ADMIRE-CD II, listed as an obligation in the Annex II. ADMIRE-CD II (Cx601-0303) is a Phase III randomised double blind, placebo controlled study to assess efficacy and safety of Cx601, adult allogeneic expanded adipose-derived stem cells (eASC) for the treatment of complex perianal fistula(s) in patients with Crohn's disease. The Annex II is updated accordingly. In addition, the MAH took the opportunity to introduce minor changes to the PI, including to section 4.2 of the SmPC and to the package leaflet.

3 x (C.I.13): Submission of interim results from studies Darvadstrocel-3003 and Alofisel-5003 (INSPIRE) and final results from study Darvadstrocel-3002 to support the benefit-risk assessment of darvadstrocel based on all new available clinical data
The RMP version 8.0 has also been submitted

[34] Article 58 of Regulation (EC) No 726/2004 allows the Committee for Medicinal Products for Human Use (CHMP) to give opinions, in co-operation with the World Health Organisation (WHO) on medicinal products for human use that are intended exclusively for markets outside of the European Union (EU)

15.3.9. Dengue tetravalent vaccine[35] (live, attenuated) - DENGUE TETRAVALENT VACCINE (LIVE, ATTENUATED) TAKEDA (Art 58[36]) - EMEA/H/W/005362/WS2695/0015; Dengue tetravalent vaccine (live, attenuated) - QDENGA (CAP) - EMEA/H/C/005155/WS2695/0016

Applicant: Takeda GmbH

PRAC Rapporteur: Liana Martirosyan

Scope: Update of section 4.4 and 4.8 of the SmPC in order to add anaphylactic reaction to the list of adverse drug reactions (ADRs) with frequency not known, based on post-authorisation experience. The package leaflet is updated accordingly. The RMP version 1.2 has also been submitted. In addition, the MAH took the opportunity to bring the PI in line with the latest QRD template version 10.4 and to introduce minor editorial changes to the PI

15.3.10. Dengue tetravalent vaccine[37] (live, attenuated) - DENGUE TETRAVALENT VACCINE (LIVE, ATTENUATED) TAKEDA (Art 58[38]) - EMEA/H/W/005362/WS2593/0012; Dengue tetravalent vaccine (live, attenuated) - QDENGA (CAP) - EMEA/H/C/005155/WS2593/0013

Applicant: Takeda GmbH

PRAC Rapporteur: Liana Martirosyan

Scope: Update of section 4.5 of the SmPC in order to add co-administration information with HPV vaccine based on final results from study DEN-308 listed as a category 3 study in the RMP (MEA003/MEA004); this is a Phase 3, open-label, randomised trial to investigate the immunogenicity and safety of the co-administration of a subcutaneous dengue tetravalent vaccine (live, attenuated) (TDV) and an intramuscular recombinant 9-valent human papillomavirus (9vHPV) vaccine in subjects aged ≥9 to <15 years in an endemic country for dengue; the package leaflet is updated accordingly. The RMP version 1.1 has also been submitted. In addition, the MAH took this opportunity to introduce editorial changes and to update the text on PSUR submissions in Annex II for Dengue tetravalent vaccine

15.3.11. Eliglustat - CERDELGA (CAP) - EMEA/H/C/003724/X/0036/G, Orphan

Applicant: Sanofi B.V.

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Extension application to introduce a new strength (21 mg capsule, hard) grouped with an extension of indication (C.I.6.a) to include treatment of paediatric patients with GD1 who are 6 years and older with a minimum body weight of 15 kg, who have been

[35] Dengue virus, serotype 2, expressing Dengue virus, serotype 1, surface proteins, live, attenuated, Dengue virus, serotype 2, expressing Dengue virus, serotype 3, surface proteins, live, attenuated, Dengue virus, serotype 2, expressing Dengue virus, serotype 4, surface proteins, live, attenuated, Dengue virus, serotype 2, live, attenuated

[36] Article 58 of Regulation (EC) No 726/2004 allows the Committee for Medicinal Products for Human Use (CHMP) to give opinions, in co-operation with the World Health Organisation (WHO) on medicinal products for human use that are intended exclusively for markets outside of the European Union (EU)

[37] Dengue virus, serotype 2, expressing Dengue virus, serotype 1, surface proteins, live, attenuated, Dengue virus, serotype 2, expressing Dengue virus, serotype 3, surface proteins, live, attenuated, Dengue virus, serotype 2, expressing Dengue virus, serotype 4, surface proteins, live, attenuated, Dengue virus, serotype 2, live, attenuated

[38] Article 58 of Regulation (EC) No 726/2004 allows the Committee for Medicinal Products for Human Use (CHMP) to give opinions, in co-operation with the World Health Organisation (WHO) on medicinal products for human use that are intended exclusively for markets outside of the European Union (EU)

previously treated with enzyme replacement therapy (ERT), and who are CYP2D6 poor metabolisers (PMs), intermediate metabolisers (IMs) or extensive metabolisers (EMs) for Cerdelga, based on interim results from study EFC13738 (Open label, two cohort (with and without imiglucerase), multicenter study to evaluate pharmacokinetics, safety, and efficacy of eliglustat in pediatric patients with Gaucher disease type 1 and type 3). 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. The RMP version 8.0 has also been submitted. In addition, the MAH took this opportunity to introduce editorial changes to the PI

15.3.12. Enfortumab vedotin - PADCEV (CAP) - EMEA/H/C/005392/II/0013

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Eva Jirsová

Scope: Extension of indication to include in combination with pembrolizumab, the first-line treatment of adult patients with locally advanced or metastatic urothelial cancer who are eligible for platinum-containing chemotherapy for PADCEV, based on the final results from study KEYNOTE-A39/EV-302: "An open label, randomised, controlled phase 3 study of enfortumab vedotin in combination with pembrolizumab versus chemotherapy alone in previously untreated locally advanced (LA) or metastatic urothelial cancer (mUC)"; As a consequence, sections 4.1, 4.2, 4.4, 4.6, 4.8, 5.1, 5.2, 5.3 and 6.6 of the SmPC are updated. The package leaflet is updated in accordance. Version 3.0 of the RMP has also been submitted. As part of the application the MAH is requesting a 1-year extension of the market protection

15.3.13. Etrasimod - VELSIPITY (CAP) - EMEA/H/C/006007/II/0002/G

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Mari Thorn

Scope: A grouped application comprised of two Type II variations, as follows:

C.I.4: Update of sections 4.2, 4.3 and 5.2 of the SmPC in order to amend recommendation regarding administration to patients with severe hepatic impairment and remove contraindication for severe hepatic impairment, based on in vitro studies to further characterise the drug-drug interaction (DDI) potential of metabolites M3 and M6. The Annex II and package leaflet are updated accordingly. The RMP version 1.2 has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the PI.

C.I.13: Submission of the final report from study 24GR036 (hERG Channel Automated Patch-Clamp Test); this is an assessment of the effects of PF-08034694, PF-08034742, PF-08039030, and PF-08039032 on the Kv11.1 (hERG) potassium current

15.3.14. Evinacumab - EVKEEZA (CAP) - EMEA/H/C/005449/II/0015

Applicant: Ultragenyx Germany GmbH

PRAC Rapporteur: Mari Thorn

Scope: Extension of indication for EVKEEZA to include the treatment of paediatric patients

with homozygous familial hypercholesterolaemia aged 6 months to less than 5 years, based on the results of population PK and population PK/PD model-based extrapolation reports (R1500-PM-23202-SR-01V2 and R1500-PM-23089-SR-01V2). 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 2.0 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to implement minor changes to sections 4.2, 4.4, and 4.7 of the SmPC, along with editorial changes to the SmPC

15.3.15. Nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/WS2672/0141; Ipilimumab - YERVOY (CAP) - EMEA/H/C/002213/WS2672/0111

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Martin Huber

Scope: A Worksharing application for OPDIVO and YERVOY, as follows:

Extension of indication to include OPDIVO in combination with ipilimumab in the first-line treatment of adult patients with mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H) unresectable or metastatic colorectal cancer, based on interim results from study CA2098HW; this is a phase 3 randomised clinical trial of nivolumab alone, nivolumab in combination with ipilimumab, or investigator's choice chemotherapy in participants with microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 6.6 of the SmPC are updated. The package leaflet is updated in accordance. Version 37.0 of the RMP has also been submitted.

