27 March 2025
EMA/PRAC/468455/2024 Rev.1[1]
Human Medicines Division

# Pharmacovigilance Risk Assessment Committee (PRAC)

## Minutes of PRAC meeting on 2-5 September 2024

Chair: Ulla Wändel Liminga – 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).

[1] '12.1.4. PRAC working group - Best practice guide on using PRAC plenary time efficiently and effectively – update on the implementation of quantitative goals – Q2 2024' and '12.8.2 PRAC workload statistics – Q2 2024' added

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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[2] 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.

## 1.2. Agenda of the meeting on 02-05 September 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 08-11 July 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 08-11 July 2024 were published on the EMA website on 10 September 2024 (EMA/PRAC/337971/2024).

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

## 2.1. Newly triggered procedures

None

[2] No alternates for COMP

## 2.2. Ongoing procedures

None

## 2.3. Procedures for finalisation

### 2.3.1. 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 Bytyqi

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 for metamizole-containing products is to be concluded. The review was initiated following the fact that cases of agranulocytosis and related complications were still 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. A final assessment of the data submitted was produced by the respective (co-)Rapporteurs according to the agreed timetable. For further background, see PRAC minutes June 2024 and PRAC minutes July 2024.

**Discussion**

PRAC reviewed the totality of the data available in relation to the risk of agranulocytosis for metamizole-containing products. These data included the responses submitted in writing by the MAHs, data from EudraVigilance, scientific literature, the views expressed by a group of independent experts following their consultation as part of an ad-hoc expert group (AHEG), submissions from stakeholders and a written intervention received from a third party.

Based on the current knowledge of the established risk of agranulocytosis following the review, PRAC considered that the early recognition of symptoms suggestive of agranulocytosis, treatment interruption of metamizole and prompt clinical testing are critical to minimise the risk of complications of metamizole-induced agranulocytosis (MIA). Therefore PRAC concluded that the existing warnings in the product information of metamizole-containing products should be updated in line with the current knowledge to facilitate prompt recognition and diagnosis of MIA.

Furthermore, PRAC concluded that there is no evidence to support the effectiveness of existing recommendations for regular blood count monitoring in patients to reduce the risk of MIA-related complications. MIA is not dose-dependent and can occur at any time during treatment and shortly after treatment discontinuation. PRAC agreed that blood count monitoring should be performed on suspected cases of agranulocytosis. As a consequence,

the product information should be updated to remove references to regular blood count monitoring of patients.

PRAC also noted concerns about the use of metamizole-containing products in patients with agranulocytosis caused by metamizole (or other pyrazolones or pyrazolidines) in their medical history, or in patients with existent impaired bone marrow function or diseases of the haematopoietic system, as these patients are at an increased risk of developing agranulocytosis. PRAC concluded that contraindications in these patient groups should be reflected in the product information of metamizole-containing products.

As a consequence, PRAC considered that the benefit-risk balance of metamizole-containing products remains favourable subject to the agreed amendments to the product information mentioned above.

**Summary of recommendation(s)/conclusions**

- PRAC adopted a recommendation, by majority, to vary[3] the terms of the marketing authorisations for metamizole-containing products to be considered by CMDh for adoption of a position.
- PRAC agreed on the distribution of a direct healthcare professional communication (DHPC) together with a communication plan.

Twenty-three members voted in favour of the recommendation whilst eleven[4] members had a divergent view. The Icelandic PRAC member agreed with the recommendation, while the Norwegian PRAC member did not agree with the recommendation.

Post-meeting note 1: On 6 September 2024, the press release entitled 'EMA recommends measures to minimise serious outcomes of known side effect with painkiller metamizole' (EMA/407900/2024) was published on the EMA website.

Post-meeting note 2: On 20 September 2024, the press release (EMA/407900/2024) was published on the EMA website following the adoption of the CMDh position.

# 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] Update of sections 4.2, 4.3 and 4.4 of the SmPC. The package leaflet is updated accordingly.
[4] Annalisa Capuano (proxy to Milou-Daniel Drici), Milou-Daniel Drici, Rhea Fitzgerald, Terhi Lehtinen, Liana Martirosyan, Patricia McGettigan, Hedvig Marie Egeland Nordeng, Mari Thörn, Anette Kirstine Stark, Marie Louise Schougaard Christiansen, Tiphaine Vaillant

## 3.4. Re-examination procedures[5]

None

## 3.5. Others

None

# 4. Signals assessment and prioritisation[6]

For further details, see also the adopted PRAC recommendations on signals under the corresponding month.