Extension of indication to include YERVOY in combination with nivolumab in the first-line treatment of adult patients with mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H) unresectable or metastatic colorectal cancer, based on interim results from study CA2098HW; this is a phase 3 randomised clinical trial of nivolumab alone, nivolumab in combination with ipilimumab, or investigator's choice chemotherapy in participants with microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The package leaflet is updated in accordance. Version 41.0 of the RMP has also been submitted

15.3.16. Isatuximab - SARCLISA (CAP) - EMEA/H/C/004977/II/0030

Applicant: Sanofi Winthrop Industrie

PRAC Rapporteur: Monica Martinez Redondo

Scope: Extension of indication to include in combination with bortezomib, lenalidomide, and dexamethasone the treatment of adult patients with newly diagnosed active multiple myeloma who are not eligible for autologous stem cell transplant (ASCT) or with no intent for ASCT as initial therapy for Sarclisa, based on results from EFC12522 (IMROZ) pivotal phase III study and the supportive TCD13983 phase 1b/2 study. EFC12522 is an ongoing prospective, multicenter, international, randomised, open-label, 2-arm parallelgroup study to assess the clinical benefit of VRd (control group) versus IVRd (active group) for the treatment of participants with NDMM who are not eligible for ASCT. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.7, 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

15.3.17. Letermovir - PREVYMIS (CAP) - EMEA/H/C/004536/X/0037/G, Orphan

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Kirsti Villikka

Scope: Extension applications to introduce a new pharmaceutical form (granules in sachet) associated with new strengths (20 and 120 mg) grouped with a type II variation (C.I.6.a) to include treatment of paediatric patients from birth up to 18 years old based on the final results from studies P030 and P031.
Study P030 was a Phase 2b, open-label, single-arm study to evaluate PK, efficacy, safety, and tolerability of letermovir (LET) when used for CMV prophylaxis in pediatric participants from birth to <18 years of age who are at risk of developing clinically significant CMV infection (CS-CMVi) following an allogeneic hematopoietic stem cell transplant (HSCT).
Study P031 was an open-label, single-dose, four-period, seven-treatment, crossover study designed to evaluate the bioavailability of 2 pediatric formulations of MK-8228 (Formulations A and B) administered alone or in soft food (applesauce and vanilla pudding) compared to a currently marketed tablet formulation.
As a consequence, sections 4.1, 4.2, 4.5, 4.8, 4.9, 5.1 and 5.2 of the SmPC are updated. The package leaflet is updated in accordance. Version 5.1 of the RMP has also been submitted. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet and to introduce editorial changes

15.3.18. Levetiracetam - KEPPRA (CAP) - EMEA/H/C/000277/WS2529/0200

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Jo Robays

Scope: Type II - B.IV.1.a.3 An updated RMP version 10.0 and a DHPC are proposed. In addition, the Applicant has taken the opportunity to include the change in the local representatives of the Marketing Authorisation Holder in Estonia, Latvia, and Lithuania.

15.3.19. Meningococcal group A, C, W135 and Y conjugate vaccine - MENVEO (CAP) - EMEA/H/C/001095/X/0119

Applicant: GSK Vaccines S.r.l

PRAC Rapporteur: Liana Martirosyan

Scope: Extension application to introduce a new pharmaceutical form (solution for injection). The RMP (version 11.0) is updated in accordance

15.3.20. Mycophenolate mofetil - CELLCEPT (CAP) - EMEA/H/C/000082/II/0170/G

Applicant: Roche Registration GmbH

PRAC Rapporteur: Karin Erneholm

Scope: C.I.6.a: Extension of indication to include paediatric patients (3 months to 18 years of age) for hepatic and cardiac transplants and to extend the indication for renal transplants for paediatric patients starting from 3 months, based on pharmacokinetic data, published

literature and the Roche Global Safety Database. As a consequence, sections 4.1, 4.2, 4.8 and 5.2 of the SmPC are updated. The package leaflet is updated accordingly.

Type IB (C.I.z): To update section 4.2 of the SmPC for the CellCept 500 mg tablets formulation in order to be in line with the other three CellCept formulations. For alignment with the current QRD guidance, the package leaflet was updated to cross reference section 2 in section 6 for sodium content.

In addition, the MAH took the opportunity to introduce minor editorial changes to the PI and bring the PI in line with the latest QRD template version 10.3

15.3.21. Nintedanib - OFEV (CAP) - EMEA/H/C/003821/X/0057/G

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Barbara Kovacic Bytyqi

Scope: Extension application to add a new strength of 25 mg hard capsules, grouped with an extension of indication (C.I.6.a) to include treatment of fibrosing Interstitial Lung Diseases (ILDs) in children and adolescents from 6 to 17 years of age for Ofev, following the assessment of procedure X/0052/G, based on final results from study 1199-0337 (A Double Blind, Randomised, Placebo-controlled Trial to Evaluate the Dose-exposure and Safety of Nintedanib Per os on Top of Standard of Care for 24 Weeks, Followed by Open Label Treatment With Nintedanib of Variable Duration, in Children and Adolescents (6 to 17 Year-old) With Clinically Significant Fibrosing Interstitial Lung Disease), which is supplemented by the currently ongoing prospective Phase III extension trial 1199-0378 (An Open-label Trial of the Long-term Safety and Tolerability of Nintedanib Per os, on Top of Standard of Care, Over at Least 2 Years, in Children and Adolescents With Clinically Significant Fibrosing Interstitial Lung Disease). The main objective of the study 1199-0337 was to evaluate dose-exposure and safety of nintedanib in children and adolescents with fibrosing Interstitial Lung Disease (ILD). 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 and Labelling are updated in accordance. Version 12.0 of the RMP has also been submitted

15.3.22. Nirmatrelvir, Ritonavir - PAXLOVID (CAP) - EMEA/H/C/005973/II/0057/G

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Martin Huber

Scope: Grouped application consisting of:
C.I.4: Update of sections 4.2, 4.4, 4.8 and 5.2 of the SmPC in order to provide a new dosing recommendation in patients with severe renal impairment based on final results from study C4671028; this is a Phase 1, Open-Label, Non-Randomised Study to Investigate the Safety and PK Following Multiple Oral Doses of PF-07321332 (Nirmatrelvir)/Ritonavir in Adult Participants With COVID-19 and Severe Renal Impairment Either on Hemodialysis or Not on Hemodialysis. The package leaflet and Labelling are updated accordingly. The updated RMP version 3.1 has also been submitted. In addition, the MAH took the opportunity to implement editorial changes to the SmPC.
B.II.e.5.a.2

15.3.23. Ocrelizumab - OCREVUS (CAP) - EMEA/H/C/004043/II/0041

Applicant: Roche Registration GmbH

PRAC Rapporteur: Gabriele Maurer

Scope: Update of sections 4.6 and 5.3 of the SmPC in order to amend the recommendations for breast-feeding during ocrelizumab therapy, based on newly available clinical data. The package leaflet is updated accordingly. The RMP version 10.0 has also been submitted. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet

15.3.24. Opicapone - ONGENTYS (CAP) - EMEA/H/C/002790/WS2702/0066; Opicapone - ONTILYV (CAP) - EMEA/H/C/005782/WS2702/0021

Applicant: Bial - Portela & Cª, S.A.

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Update of section 4.8 of the SmPC in order to add 'fall' and 'fatigue' to the list of adverse drug reactions (ADRs) with frequency uncommon based on the cumulative review of literature. The package leaflet is updated accordingly. The Ongentys RMP version 6.0 has also been submitted. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet, to bring the PI in line with the latest QRD template version 10.4 and to introduce minor editorial changes to the product information

15.3.25. Osimertinib - TAGRISSO (CAP) - EMEA/H/C/004124/II/0056

Applicant: AstraZeneca AB

PRAC Rapporteur: Bianca Mulder

Scope: Extension of indication to include treatment of adult patients with locally advanced, unresectable (stage III) NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations and whose disease has not progressed during or following platinum-based chemoradiation therapy for TAGRISSO as monotherapy, based on results from study D5160C00048 (LAURA); this is a Phase III, randomised, double-blind, placebo-controlled, multicentre international study of osimertinib as maintenance therapy in patients with locally advanced unresectable EGFR mutation-positive non-small cell lung cancer (stage III) whose disease has not progressed following definitive platinum-based chemoradiation therapy. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The package leaflet is updated in accordance. Version 17.0 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the product information

15.3.26. Ozanimod - ZEPOSIA (CAP) - EMEA/H/C/004835/II/0024/G

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Grouped application comprising two variations as follows:
Type II (C.I.4) – Update of sections 4.4 and 4.8 the SmPC in order to add a new warning on liver injury, to add Liver injury to the list of adverse drug reactions (ADRs) with frequency

rare based on the cumulative review of the MAH safety database, clinical trials and literature search. The RMP version 8.0 also been submitted.
Type IA (A.6) – To change the ATC code from L04AA38 to L04AE02

15.3.27. Pembrolizumab - KEYTRUDA (CAP) - EMEA/H/C/003820/II/0150

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Bianca Mulder

Scope: Extension of indication to include in combination with enfortumab vedotin, the first-line treatment of locally advanced or metastatic urothelial carcinoma in adults, based on the final results from KEYNOTE-A39/EV-302: "An open label, randomised, controlled phase 3 study of enfortumab vedotin in combination with pembrolizumab versus chemotherapy alone in previously untreated locally advanced (LA) or metastatic urothelial cancer (mUC)"; 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 45.1 of the RMP has also been submitted

15.3.28. Pembrolizumab - KEYTRUDA (CAP) - EMEA/H/C/003820/II/0154

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Bianca Mulder

Scope: Extension of indication to include in combination with pemetrexed and platinum chemotherapy the first-line treatment of adults and adolescents aged 12 years and older with unresectable advanced or metastatic malignant pleural mesothelioma for Keytruda, based on final results from study KEYNOTE-483; this is a multicenter, open-label, Phase 2/3 randomised study to evaluate the efficacy and safety of pembrolizumab in combination with pemetrexed/platinum chemotherapy in participants with unresectable advanced or metastatic malignant pleural mesothelioma (MPM). As a consequence, sections 4.1, 4.2 and 5.1 of the SmPC are updated. The package leaflet is updated in accordance. Version 47.1 of the RMP has also been submitted

15.3.29. Pemigatinib - PEMAZYRE (CAP) - EMEA/H/C/005266/II/0015, Orphan

Applicant: Incyte Biosciences Distribution B.V.

PRAC Rapporteur: Bianca Mulder

Scope: Extension of indication to include treatment of adults with myeloid/lymphoid neoplasms (MLNs) with Fibroblast Growth Factor Receptor1 (FGFR1) rearrangement for PEMAZYRE, based on final results from study INCB 54828-203 (FIGHT-203); this is a phase 2, open-label, monotherapy, multicenter study to evaluate the efficacy and safety of INCB054828 in subjects with myeloid/lymphoid neoplasms with FGFR1 rearrangement. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8 and 5.1 of the SmPC are updated. The package leaflet is updated in accordance. Version 3.0 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce minor changes to the PI. As part of the application, the MAH is requesting a 1-year extension of the market protection

15.3.30. Respiratory syncytial virus, glycoprotein F, recombinant, stabilised in the pre-fusion conformation, adjuvanted with AS01E - AREXVY (CAP) - EMEA/H/C/006054/II/0008

Applicant: GlaxoSmithkline Biologicals S.A.

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Extension of indication to include treatment of adults 50-59 years of age who are at increased risk for RSV disease for AREXVY, based on results from study 219238 (RSV OA=ADJ-018); this is a phase 3, observer-blind, placebo-controlled, randomised, multi-country, multi-center, non-inferiority study with 2 cohorts to evaluate immunogenicity, reactogenicity and safety of a single dose of RSVPreF3 OA in adults 50-59 years of age. As a consequence, sections 4.1, 4.6, 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 Marketing authorisation holder (MAH) took the opportunity to introduce minor editorial changes to the PI, to bring it in line with the latest QRD template version 10.3, and to update the list of local representatives in the package leaflet. As part of the application, the MAH is requesting a 1-year extension of the market protection

15.3.31. Rilpivirine - EDURANT (CAP) - EMEA/H/C/002264/X/0042/G

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Liana Martirosyan

Scope: Extension application to introduce a new pharmaceutical form associated with new strength (2.5 mg dispersible tablets). The new presentation is indicated, in combination with other antiretroviral medicinal products, for the treatment of HIV-1 infection in patients ≥2 to <18 years of age and weighing at least 10 kg to less than 25 kg. The PI and RMP have been updated in accordance.

Type II variation (C.I.6.a) to modify the approved therapeutic indication of the already authorised 25 mg film-coated tablets presentation to include, in combination with other antiretroviral medicinal products, treatment of human immunodeficiency virus type 1 (HIV-1) infection in antiretroviral treatment-naïve and virologically suppressed (HIV-1 RNA less than 50 copies per ml) paediatric patients from 2 to less than 12 years weighing at least 25 kg, based on final results from study studies TMC278-TiDP38-C213 Cohort 2. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The package leaflet and Labelling are updated in accordance. The updated RMP version 10.1 has also been submitted. In addition, the MAH took the opportunity to implement editorial changes to Annex II and to update the list of local representatives in the package leaflet

15.3.32. Selpercatinib - RETSEVMO (CAP) - EMEA/H/C/005375/II/0032

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Bianca Mulder

Scope: Update of sections 4.8, 5.1 and 5.2 of the SmPC in order to add urinary tract infections, stomatitis, calcium decreased, albumin decreased, sodium decreased and potassium decreased to the list of adverse drug reactions (ADRs) with frequency Very common and to update efficacy, safety and pk information based on results from study LIBRETTO-531 (JZJB) listed as a specific obligation in the Annex II; This study is a Phase 3

confirmatory study comparing selpercatinib to physicians choice of cabozantinib or vandetanib in patients with progressive advanced, kinase inhibitor naive RET-mutant medullary thyroid cancer (MTC). The package leaflet and Annex II are updated accordingly. The RMP version 9.1 has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the PI

15.3.33. Selpercatinib - RETSEVMO (CAP) - EMEA/H/C/005375/X/0031

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Bianca Mulder

Scope: Extension application to introduce a new pharmaceutical form (film-coated tablets) associated with new strengths (40 mg, 80 mg, 120 mg and 160 mg).
The RMP (version 7.1) is updated in accordance

15.3.34. Semaglutide - RYBELSUS (CAP) - EMEA/H/C/004953/II/0041

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Mari Thorn

Scope: Update of section 4.6 of the SmPC in order to update information on breast-feeding based on final results from study NN9924-4669. This was an open-label, single-armed, multiple-dose, multi-centre study evaluating the semaglutide and SNAC concentrations in breastmilk from healthy lactating women dosed once daily with oral semaglutide for 10 days (3 mg for 5 days followed by 7 mg for 5 days). The primary endpoints were evaluated during a 24 hours pharmacokinetic (PK) sampling period after the 10th dose. The package leaflet is updated accordingly. The RMP version 9.0 has also been submitted

15.3.35. Smallpox and monkeypox vaccine (live modified vaccinia virus Ankara) - IMVANEX (CAP) - EMEA/H/C/002596/II/0100

Applicant: Bavarian Nordic A/S

PRAC Rapporteur: Gabriele Maurer

Scope: Update of section 5.1 of the SmPC in order to add vaccine effectiveness data, and the removal of the two open specific obligations (POX-MVA-039 (SOB02) and SEMVAc (SOB03)), based on the IMVANEX vaccine effectiveness data in real-world use during the 2022 monkeypox outbreak. Consequently, the MAH proposes a switch from exceptional marketing authorisation to full marketing authorisation. The Annex II and package leaflet are updated accordingly. The RMP version 10.0 has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the PI

15.3.36. Teclistamab - TECVAYLI (CAP) - EMEA/H/C/005865/II/0009

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Jana Lukacisinova

Scope: Update of section 4.4 of the SmPC in order to update the warning on Progressive Multifocal Leukoencephalopathy (PML) based on a cumulative safety review. The package leaflet is updated accordingly. The RMP version 4.1 has also been submitted. In addition,

the MAH took the opportunity to introduce minor updates to the PI and to update the list of local representatives in the package leaflet

15.3.37. Velaglucerase alfa - VPRIV (CAP) - EMEA/H/C/001249/II/0063

Applicant: Takeda Pharmaceuticals International AG Ireland Branch

PRAC Rapporteur: Martin Huber

Scope: Update of section 4.2 of the SmPC in order to add information to support at-home self-administration of VPRIV by a trained patient and/or a caregiver based on post-marketing data and literature. The package leaflet and Annex IID are updated accordingly. The updated RMP version 13.0 has also been submitted

15.3.38. Zoonotic influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) - AFLUNOV (CAP) - EMEA/H/C/002094/II/0086

Applicant: Seqirus S.r.l

PRAC Rapporteur: Amelia Cupelli

Scope: Extension of indication to include treatment of individuals 6 months of age and older for AFLUNOV, based on final results from study V87_30. This is a Phase 2, Randomised, Observer-Blind, Multicenter Study to Evaluate the Immunogenicity and Safety of Several Doses of Antigen and MF59 Adjuvant Content in a Monovalent H5N1 Pandemic Influenza Vaccine in Healthy Pediatric Subjects 6 Months to < 9 Years of Age.
As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The package leaflet is updated accordingly. Version 5.3 of the RMP has also been submitted. In addition, the Marketing authorisation holder (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. Angiotensin II - GIAPREZA (CAP) - PSUSA/00010785/202312

Applicant: Paion Deutschland GmbH

PRAC Rapporteur: Bianca Mulder

Scope: Evaluation of a PSUSA procedure

16.1.2. Artesunate - ARTESUNATE AMIVAS (CAP) - PSUSA/00010958/202312

Applicant: Amivas Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.3. Atidarsagene autotemcel - LIBMELDY (CAP) - PSUSA/00010899/202312

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

PRAC Rapporteur: Gabriele Maurer

Scope: Evaluation of a PSUSA procedure

16.1.4. Dalbavancin - XYDALBA (CAP) - PSUSA/00010350/202311

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Rugile Pilviniene

Scope: Evaluation of a PSUSA procedure

16.1.5. Efgartigimod alfa - VYVGART (CAP) - PSUSA/00011014/202312

Applicant: Argenx

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

16.1.6. Elacestrant - ORSERDU (CAP) - PSUSA/00000120/202312

Applicant: Stemline Therapeutics B.V.