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

See also Annex I 14.1.

### 4.1.1. Canagliflozin – INVOKANA (CAP); canagliflozin, metformin – VOKANAMET (CAP); dapagliflozin - DAPAGLIFLOZIN VIATRIS, EDISTRIDE, FORXIGA (CAP), NAP; dapagliflozin, metformin - EBYMECT, XIGDUO (CAP), NAP; saxagliptin, dapagliflozin – QTERN (CAP)

Applicants: AstraZeneca AB (Ebymect, Edistride, Forxiga, Qtern, Xigduo), , Janssen-Cilag International N.V. (Invokana), Viatris Limited (Dapagliflozin Viatris), various

PRAC Rapporteur: Mari Thorn

Scope: Signal of sarcopenia

**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 sarcopenia was identified by EMA, based on a published meta-analysis by *Zhang et al., 2023*[7], 15 cases retrieved from EudraVigilance and the literature. 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, including the published meta-analysis by *Zhang et al., 2023*, PRAC agreed that further evaluation on the signal of sarcopenia following administration of the sodium-glucose

[5] Re-examination of PRAC recommendation under Article 32 of Directive 2001/83/EC
[6] 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
[7] Zhang S, Qi Z, Wang Y, et al. Effect of sodium-glucose transporter 2 inhibitors on sarcopenia in patients with type 2 diabetes mellitus: a systematic review and meta-analysis. Front Endocrinol (Lausanne) 2023;14:1203666. https://doi.org/10.3389/fendo.2023.1203666

co-transporter 2 (SGLT2) inhibitors of canagliflozin, dapagliflozin, empagliflozin and ertugliflozin-containing mono products and their combinations is warranted.

**Summary of recommendation(s)**

- The MAHs for Invokana (canagliflozin), Vokanamet (canagliflozin, metformin), dapagliflozin-containing medicinal products including Dapagliflozin Viatris, Edistride, Forxiga and its combinations with metformin including Ebymect and Xigduo, as well as Qtern (saxagliptin, dapagliflozin) should submit to EMA, within 60 days, a cumulative review of the signal, including an analysis of all case reports of the preferred terms (PTs) of muscle atrophy, muscle necrosis, muscle spasms, muscular weakness, myopathy and myalgia and related terms, including a review of the clinical trial data, published literature along with the meta-analysis by *Zhang et al., 2023*, data from post-marketing reports, as well as a discussion on possible biological plausibility and mechanism of this association; consideration should be given to all approved indications of the class, including type 2 diabetes mellitus, chronic heart failure and chronic kidney disease as relevant, and the data should be presented in accordance with the given indication of use. In addition, the MAHs should discuss the need for any potential amendment to the product information (PI) and/ or the risk management plan (RMP) as warranted.
- A 90-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

## 4.2. Signals follow-up and prioritisation

### 4.2.1. Medroxyprogesterone acetate (NAP)

Applicant: various

PRAC Rapporteur: Bianca Mulder

Scope: Signal of meningioma

**Background**

For background information, see PRAC minutes March 2024.

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

**Discussion**

Having considered the available evidence in EudraVigilance, the literature, and the cumulative review submitted by the MAHs, PRAC concluded that there is sufficient evidence to establish a causal association between medroxyprogesterone acetate (MPA) and meningioma. Therefore, the product information should be updated to add meningioma as a contraindication and a warning, taking into account the already existing wording in some nationally authorised products, as well as an undesirable effect with a frequency 'not known' for all injectable formulations and ≥100 mg oral formulations containing MPA.

**Summary of recommendation(s)**

- The MAHs for MAP-containing medicinal products should submit a variation to national competent authorities, within 60 days, to amend the product information[8].
- The MAH Pfizer Limited should distribute to all member states a direct healthcare professional communication (DHPC) to communicate the risk of developing meningioma with high dose medroxyprogesterone acetate containing medicines (all injectable formulations and ≥100 mg oral formulations). In addition, to ensure further monitoring of the potential risk of meningioma and low dose oral formulations of MPA (<100 mg oral formulations) and combination products containing MPA, a targeted follow-up questionnaire should be implemented for cases of meningiomas, as warranted.

## 4.3. Variation procedure(s) resulting from signal evaluation

None

# 5. Risk management plans (RMPs)

## 5.1. Medicines in the pre-authorisation phase

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

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

See also Annex I 15.1.

### 5.1.1. Belzutifan (CAP MAA) - EMEA/H/C/005636

Scope (pre D-180 phase): Treatment of adult patients with advanced renal cell carcinoma (RCC) and treatment of adult patients with von Hippel-Lindau (VHL) disease

### 5.1.2. Garadacimab (CAP MAA) - EMEA/H/C/006116, Orphan

Applicant: CSL Behring GmbH

Scope (pre D-180 phase): Routine prevention of attacks of hereditary angioedema (HAE)

### 5.1.3. Givinostat (CAP MAA) - EMEA/H/C/006079, Orphan

Applicant: Italfarmaco S.p.A.

Scope (pre D-180 phase): Treatment of Duchenne muscular dystrophy (DMD)

### 5.1.4. Lazertinib (CAP MAA) - EMEA/H/C/006074

Scope (pre D-180 phase): Treatment of adult patients with advanced non-small cell lung cancer (NSCLC)

[8] Update of sections 4.3, 4.4, 4.8 and 5.1. The package leaflet is updated accordingly.

### 5.1.5. Repotrectinib (CAP MAA) - EMEA/H/C/006005

Scope (pre D-180 phase): Treatment of ROS1-positive locally advanced or metastatic non-small cell lung cancer (NSCLC) and for solid tumours

### 5.1.6. Sipavibart (CAP MAA) - EMEA/H/C/006291

Scope (pre D-120 phase, accelerated assessment): Indicated for the pre-exposure prophylaxis of COVID-19 in adults and adolescents 12 years of age and older

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

See Annex I 15.2.

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

See Annex I 15.3.

# 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. Apalutamide - ERLEADA (CAP) - PSUSA/00010745/202402

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

**Background**

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Erleada, a centrally authorised medicine containing apalutamide 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 Erleada (apalutamide) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add lichenoid eruption as an undesirable effect with a frequency 'not known' and to include decreased appetite in the

summary of the safety profile. Therefore, the current terms of the marketing authorisation(s) should be varied[9].

- In the next PSUR, the MAH should provide a thorough assessment of the cases of hepatotoxicity included for review, as well as cases from literature. Additionally, the MAH should also present all the available data and provide more details on cases previously deemed not relevant. Also, the MAH should closely monitor cases of drug-drug interaction between apalutamide and nirmatrelvir/ritonavir.

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

### 6.1.2. Besilesomab - SCINTIMUN (CAP) - PSUSA/00000385/202401

Applicant: CIS BIO International

PRAC Rapporteur: Monica Martinez Redondo

Scope: Evaluation of a PSUSA procedure

**Background**

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Scintimun, a centrally authorised medicine containing besilesomab 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 Scintimun (besilesomab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to remove the DHPC and the patient card as additional minimisation measures put in place to address the risks of human anti-mouse antibody (HAMA) generation, hypersensitivity reactions and acute hypotension. Therefore, the current terms of the marketing authorisation(s) should be varied[10].
- An updated RMP v.15.4 was approved in order to remove misdiagnosis and hypersensitivity reactions from the list of safety concerns, as well as the DHPC and the patient card.
- In the next PSUR, the MAH should continue to monitor cases of off-label use and provide cumulative analysis of these cases.

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

### 6.1.3. Brivaracetam - BRIVIACT (CAP) - PSUSA/00010447/202401

Applicant: UCB Pharma S.A.

[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.
[10] Update of Annex II-D. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

**Background**

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Briviact, a centrally authorised medicine containing brivaracetam 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 Briviact (brivaracetam) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add a warning regarding Stevens-Johnson syndrome, and add it as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[11].
- In the next PSUR, the MAH should provide all the reports for brivaracetam regarding pregnancy cases from EURAP and from NAAPR, case reports and case series in published literature, , and clarify available information about the topic of psychiatric and neurodevelopment disorders.