PRAC Rapporteur: Sonja Hrabcik

Scope: Evaluation of a PSUSA procedure

16.1.7. Eladocagene exuparvovec - UPSTAZA (CAP) - PSUSA/00011004/202312

Applicant: PTC Therapeutics International Limited, ATMP

PRAC Rapporteur: Gabriele Maurer

Scope: Evaluation of a PSUSA procedure

16.1.8. Elasomeran (Spikevax), elasomeran, imelasomeran (Spikevax bivalent Original/Omicron BA.1), elasomeran, davesomeran (Spikevax bivalent Original/Omicron BA.4-5), andusomeran (Spikevax XBB.1.5) - SPIKEVAX (CAP) - PSUSA/00010897/202312 (with RMP)

Applicant: Moderna Biotech Spain S.L.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Evaluation of a PSUSA procedure

16.1.9. Entrectinib - ROZLYTREK (CAP) - PSUSA/00010874/202312

Applicant: Roche Registration GmbH

PRAC Rapporteur: Bianca Mulder

Scope: Evaluation of a PSUSA procedure

16.1.10. Eribulin - HALAVEN (CAP) - PSUSA/00001254/202311

Applicant: Eisai GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.11. Follitropin delta - REKOVELLE (CAP) - PSUSA/00010554/202311

Applicant: Ferring Pharmaceuticals A/S

PRAC Rapporteur: Bianca Mulder

Scope: Evaluation of a PSUSA procedure

16.1.12. Formoterol fumarate dihydrate, glycopyrronium bromide, budesonide - RILTRAVA AEROSPHERE (CAP); TRIXEO AEROSPHERE (CAP) - PSUSA/00010908/202312

Applicant: AstraZeneca AB

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.1.13. Inclisiran - LEQVIO (CAP) - PSUSA/00010904/202312

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

16.1.14. Inebilizumab - UPLIZNA (CAP) - PSUSA/00010996/202312

Applicant: Horizon Therapeutics Ireland DAC

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.1.15. Inotuzumab ozogamicin - BESPONSA (CAP) - PSUSA/00010659/202312

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Gabriele Maurer

Scope: Evaluation of a PSUSA procedure

16.1.16. Levodopa - INBRIJA (CAP) - PSUSA/00107800/202312

Applicant: Acorda Therapeutics Ireland Limited

PRAC Rapporteur: Barbara Kovacic Bytyqi

Scope: Evaluation of a PSUSA procedure

16.1.17. Lonoctocog alfa - AFSTYLA (CAP) - PSUSA/00010559/202401

Applicant: CSL Behring GmbH

PRAC Rapporteur: Sonja Hrabcik

Scope: Evaluation of a PSUSA procedure

16.1.18. Nirmatrelvir, ritonavir - PAXLOVID (CAP) - PSUSA/00010984/202312

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.19. Octreotide[39] - MYCAPSSA (CAP) - PSUSA/00011036/202312

Applicant: Amryt Pharmaceuticals DAC

PRAC Rapporteur: Eamon O'Murchu

Scope: Evaluation of a PSUSA procedure

16.1.20. Olaparib - LYNPARZA (CAP) - PSUSA/00010322/202312

Applicant: AstraZeneca AB

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.1.21. Osimertinib - TAGRISSO (CAP) - PSUSA/00010472/202311

Applicant: AstraZeneca AB

PRAC Rapporteur: Bianca Mulder

Scope: Evaluation of a PSUSA procedure

16.1.22. Pneumococcal polysaccharide conjugate vaccine (20-valent, adsorbed) - PREVENAR 20 (CAP) - PSUSA/00010981/202312

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

[39] For centrally authorised products only

16.1.23. Ponatinib - ICLUSIG (CAP) - PSUSA/00010128/202312

Applicant: Incyte Biosciences Distribution B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.24. Prasterone[40] - INTRAROSA (CAP) - PSUSA/00010672/202311

Applicant: Endoceutics S.A.

PRAC Rapporteur: Bianca Mulder

Scope: Evaluation of a PSUSA procedure

16.1.25. Quizartinib - VANFLYTA (CAP) - PSUSA/00000176/202312

Applicant: Daiichi Sankyo Europe GmbH

PRAC Rapporteur: John Joseph Borg

Scope: Evaluation of a PSUSA procedure

16.1.26. Raloxifene - EVISTA (CAP); OPTRUMA (CAP) - PSUSA/00002603/202312

Applicant: Substipharm (Evista), Eli Lilly Nederland B.V. (Optruma)

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

16.1.27. Ravulizumab - ULTOMIRIS (CAP) - PSUSA/00010787/202312

Applicant: Alexion Europe SAS

PRAC Rapporteur: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

16.1.28. Ritlecitinib - LITFULO (CAP) - PSUSA/00000133/202312

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.29. Rotavirus vaccine pentavalent (live, oral) - ROTATEQ (CAP) - PSUSA/00002666/202311

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

[40] Pessary, vaginal use only

16.1.30. Rucaparib - RUBRACA (CAP) - PSUSA/00010694/202312

Applicant: Pharmaand GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.31. Coronavirus (COVID-19) vaccine (recombinant, adjuvanted) - NUVAXOVID (CAP) - PSUSA/00010972/202312

Applicant: Novavax CZ a.s.

PRAC Rapporteur: Gabriele Maurer

Scope: Evaluation of a PSUSA procedure

16.1.32. Tabelecleucel - EBVALLO (CAP) - PSUSA/00011028/202312

Applicant: Pierre Fabre Medicament, ATMP

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.1.33. Tagraxofusp - ELZONRIS (CAP) - PSUSA/00010896/202312

Applicant: Stemline Therapeutics B.V.

PRAC Rapporteur: Bianca Mulder

Scope: Evaluation of a PSUSA procedure

16.1.34. Tezepelumab - TEZSPIRE (CAP) - PSUSA/00011015/202312

Applicant: AstraZeneca AB

PRAC Rapporteur: Eva Jirsová

Scope: Evaluation of a PSUSA procedure

16.1.35. Tirbanibulin - KLISYRI (CAP) - PSUSA/00010943/202312

Applicant: Almirall, S.A.

PRAC Rapporteur: Anna Mareková

Scope: Evaluation of a PSUSA procedure

16.1.36. Tislelizumab - TEVIMBRA (CAP) - PSUSA/00000136/202312

Applicant: Beigene Ireland Limited

PRAC Rapporteur: Bianca Mulder

Scope: Evaluation of a PSUSA procedure

16.1.37. Tozinameran (COMIRNATY), tozinameran, riltozinameran (COMIRNATY Original/Omicron BA.1), tozinameran, famtozinameran (COMIRNATY Original/Omicron BA.4-5), raxtozinameran (COMIRNATY Omicron XBB.1.5) - COMIRNATY (CAP) - PSUSA/00010898/202312

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Liana Martirosyan

Scope: Evaluation of a PSUSA procedure

16.1.38. Tralokinumab - ADTRALZA (CAP) - PSUSA/00010937/202312

Applicant: LEO Pharma A/S

PRAC Rapporteur: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

16.1.39. Trastuzumab deruxtecan - ENHERTU (CAP) - PSUSA/00010894/202312

Applicant: Daiichi Sankyo Europe GmbH

PRAC Rapporteur: Carla Torre

Scope: Evaluation of a PSUSA procedure

16.1.40. Ublituximab - BRIUMVI (CAP) - PSUSA/00000045/202312

Applicant: Neuraxpharm Pharmaceuticals S.L.

PRAC Rapporteur: Liana Martirosyan

Scope: Evaluation of a PSUSA procedure

16.1.41. Vadadustat - VAFSEO (CAP) - PSUSA/00011050/202312

Applicant: Medice Arzneimittel Pütter GmbH & Co. KG

PRAC Rapporteur: Eva Jirsová

Scope: Evaluation of a PSUSA procedure

16.1.42. Vonicog alfa - VEYVONDI (CAP) - PSUSA/00010714/202312

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Mari Thorn

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. Erlotinib - TARCEVA (CAP); NAP - PSUSA/00001255/202311

Applicants: Roche Registration GmbH (Tarceva), various

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Evaluation of a PSUSA procedure

16.2.2. Human hepatitis B immunoglobulin - ZUTECTRA (CAP); NAP - PSUSA/00001631/202311

Applicants: Biotest Pharma GmbH (Zutectra), various

PRAC Rapporteur: Gabriele Maurer

Scope: Evaluation of a PSUSA procedure

16.2.3. Riluzole - RILUTEK (CAP); RILUZOLE ZENTIVA (CAP); NAP - PSUSA/00002645/202312

Applicants: Sanofi Winthrop Industrie (Rilutek), Zentiva, k.s. (Riluzole Zentiva), various

PRAC Rapporteur: Karin Erneholm

Scope: Evaluation of a PSUSA procedure

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

16.3.1. Carbimazole (NAP) - PSUSA/00000550/202312

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.3.2. Ciprofloxacin hydrochloride, hydrocortisone (NAP) - PSUSA/00000774/202311

Applicant(s): various

PRAC Lead: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.3.3. Danaparoid (NAP) - PSUSA/00000923/202312

Applicant(s): various

PRAC Lead: Eamon O'Murchu

Scope: Evaluation of a PSUSA procedure

16.3.4. Diphtheria, tetanus, pertussis (acellular, component), poliomyelitis (inactivated), haemophilus type b conjugate vaccine (adsorbed) (NAP) - PSUSA/00001124/202311

Applicant(s): various

PRAC Lead: Gabriele Maurer

Scope: Evaluation of a PSUSA procedure

16.3.5. Ethanol extracts of: Iberis amara L., planta tota recens, Angelica archangelica L., radix, Matricaria recutita L., flos, Carum carvi L., fructus, Silybum marianum (L.) Gaertn., fructus, Melissa officinalis L., folium, Mentha piperita L., folium, Chelidonium majus L., herba, Glycyrrhiza glabra L., radix (NAP) - PSUSA/00010800/202311

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.3.6. Flupentixol (NAP) - PSUSA/00001444/202311

Applicant(s): various

PRAC Lead: Jana Lukačišinová

Scope: Evaluation of a PSUSA procedure

16.3.7. Flupentixol, melitracene (NAP) - PSUSA/00001445/202311

Applicant(s): various

PRAC Lead: Jana Lukačišinová

Scope: Evaluation of a PSUSA procedure

16.3.8. Imidapril (NAP) - PSUSA/00001726/202312

Applicant(s): various

PRAC Lead: John Joseph Borg

Scope: Evaluation of a PSUSA procedure

16.3.9. Ketoconazole (NAP) - PSUSA/00001808/202312

Applicant(s): various

PRAC Lead: Guðrún Þengilsdóttir

Scope: Evaluation of a PSUSA procedure

16.3.10. Ketoprofen, sucralfate (NAP) - PSUSA/00002797/202312

Applicant(s): various

PRAC Lead: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.3.11. Lisinopril, torasemide (NAP) - PSUSA/00010685/202312

Applicant(s): various

PRAC Lead: Jana Lukačišinová

Scope: Evaluation of a PSUSA procedure

16.3.12. Nabilone (NAP) - PSUSA/00002100/202312

Applicant(s): various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.3.13. Neomycin sulfate, nystatin, triamcinolone acetonide (NAP) - PSUSA/00002140/202312

Applicant(s): various

PRAC Lead: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.3.14. Sulfasalazine (NAP) - PSUSA/00002816/202312

Applicant(s): various

PRAC Lead: Marie Louise Schougaard Christiansen

Scope: Evaluation of a PSUSA procedure

16.3.15. Tafluprost, timolol (NAP) - PSUSA/00010324/202312

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.3.16. Tinzaparin (NAP) - PSUSA/00002967/202312

Applicant(s): various

PRAC Lead: Jo Robays

Scope: Evaluation of a PSUSA procedure

16.4. Follow-up to PSUR/PSUSA procedures

None

16.5. Variation procedure(s) resulting from PSUSA evaluation

16.5.1. Blinatumomab - BLINCYTO (CAP) - EMEA/H/C/003731/II/0054, Orphan

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Jana Lukacisinova

Scope: To update sections 4.2, 4.4, 4.8 of the SmPC to include Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS); and to update section D of Annex II to remove educational materials for physicians, pharmacists and nurses and to include ICANS within neurologic events in educational material for patient/caregivers and patient alert card following the outcome of PSUR procedure EMEA/H/C/PSUSA/00010460/202212. The package leaflet is updated accordingly. The RMP version 17.0 has also been submitted

16.6. Expedited summary safety reviews[41]

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)[42]

17.1.1. Valproate - EMEA/H/N/PSP/J/0094.4

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

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Progress report & substantial amendment: Characterization of neurodevelopmental disorders in children exposed in utero to valproate and/or other antiepileptic drugs with long-term followup: retrospective study of multiple European data sources

17.1.2. Topiramate - EMEA/H/N/PSP/J/0106

Applicant: Janssen (on behalf of a consortium)

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Drug evaluation study (DUS) to evaluate the effectiveness of the implemented risk minimisation measures, particularly focusing on preventing pregnancies and further characterising the prescribing patterns for topiramate in the target populations for pregnancy prevention

[41] 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

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

17.1.3. Topiramate - EMEA/H/N/PSP/J/0107

Applicant: Janssen (on behalf of a consortium)

PRAC Rapporteur: Ulla Wändel Liminga

Scope: PASS survey among healthcare professionals and patients to assess their knowledge and behaviour regarding the risks of topiramate use during pregnancy, the measures implemented to prevent pregnancy, and the receipt/use of educational materials as part of the pregnancy prevention program

17.2. Protocols of PASS non-imposed in the marketing authorisation(s)[43]

17.2.1. Agalsidase beta - FABRAZYME (CAP) - EMEA/H/C/000370/MEA 065.1

Applicant: Sanofi B.V.

PRAC Rapporteur: Liana Martirosyan

Scope: MAH's responses to MEA 065 [***EPIDEMIOLOGY STUDY PROTOCOL*** / Study no.: EPM0086] RSI as adopted in February 2024.
Fabrazyme (agalsidase beta) home infusion educational materials effectiveness evaluation: a survey of nurses administering home infusions

17.2.2. Bimekizumab - BIMZELX (CAP) - EMEA/H/C/005316/MEA 004.4

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Liana Martirosyan

Scope: MAH response to MEA 004.3 [***Protocol Study No. PS0037***] RSI and protocol amendment (Version 2.0, amendment #3) as adopted in April 2024.
An observational cohort study to evaluate bimekizumab exposure during pregnancy. To monitor the safety of bimekizumab use in pregnancy

17.2.3. Cabotegravir - APRETUDE (CAP) - EMEA/H/C/005756/MEA 003.1

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Martin Huber

Scope: MAH's responses to MEA 003 [***Draft Protocol***CAB LA PrEP Cohort] RSI and an updated revised study protocol draft as adopted in March 2024.
CAB LA PrEP Cohort: Prospective Cohort Study to Assess Adherence and Effectiveness of, and Monitor for Hepatotoxicity and Resistance to Cabotegravir for Pre-Exposure Prophylaxis in Europe

17.2.4. Darbepoetin alfa - ARANESP (CAP) - EMEA/H/C/000332/MEA 092.6

Applicant: Amgen Europe B.V.