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. Dapagliflozin, metformin - EBYMECT (CAP); XIGDUO (CAP) - PSUSA/00010294/202401

Applicant: AstraZeneca AB

PRAC Rapporteur: Bianca Mulder

Scope: Evaluation of a PSUSA procedure

**Background**

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Ebymect and Xigduo, centrally authorised medicines containing dapagliflozin/metformin 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 the dapagliflozin/metformin-containing medicinal products Ebymect and Xigduo in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add a warning regarding increased haematocrit. Therefore, the current terms of the marketing authorisation(s) should be varied[12].

[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.
[12] Update of SmPC section 4.4. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion.

- In the next PSUR, the MAH should provide a cumulative review of (groin) abscesses on different locations in patients treated with dapagliflozin/metformin, as well as to discuss any amendments on the product information, as warranted. In addition, the MAH should review all cases of Fournier's gangrene reported with dapagliflozin in the context of urological surgery, to follow the outcome of the evaluation of PSUSA for dapagliflozin (EMEA/H/C/PSUSA/00010029/202310).

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. Daridorexant - QUVIVIQ (CAP) - PSUSA/00010993/202401

Applicant: Idorsia Pharmaceuticals Deutschland GmbH

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

**Background**

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Quviviq, a centrally authorised medicine containing daridorexant 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 Quviviq (daridorexant) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add hypersensitivity (including rash, urticaria), abnormal dreams, nightmares and somnambulism as undesirable effects with a frequency 'uncommon'. Therefore, the current terms of the marketing authorisation(s) should be varied[13].

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

### 6.1.6. Elranatamab - ELREXFIO (CAP) - PSUSA/00000225/202402

Applicant: Pfizer Europe Ma EEIG

PRAC Rapporteur: Barbara Kovacic Bytyqi

Scope: Evaluation of a PSUSA procedure

**Background**

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

**Summary of recommendation(s) and conclusions**

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

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Elrexfio (elranatamab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the warning on infections and add cytomegalovirus infection as an undesirable effect with a frequency 'common'. Therefore, the current terms of the marketing authorisation(s) should be varied[14].
- In the next PSUR, the MAH should provide an overview and analysis of safety data from the study C1071005 that showed increased early mortality and led to urgent safety measures, as well as cumulative reviews of serious infections with fatal outcome and of cardiac disorders. In addition, the MAH should continue to closely monitor all cases of drug-induced liver injury (DILI) that occurred outside of cytokine release syndrome (CRS), as well as all available cumulative and new data from clinical trials, post-marketing and literature on Grade 3 immune effector cell-associated neurotoxicity syndrome (ICANS) including the actions taken and outcomes, and to discuss these findings regarding the currently proposed management of Grade 3 ICANS.

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

### 6.1.7. Liraglutide - SAXENDA (CAP); VICTOZA (CAP) - PSUSA/00001892/202312

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Bianca Mulder

Scope: Evaluation of a PSUSA procedure

**Background**

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Saxenda and Victoza, centrally authorised medicines containing liraglutide 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 the liraglutide-containing medicinal products Saxenda and Victoza in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add information on rotation of the injection site and to add cutaneous amyloidosis as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[15].
- In the next PSUR, the MAH should discuss case of suicide, suicide attempt and/or suicidal ideation cases.

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

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

### 6.1.8. Odevixibat - BYLVAY (CAP) - PSUSA/00010949/202401

Applicant: Ipsen Pharma

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

**Background**

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Bylvay, a centrally authorised medicine containing odevixibat 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 Bylvay (odevixibat) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to strengthen the warning on liver monitoring, as well as to add ALT increased and AST increased as undesirable effects with a frequency 'very common' and 'common', respectively. Therefore, the current terms of the marketing authorisation(s) should be varied[16].

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

### 6.1.9. Osilodrostat - ISTURISA (CAP) - PSUSA/00010820/202401

Applicant: Recordati Rare Diseases

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

**Background**

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Isturisa, a centrally authorised medicine containing osilodrostat 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 Isturisa (osilodrostat) in the approved indication(s) remains unchanged.

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

- Nevertheless, the product information should be updated to add a warning regarding sustained cortisol reduction after treatment interruption. Therefore, the current terms of the marketing authorisation(s) should be varied[17].
- In the next PSUR, the MAH should provide a cumulative review of cerebrovascular accidents with information from the different sources with a discussion of the causality role of osilodrostat, as well as cumulative reviews of pruritus and of neutropenia. In addition, the MAHs should closely monitor hyperkalaemia (including cases associated to hypocortisolism or cases that may suggest adrenal insufficiency, and cases that have associated cardiac related PTs, use in non-Cushing disease (CD) Cushing syndrome (CS) patients, including long-term effects, along with the results of the non-interventional study performed in France to evaluate the safety and effectiveness of osilodrostat for the treatment of these patients, depression and suicidal ideation, sustained cortisol reduction after interruption including details of the cases of adrenocortical insufficiency acute, as well as hepatocellular injury including a discussion on any changes in the product information as warranted. The MAH should also provide a brief safety summary of the findings from the non-interventional study LCI699-RECAG-NI-0596, and the relevant safety results of CLCI699C2X01B study concerning the important identified risk of QT prolongation. Furthermore, the MAH should consider pituitary tumour enlargement as a PSUR important potential risk, while the PSUR important potential risks of pancreatitis and renal impairment should be removed; sepsis and fatal cases should stop to be closely monitored, unless new information arises. Regarding the important potential risk 'reproductive toxicity/embryofetal development', the MAH should ensure that valuable information is collected and presented if new cases arise. Finally, the MAH should update the RMP in the next regulatory opportunity to remove the missing information on breastfeeding women unless relevant data arises from literature, clinical trials or non-interventional studies.

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.

### 6.1.10. Relugolix - ORGOVYX (CAP) - PSUSA/00010994/202401

Applicant: Accord Healthcare S.L.U.

PRAC Rapporteur: Karin Erneholm

Scope: Evaluation of a PSUSA procedure

**Background**

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Orgovyx, a centrally authorised medicine containing relugolix 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 Orgovyx (relugolix) in the approved indication(s) remains unchanged.

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

- Nevertheless, the product information should be updated to amend the frequency of the undesirable effect myocardial infarction from 'rare' to 'common'. Therefore, the current terms of the marketing authorisation(s) should be varied[18].
- In the next PSUR, the MAH should consider QTc prolongation and myocardial infarction as important identified risks, and major adverse cardiovascular events (MACE) excluding myocardial infarction as an important potential risk. In addition, the MAH should further evaluate cases of the medication error regarding 'incorrect dose administered' considering data from all sources and discuss any regulatory actions, as warranted. Finally, the MAH should discuss whether the change in the product information regarding the updated frequency of 'myocardial infarction', should warrant implementation of additional risk minimisation measures.

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

### 6.1.11. Secukinumab - COSENTYX (CAP) - PSUSA/00010341/202312

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Monica Martinez Redondo

Scope: Evaluation of a PSUSA procedure

**Background**

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Cosentyx, a centrally authorised medicine containing secukinumab 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 Cosentyx (secukinumab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add angioedema and eczema as undesirable effects with a frequency 'rare' and 'common' respectively, as well as a warning regarding angioedema and hepatitis B reactivation. Therefore, the current terms of the marketing authorisation(s) should be varied[19].
- In the next PSUR, the MAH should provide cumulative reviews of all cases of erectile dysfunction, oesophageal candidiasis, alopecia areata and paradoxical drug reactions with secukinumab, as well as of injection site reactions along with a discussion on whether the product information update is warranted. In addition, the MAH should provide new arising cases, including literature review, of lentigo and severe cutaneous adverse reaction (SCARs), as well as of IgA vasculitis (Henoch-Schonlein purpura).
- The MAH is also requested to submit, within 60 days, a cumulative review of tuberculosis and hepatitis C virus as part of a post-authorisation measure (PAM-LEG).

[18] 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.
[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 CHMP for adoption of an opinion.

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

### 6.1.12. Selexipag - UPTRAVI (CAP) - PSUSA/00010503/202312

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Nathalie Gault

Scope: Evaluation of a PSUSA procedure

**Background**

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Uptravi, a centrally authorised medicine containing selexipag 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 Uptravi (selexipag) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add angioedema as an undesirable effect with a frequency 'common'. Therefore, the current terms of the marketing authorisation(s) should be varied[20].
- In the next PSUR, the MAH should provide a cumulative number of pregnancy cases with known outcome in the first trimester.

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.