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

PRAC Rapporteur: Martin Huber

Scope: MAH Response to MEA 092.5 RSI and REVISED PASS PROTOCOL / STUDY 20190404 as adopted in March 2024.
Title: Use of Erythropoiesis Stimulating Agents (ESAs) in Subjects Receiving Myelosuppressive Chemotherapy in Europe

17.2.5. Mirikizumab - OMVOH (CAP) - EMEA/H/C/005122/MEA 001.1

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Sonja Hrabcik

Scope: MAH response to questions on MEA 001 [Protocol / I6T-MC-B003] and an Updated Protocol / I6T-MC-B003 as adopted in February 2024.
Observational Study of Pregnancy and Infant Outcomes Among Women Exposed to Mirikizumab During Pregnancy in US-based Administrative Claims Data

17.2.6. Mirikizumab - OMVOH (CAP) - EMEA/H/C/005122/MEA 002.1

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Sonja Hrabcik

Scope: MAH's response to questions on MEA 002 [Protocol / I6T-MC-B004] and an updated revised protocol I6T-MC-B004 as adopted in February 2024.
Observational Secondary Database Study to Assess the Long-Term Safety of Mirikizumab in Routine Clinical Practice Using US Administrative Claims Data

17.2.7. Plasmodium falciparum and hepatitis B vaccine (recombinant, adjuvanted) - MOSQUIRIX (Art 58[44]) - EMEA/H/W/002300/MEA 003.10

Applicant: GlaxoSmithkline Biologicals SA

PRAC Rapporteur: Jean-Michel Dogné

Scope: **Protocol Amendment (version 3) / EPI-MALARIA-003 study protocol**
The EPI-MAL-003 study is a Phase IV prospective observational study to evaluate the safety, effectiveness and impact of the RTS,S/AS01E vaccine in young children in sub-Saharan Africa

17.2.8. Rimegepant - VYDURA (CAP) - EMEA/H/C/005725/MEA 001.3

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Karin Erneholm

Scope: MAH's response to MEA 001.2 [Rimegepant Pregnancy Registry study C4951005 (formerly no BHV3000-402) **UPDATED PROTOCOL / ANNUAL INTERIM REPORT**], revised protocol (v4.0) and SAP (v3.0) as adopted in September 2023.
A Prospective, Registry-based, Observational Study to Assess Maternal, Fetal and Infant Outcomes Following Exposure to Rimegepant: The Migraine Observational Nurtec Pregnancy

[44] Article 58 of Regulation (EC) No 726/2004 allows the Committee for Medicinal Products for Human Use (CHMP) to give opinions, in co-operation with the World Health Organisation (WHO) on medicinal products for human use that are intended exclusively for markets outside of the European Union (EU)

Registry (MONITOR)

17.2.9. Selexipag - UPTRAVI (CAP) - EMEA/H/C/003774/MEA 003.6

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Nathalie Gault

Scope: ***Protocol Amendment*** / study AC-065A403 (version 5):
A PASS to evaluate risk minimisation measures for mEDication errors with Uptravi (selexipag) during the titration phase in patients with pulmonary arterial hypertension (PAH) in Clinical prAcTicE (EDUCATE)

17.2.10. Tildrakizumab - ILUMETRI (CAP) - EMEA/H/C/004514/MEA 003.9

Applicant: Almirall S.A

PRAC Rapporteur: Adam Przybylkowski

Scope: MAH response to MEA 003.8 and revised protocol [***FOURTH Annual Interim Results*** / Study No.: M-14745-40] as adopted in March 2024.
Title: Tildrakizumab Post-Authorisation Safety Study (PASS) in European Psoriasis Registries.
To collect long-term safety data in particular relating to event of special interest (important potential risks and pregnancy related outcomes) for tildrakizumab. (Malignancies, MACEs, Serious infections, SIBH, Hypersensitivity, IBD, Safety in pregnant and lactating women)

17.3. Results of PASS imposed in the marketing authorisation(s)[45]

None

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

17.4.1. Adalimumab - HUMIRA (CAP) - EMEA/H/C/000481/II/0218

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Mari Thorn

Scope: Submission of the final report for study P10-023 listed as a category 3 study in the RMP. This is a 10-year, post marketing, observational registry to assess long term safety of Humira (adalimumab) in adult patients with chronic plaque psoriasis (Ps)

17.4.2. Edoxaban - LIXIANA (CAP) - EMEA/H/C/002629/WS2705/0050; Edoxaban - ROTEAS (CAP) - EMEA/H/C/004339/WS2705/0036

Applicant: Daiichi Sankyo Europe GmbH

PRAC Rapporteur: Nathalie Gault

Scope: Submission of a Summary of Changes for the DSE-EDO-05-14-EU clinical study report, as an erratum detailing the updates.

[45] In accordance with Article 107p-q of Directive 2001/83/EC
[46] 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

DSE-EDO-05-14-EU is a non-interventional PASS on Edoxaban treatment in routine clinical practice for patients with acute venous thromboembolism in Europe (ETNA-VTE-Europe) which was listed as a category 3 study in the RMP (MEA 007)

17.4.3. Elasomeran - SPIKEVAX (CAP) - EMEA/H/C/005791/II/0131

Applicant: Moderna Biotech Spain S.L.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Submission of the final report from study mRNA-1273-919 - An Observational Study to Assess Maternal and Infant Outcomes Following Exposure to Spikevax During Pregnancy, listed as a category 3 study in the RMP

17.4.4. Epoetin alfa - ABSEAMED (CAP) - EMEA/H/C/000727/WS2615/0108; Epoetin alfa - BINOCRIT (CAP) - EMEA/H/C/000725/WS2615/0108; Epoetin alfa - EPOETIN ALFA HEXAL (CAP) - EMEA/H/C/000726/WS2615/0108

Applicant: Sandoz GmbH

PRAC Rapporteur: Tiphaine Vaillant

Scope: Submission of the final report from Non-Interventional Post authorisation Safety Study, NI-PASS HX575-507 listed as a category 3 study in the RMP. The non-interventional study (NIS PASS) study HX575-507 was conducted to address a post-approval requirement (MEA 13.5) to evaluate the safety profile of HX575 administered s.c. in patients with CKD-induced anemia under real-life conditions, in order to increase confidence on the safe use of s.c. HX575. The RMP version 19.0 has also been submitted

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

17.5.1. Avapritinib - AYVAKYT (CAP) - EMEA/H/C/005208/SOB 009.3

Applicant: Blueprint Medicines (Netherlands) B.V.

PRAC Rapporteur: Bianca Mulder

Scope: MAH's responses to SOB 009.2 [Study BLU-285-1406] RSI as adopted in March 2024.
Study BLU-285-1406 is a multinational, open-label, observational post-authorisation safety study that will evaluate the long-term safety and efficacy of avapritinib for the first-line treatment or following ≤4 months of imatinib treatment in at least 50 patients with PDGFRA D842V-mutated GIST

17.5.2. Burosumab - CRYSVITA (CAP) - EMEA/H/C/004275/MEA 004.4

Applicant: Kyowa Kirin Holdings B.V.

PRAC Rapporteur: Gabriele Maurer

Scope: ***Second interim study report*** [Study No EUPAS32190]
Non-interventional PASS of Burosumab in the Treatment of Children >1 year of age, Adolescents and Adults with X-linked Hypophosphataemia (protocol number 2019-36-EU-

CRY)

17.5.3. Covid-19 Vaccine (recombinant, adjuvanted) - NUVAXOVID (CAP) - EMEA/H/C/005808/MEA 004.6

Applicant: Novavax CZ a.s.

PRAC Rapporteur: Gabriele Maurer

Scope: MAH's response to MEA 004.5 [Protocol, study no. 2019nCoV-402] RSI as adopted in January 2024.
UK PASS Using the Clinical Practice Research Datalink (CPRD): A surveillance study to characterise the safety profile of Nuvaxovid in adults aged 18 years and older in the real-world setting using the UK CPRD

17.5.4. Diroximel fumarate - VUMERITY (CAP) - EMEA/H/C/005437/MEA 002.3

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Martin Huber

Scope: ***Annual Progress Report / Study 272MS403***
Title: An observational study utilising data from big MS data registries to evaluate the long-term safety of Vumerity and Tecfidera

17.5.5. Daratumumab - DARZALEX (CAP) - EMEA/H/C/004077/MEA 011.3

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Carla Torre

Scope: From EMEA/H/C/004077/II/0043:
Interim study result / Study AMY2009
Study AMY2009 is a multicenter, multicohort, open-label, Phase 2 study in participants with newly diagnosed systemic AL amyloidosis. The primary objective of the study is to further characterize cardiac adverse events in patients with newly diagnosed AL amyloidosis treated with subcutaneous daratumumab-based therapy in terms of the incidence, severity, clinical presentation, management, and outcome

17.5.6. Eculizumab - SOLIRIS (CAP) - EMEA/H/C/000791/MEA 062.3

Applicant: Alexion Europe SAS

PRAC Rapporteur: Monica Martinez Redondo

Scope: MAH's response to MEA 062.2 [***aHUS Registry Biennial Interim Report*** /Protocol M11-001] RSI as adopted in March 2024.
Title: An Observational, non-interventional multicenter, multinational study of patients with atypical hemolytic-uremic syndrome

17.5.7. Esketamine - SPRAVATO (CAP) - EMEA/H/C/004535/MEA 003.2

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Kirsti Villikka

Scope: MAH's responses to MEA 003.1 [***Interim Study / Study no.: PCSNSP002812***] RSI as adopted in March 2024.
Survey to Assess the Effectiveness of SPRAVATO Educational Materials for Additional Risk Minimization Measures in the European Union