### 6.1.13. Tebentafusp - KIMMTRAK (CAP) - PSUSA/00010991/202401

Applicant: Immunocore Ireland Limited

PRAC Rapporteur: Bianca Mulder

Scope: Evaluation of a PSUSA procedure

**Background**

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Kimmtrak, a centrally authorised medicine containing tebentafusp 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 Kimmtrak (tebentafusp) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the existing warning regarding Cytokine Release Syndrome (CRS) as to be associated with organ dysfunction,

[20] 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.

including hepatic, renal, pancreatic, cardiac, and pulmonary dysfunction. Therefore, the current terms of the marketing authorisation(s) should be varied[21].

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

### 6.1.14. Tecovirimat - TECOVIRIMAT SIGA (CAP) - PSUSA/00010971/202401

Applicant: SIGA Technologies Netherlands B.V.

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

**Background**

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Tecovirimat Siga, a centrally authorised medicine containing tecovirimat 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 Tecovirimat Siga (tecovirimat) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the information related to the method of administration. Therefore, the current terms of the marketing authorisation(s) should be varied[22].
- In the next PSUR, the MAH should closely monitor use in pregnancy and lactation, use in immunocompromised subjects (including resistance development), neurotoxicity events related to EEG changes, cases of anaemia, fat malabsorption and the potentially associated reduction in AUC/efficacy, as well as the efficacy and safety in patients infected with mpox clade 1b.

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.

### 6.1.15. Voclosporin - LUPKYNIS (CAP) - PSUSA/00011020/202401

Applicant: Otsuka Pharmaceutical Netherlands B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

**Background**

[21] Update of SmPC section 4.4. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion.
[22] Update of the package leaflet section 3. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion.

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Lupkynis, a centrally authorised medicine containing voclosporin 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 Lupkynis (voclosporin) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add the following as undesirable effects: hypersensitivity with a frequency 'not known', and pneumonia and mouth ulceration with a frequency 'common'. Therefore, the current terms of the marketing authorisation(s) should be varied[23].

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

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

See also Annex I 16.2.

### 6.2.1. Estradiol, nomegestrol acetate - ZOELY (CAP); NAP - PSUSA/00002182/202401

Applicants: Theramex Ireland Limited (Zoely), various

PRAC Rapporteur: Nathalie Gault

Scope: Evaluation of a PSUSA procedure

**Background**

Nomegestrol acetate and estradiol is a combined hormonal contraceptive tablet indicated for oral contraception or indicated in menopausal hormone replacement therapy (HRT), as warranted.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of Zoely, (a) centrally authorised medicine(s) containing estradiol/nomegestrol acetate, and nationally authorised medicines containing estradiol/nomegestrol acetate 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 estradiol/nomegestrol acetate-containing product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the warning on the interaction between estradiol/nomegestrol and hepatitis C treatments, as well as to amend the drug-drug interaction between direct acting antiviral agents (DAAs) and ethinylestradiol-containing medicinal products such as combined hormonal

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

contraception (CHC). Therefore, the current terms of the marketing authorisations should be varied[24].

- In the next PSUR, the MAH should monitor the safety concerns, especially meningioma and provide a summary of the value of the follow-up questionnaires send to reporters, as well as the investigations for the ongoing signals regarding drug-induced liver injury (DILI) associated with the CHC use and gastro-oesophageal reflux (GERD) associated with either hormone replacement therapy or CHC use.

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

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

See also Annex I 16.2.1.

### 6.3.1. 5 fluorouracil[25] (NAP) - PSUSA/00000007/202312

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

**Background**

5 fluorouracil is an antineoplastic agent indicated for the treatment of several different solid tumours including gastrointestinal tumours (e.g. colon cancer, rectal cancer, gastric cancer, pancreatic cancer, oesophageal cancer), head neck cancers and breast cancer.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing 5 fluorouracil 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 5 fluorouracil-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the warnings on phenotyping for DPD deficiency and encephalopathy, and to add vitamin B1 deficiency, Wernicke's encephalopathy, hypertriglyceridaemia, infusion site reactions caused by extravasation, colitis (including necrotising colitis) and enterocolitis as undesirable effects with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[26].

[24] Update of SmPC sections 4.4 and 4.5. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion.
[25] Intravenous use only
[26] 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.