17.5.8. Lisocabtagene maraleucel, Lisocabtagene maraleucel - BREYANZI (CAP) - EMEA/H/C/004731/MEA 007.1

Applicant: Bristol-Myers Squibb Pharma EEIG, ATMP

PRAC Rapporteur: Gabriele Maurer

Scope: MAH's response to MEA 007 [LTFU study (GC LTFU 001)] RSI as adopted in January 2024.
Long-term follow-up of safety and efficacy for all paediatric and adult subjects exposed do a GM T cell therapy in Bristol-Myers Squibb sponsored, or Bristol Myers Squibb alliance partner sponsored, clinical trials in accordance with Health Authorities' guidance for long-term (up to 15 years) follow-up of subjects treated with gene therapy products

17.5.9. Mexiletine - NAMUSCLA (CAP) - EMEA/H/C/004584/MEA 001.4

Applicant: Lupin Europe GmbH

PRAC Rapporteur: Eva Jirsová

Scope: Registry study to determine the long-term safety and tolerability of Namuscla for the symptomatic treatment of myotonia in adult patients with non-dystrophic myotonic disorder. (Cat. 3 study in the RMP)
SECOND INTERIM STUDY REPORT, Study LUP/MEX/2018/001

17.5.10. Nonacog beta pegol - REFIXIA (CAP) - EMEA/H/C/004178/ANX 001.1

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Gabriele Maurer

Scope: MAH response to ANX 001 [***Fifth Progress Report (yearly) for PASS NN7999-4031/Paradigm 8***] RSI as adopted in 21 March 2024.
A Non-Interventional PASS in male haemophilia B patients receiving Nonacog Beta Pegol (N9-GP) prophylaxis treatment

17.5.11. Ofatumumab - KESIMPTA (CAP) - EMEA/H/C/005410/MEA 002.5

Applicant: Novartis Ireland Limited

PRAC Rapporteur: Amelia Cupelli

Scope: MAH Response to MEA 002.4 [Study COMB157G2407 / PRIM] RSI as adopted in March 2024:
Provision of the answers to the outstanding concerns raised in the assessment report of EMEA/H/C/005410/MEA/002.4 pertaining to second interim report for the Pregnancy outcomes Intensive Monitoring (PRIM), study (COMB157G2407) report for Kesimpta (ofatumumab)

17.5.12. Rimegepant - VYDURA (CAP) - EMEA/H/C/005725/MEA 002.3

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Karin Erneholm

Scope: MAH response to MEA 002.2 [Rimegepant Pregnancy Outcomes study C4951006 (formerly BHV3000-403)**UPDATED PROTOCOL / ANNUAL INTERIM REPORT / UPDATED SAP**], revised protocol (v6.0) and revised SAP (v2.0) as adopted in September 2023. Retrospective Cohort Study of Pregnancy Outcomes in Women Exposed to Rimegepant During Pregnancy

17.5.13. Somatrogon - NGENLA (CAP) - EMEA/H/C/005633/MEA 001.2

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Martirosyan

Scope: From Initial MAA:
Statistical Analysis Plan PASS C0311023
An Active Surveillance PASS to Monitor the Real-World Long-term Safety of Somatrogon Among Paediatric Patients in Europe to estimate the incidence rates of neoplasms, diabetes mellitus type 2, and the clinical endpoints related to immunogenicity, and medication errors in paediatric patients treated with somatrogon, and paediatric patients treated with once daily somatropin, in the course of routine clinical care

17.5.14. Sutimlimab - ENJAYMO (CAP) - EMEA/H/C/005776/MEA 003.1

Applicant: Sanofi B.V.

PRAC Rapporteur: Jan Neuhauser

Scope: From initial MAA:
Study OBS16454 (RMP category 3) PASS (non-imposed)
Title: Sutimlimab Cold Agglutinin Disease Real World Evidence Registry (CADENCE).
**ANNUAL INTERIM REPORT*

17.6. Others

17.6.1. Tozinameran - COMIRNATY (CAP) - EMEA/H/C/005735/MEA 037.6

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Liana Martirosyan

Scope: From II/0059:
Study Protocol C4591009
A non-interventional PASS in US to assess the occurrence of safety events of interest, including myocarditis and pericarditis, among individuals in the general US population and in subcohorts of interest within selected data sources participating in the US Sentinel System.
Monitoring report, Study C4591009

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. Amifampridine - FIRDAPSE (CAP) - EMEA/H/C/001032/S/0077 (without RMP)

Applicant: SERB SA

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Annual reassessment of the marketing authorisation

18.1.2. Chenodeoxycholic acid - CHENODEOXYCHOLIC ACID LEADIANT (CAP) - EMEA/H/C/004061/S/0024 (without RMP)

Applicant: Leadiant GmbH

PRAC Rapporteur: Adam Przybylkowski

Scope: Annual reassessment of the marketing authorisation

18.1.3. Idursulfase - ELAPRASE (CAP) - EMEA/H/C/000700/S/0116 (without RMP)

Applicant: Takeda Pharmaceuticals International AG Ireland Branch

PRAC Rapporteur: Liana Martirosyan

Scope: Annual reassessment of the marketing authorisation

18.1.4. Susoctocog alfa - OBIZUR (CAP) - EMEA/H/C/002792/S/0056 (without RMP)

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Gabriele Maurer

Scope: Annual reassessment of the marketing authorisation

18.1.5. Zanamivir - DECTOVA (CAP) - EMEA/H/C/004102/S/0018 (without RMP)

Applicant: GlaxoSmithKline Trading Services Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Annual reassessment of the marketing authorisation

18.2. Conditional renewals of the marketing authorisation

18.2.1. Pralsetinib - GAVRETO (CAP) - EMEA/H/C/005413/R/0019 (without RMP)

Applicant: Roche Registration GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Conditional renewal of the marketing authorisation

18.3. Renewals of the marketing authorisation

18.3.1. Adalimumab - AMSPARITY (CAP) - EMEA/H/C/004879/R/0008 (with RMP)

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Mari Thorn

Scope: 5-year renewal of the marketing authorisation

18.3.2. Arsenic trioxide - ARSENIC TRIOXIDE ACCORD (CAP) - EMEA/H/C/005175/R/0009 (without RMP)

Applicant: Accord Healthcare S.L.U.

PRAC Rapporteur: Tiphaine Vaillant

Scope: 5-year renewal of the marketing authorisation

18.3.3. Bortezomib - BORTEZOMIB FRESENIUS KABI (CAP) - EMEA/H/C/005074/R/0010 (without RMP)

Applicant: Fresenius Kabi Deutschland GmbH

PRAC Rapporteur: Amelia Cupelli

Scope: 5-year renewal of the marketing authorisation

18.3.4. Brolucizumab - BEOVU (CAP) - EMEA/H/C/004913/R/0030 (without RMP)

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Gabriele Maurer

Scope: 5-year renewal of the marketing authorisation

18.3.5. Deferasirox - DEFERASIROX ACCORD (CAP) - EMEA/H/C/005156/R/0011 (without RMP)

Applicant: Accord Healthcare S.L.U.

PRAC Rapporteur: Tiphaine Vaillant

Scope: 5-year renewal of the marketing authorisation

18.3.6. Fostamatinib - TAVLESSE (CAP) - EMEA/H/C/005012/R/0018 (with RMP)

Applicant: Instituto Grifols, S.A.

PRAC Rapporteur: Bianca Mulder

Scope: 5-year renewal of the marketing authorisation

18.3.7. Imipenem, Cilastatin, Relebactam - RECARBRIO (CAP) - EMEA/H/C/004808/R/0029 (without RMP)

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: 5-year renewal of the marketing authorisation

18.3.8. Osilodrostat - ISTURISA (CAP) - EMEA/H/C/004821/R/0022 (without RMP)

Applicant: Recordati Rare Diseases

PRAC Rapporteur: Maria del Pilar Rayon

Scope: 5-year renewal of the marketing authorisation

18.3.9. Ospemifene - SENSHIO (CAP) - EMEA/H/C/002780/R/0048 (without RMP)

Applicant: Shionogi B.V.

PRAC Rapporteur: Kirsti Villikka

Scope: 5-year renewal of the marketing authorisation

18.3.10. Siponimod - MAYZENT (CAP) - EMEA/H/C/004712/R/0029 (without RMP)

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Maria del Pilar Rayon

Scope: 5-year renewal of the marketing authorisation

18.3.11. Upadacitinib - RINVOQ (CAP) - EMEA/H/C/004760/R/0051 (without RMP)

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Petar Mas

Scope: 5-year renewal of the marketing authorisation

19. Annex II – List of participants

List of participants including any restrictions with respect to involvement of members/alternates/experts following evaluation of declared interests for the 8-11 July 2024 PRAC meeting, which was held in-person.

An asterisk (*) after the role, in the second column, signals that the member/alternate attended remotely. Additional experts participated in (part of) the meeting, either in person or remotely.

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	
Petar Mas	Member	Croatia	No interests declared	
Barbara Bytyqi	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	
Marie Louise Schougaard Christiansen	Member	Denmark	No interests declared	
Karin Erneholm	Alternate*	Denmark	No interests declared	
Maia Uusküla	Member	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 discussion, final deliberations and voting on:	**4.1.2.** Atezolizumab – TECENTRIQ (CAP); Avelumab – BAVENCIO (CAP); Cemiplimab – LIBTAYO (CAP); Dostarlimab – JEMPERLI (CAP); Durvalumab - IMFINZI (CAP); Ipilimumab – YERVOY (CAP); Nivolumab - OPDIVO (CAP), OPDUALAG (CAP); Pembrolizumab – KEYTRUDA (CAP); Retifanlimab - ZYNYZ (CAP); Tislelizumab – TEVIMBRA (CAP); Tremelimumab - IMJUDO (CAP) **15.3.15.** Nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/WS2672/0141; Ipilimumab - YERVOY (CAP)

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				- EMEA/H/C/002213/WS2672/0111
Sofia Trantza	Member	Greece	No interests declared	
Georgia Gkegka	Alternate*	Greece	No interests declared	
Julia Pallos	Member	Hungary	No participation in discussion, final deliberations and voting on:	**4.1.2.** Atezolizumab – TECENTRIQ (CAP); Avelumab – BAVENCIO (CAP); Cemiplimab – LIBTAYO (CAP); Dostarlimab – JEMPERLI (CAP); Durvalumab - IMFINZI (CAP); Ipilimumab – YERVOY (CAP); Nivolumab - OPDIVO (CAP), OPDUALAG (CAP); Pembrolizumab – KEYTRUDA (CAP); Retifanlimab - ZYNYZ (CAP); Tislelizumab – TEVIMBRA (CAP); Tremelimumab - IMJUDO (CAP) **6.3.7.** Hydroxycarbamide (NAP) - PSUSA/00009182/202312 **15.3.15.** Nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/WS2672/0141;

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				Ipilimumab - YERVOY (CAP) - EMEA/H/C/002213/WS2672/0111 **15.3.26.** Ozanimod - ZEPOSIA (CAP) - EMEA/H/C/004835/II/0024/G **17.5.8.** Lisocabtagene maraleucel, Lisocabtagene maraleucel - BREYANZI (CAP) - EMEA/H/C/004731/MEA 007.1
Guðrún Þengilsdóttir	Alternate	Iceland	No interests declared	
Rhea Fitzgerald	Member	Ireland	No interests declared	
Eamon O Murchu	Alternate	Ireland	No interests declared	
Amelia Cupelli	Member	Italy	No interests declared	
Zane Neikena	Member	Latvia	No interests declared	
Rugile Pilviniene	Member	Lithuania	No interests declared	
Lina Seibokiene	Alternate*	Lithuania	No restrictions applicable to this meeting	
Nadine Petitpain	Member	Luxembourg	No restrictions applicable to this meeting	
John Joseph Borg	Member	Malta	No interests declared	
Liana Martirosyan	Member	Netherlands	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Bianca Mulder	Alternate	Netherlands	No interests declared	
David Olsen	Member	Norway	No participation in discussion, final deliberations and voting on:	**4.1.1.** Angiotensin II receptor blockers: azilsartan - EDARBI (CAP), NAP; irbesartan - APROVEL (CAP); IFIRMASTA (CAP); IRBESARTAN TEVA (CAP); IRBESARTAN ZENTIVA (CAP); KARVEA (CAP), NAP; irbesartan, hydrochlorothiazide - COAPROVEL (CAP); IFIRMACOMBI (CAP); IRBESARTAN HYDROCHLOROTHIAZIDE ZENTIVA (CAP); IRBESARTAN/HYDROCHLOROTHIAZIDE TEVA (CAP); KARVEZIDE (CAP), NAP; telmisartan - KINZALMONO (CAP), MICARDIS (CAP), PRITOR (CAP), TELMISARTAN ACTAVIS (CAP), TELMISARTAN TEVA PHARMA (CAP), TOLURA (CAP), NAP; telmisartan, amlodipine – TWYNSTA (CAP), NAP;

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				telmisartan, hydrochlorothiazide - ACTELSAR HCT (CAP), KINZALKOMB (CAP), MICARDISPLUS (CAP), PRITORPLUS (CAP), TOLUCOMBI (CAP), NAP; valsartan, sacubitril – ENTRESTO (CAP), NEPARVIS (CAP); valsartan, amlodipine – COPALIA (CAP), DAFIRO (CAP), EXFORGE (CAP), NAP; valsartan, amlodipine, hydrochlorothiazide - COPALIA HCT (CAP), DAFIRO HCT (CAP), EXFORGE HCT (CAP), NAP; other fixed-dose combinations containing angiotensin II receptor blockers (NAP) **4.1.3.** Paracetamol (NAP); fixed dose combinations containing paracetamol (NAP) **15.2.3.** Larotrectinib - VITRAKVI (CAP) -

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				EMEA/H/C/004 919/II/0036
Pernille Harg	Alternate*	Norway	No interests declared	
Adam Przybylkowski	Member	Poland	No interests declared	
Ana Sofia Diniz Martins	Member	Portugal	No interests declared	
Carla Torre	Alternate	Portugal	No interests declared	
Irina Sandu	Alternate	Romania	No interests declared	
Anna Mareková	Member	Slovakia	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 restrictions applicable to this meeting	
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 restrictions applicable to this meeting	
Anette Kirstine Stark	Member	Independent scientific expert	No interests declared	
Roberto Frontini	Member	Healthcare Professionals' Representative	No restrictions applicable to this meeting	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Salvatore Antonio Giuseppe Messana	Alternate	Healthcare Professionals' Representative	No interests declared	
Marko Korenjak	Member	Patients' Organisation Representative	No interests declared	
Michal Rataj	Alternate	Patients' Organisation Representative	No interests declared	
Christelle Bizimungu	Expert	Belgium	No restrictions applicable to this meeting	
Evelien de Clercq	Expert	Belgium	No interests declared	
Laurence de Fays	Expert	Belgium	No interests declared	
Dominik Dautović	Expert	Croatia	No interests declared	
Ivana Ljubičić	Expert	Croatia	No interests declared	
Lara Miletić	Expert	Croatia	No restrictions applicable to this meeting	
Lora Pavlinović	Expert	Croatia	No interests declared	
Lucie Skálová	Expert	Czech Republic	No interests declared	
Karina Suciu-Subert	Expert	Czech Republic	No interests declared	
Marian Hjortlund Allon	Expert	Denmark	No interests declared	
Annette Cleveland Nielsen	Expert	Denmark	No restrictions applicable to this meeting	
Kristina Laursen	Expert	Denmark	No interests declared	
Line Michan	Expert	Denmark	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Moritz Sander	Expert	Denmark	No restrictions applicable to this meeting	
Aynur Sert	Expert	Denmark	No interests declared	
Per Sindahl	Expert	Denmark	No interests declared	
Ditte Søgaard	Expert	Denmark	No interests declared	
Helene Stenbæk Hansen	Expert	Denmark		
Louise Wenzel-Petersen	Expert	Denmark	No interests declared	
Pauline Dayani	Expert	France	No interests declared	
Camille De-Kervasdoue	Expert	France	No interests declared	
Dina Habib-Hanawy	Expert	France	No interests declared	
Jelena Katic	Expert	Germany	No interests declared	
Dennis Lex	Expert	Germany	No interests declared	
Tania Meier	Expert	Germany	No interests declared	
Vahid Taravati	Expert	Germany	No interests declared	
Bernadett Murárik	Expert	Hungary	No restrictions applicable to this meeting	
Luana Mifsud Buhagiar	Expert	Malta	No interests declared	
Nanneke Hendricks	Expert	Netherlands	No interests declared	
Emma van Beuzekom	Expert	Netherlands	No interests declared	
Menno van der Elst	Expert	Netherlands	No interests declared	
Martina Raud	Expert	Sweden	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Charlotte Welsh	Expert	Sweden	No restrictions applicable to this meeting	
A representative from the European Commission attended the meeting				
Observers from Health Canada (Canada), FDA and WHO attended the meeting.				
Meeting run with support from relevant EMA staff				

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

20. Annex III - List of acronyms and abbreviations

For a list of acronyms and abbreviations used in the PRAC minutes, see:

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: Referral procedures: human medicines | European Medicines Agency (europa.eu)

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