- In the next PSUR, the MAH should provide cumulative reviews of gastrointestinal necrosis, of gastrointestinal perforation and of mania, as well as should discuss the need for an update of the product information, as warranted.

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

### 6.3.2. Allopurinol (NAP) - PSUSA/00000095/202312

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

**Background**

Allopurinol is a xanthine-oxidase inhibitor indicated for the treatment of gout, primary and secondary hyperuricemia and resulting diseases (urate nephropathy, urea acid and calcium oxalate stones), for reducing urate/uric acid formation in conditions, where urate/uric acid deposition has already occurred (e.g. gouty arthritis, skin tophi, nephrolithiasis), or is a predictable clinical risk (e.g. treatment of malignancy potentially leading to acute uric acid nephropathy), or in enzyme disorders that lead to overproduction of urate.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing allopurinol 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 allopurinol-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the drug-drug interaction azathioprine/mercaptopurine with allopurinol and to add lichenoid drug reaction as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[27].
- In the next PSUR, the MAHs should provide a cumulative review of cases of Kounis syndrome and cases providing symptoms for Kounis syndrome and of the combination of pitavastatin, allopurinol, and valsartan as a multiple drug-drug interaction, as well as to discuss an update of the product information, as warranted. In addition, the MAHs should provide a cumulative review of cases reporting drug-drug interactions with cladribine and allopurinol, and to discuss any wording proposal for risk minimisation. The MAHs should also provide any reports on pregnancies and prospective follow-up of exposed infants (i.e. deviant and normal cases) when available. Furthermore, the MAH Aspen should evaluate if photosensitivity can be related to allopurinol. Finally, the MAH Laboratoires SMB and ACE pharmaceuticals should monitor allopurinol-induced colchicine toxicity, and provide cases with clear clinical and histopathological skin findings, indicative of allopurinol-induced colchicine skin toxicity.

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

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. Amantadine (NAP) - PSUSA/00000126/202401

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

**Background**

Amantadine is an aminoadamantane indicated for the treatment of Parkinson, and for the treatment or prevention of influenza A in adults and children.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing amantadine 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 amantadine-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add or amend the warning on the suicidality, as warranted. Therefore, the current terms of the marketing authorisation(s) should be varied[28].

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

### 6.3.4. Amiodarone (NAP) - PSUSA/00000166/202312

Applicant(s): various

PRAC Lead: Bianca Mulder

Scope: Evaluation of a PSUSA procedure

**Background**

Amiodarone is an antiarrhythmic agent indicated for the treatment of several heart rhythm disorders.

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

**Summary of recommendation(s) and conclusions**

[28] 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.

- Based on the review of the data on safety and efficacy, the benefit-risk balance of amiodarone-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add a warning regarding primary graft dysfunction post cardiac transplant and to add primary graft dysfunction post cardiac transplant as an undesirable effect with a frequency 'unknown'. Therefore, the current terms of the marketing authorisation(s) should be varied[29].
- In the next PSUR, the MAHs should provide cumulative reviews on a potential drug-drug interaction (DDI) between amiodarone and carbamazepine, between amiodarone and apixaban/rivaroxaban, as well as to closely monitoring of BRASH syndrome.

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. Amitriptyline, perphenazine (NAP) - PSUSA/00000170/202401

Applicant(s): various

PRAC Lead: Georgia Gkegka

Scope: Evaluation of a PSUSA procedure

**Background**

Amitriptyline is a tricyclic antidepressant. Perphenazine is an antipsychotic. The combination of amitriptyline/perphenazine is an antidepressant in combination with psycholeptic, indicated for the treatment of depression associated with anxiety.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing amitriptyline/perphenazine 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 amitriptyline/perphenazine-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add a waring regarding drug reaction with eosinophilia and systemic symptoms (DRESS) and add it as an undesirable effect with a frequency 'not known'. The product information of Mutabon/Neopharmed Gentili should also add the interaction with St John's Wort (Hypericum perforatum). Therefore, the current terms of the marketing authorisation(s) should be varied[30].
- In the next PSUR, the MAHs should closely monitor and report cumulative information of oral mucosal dyspigmentation, fall-related injuries associated with antidepressant use and atrial fibrillation after amitriptyline overdose, gestational diabetes, Brugada

[29] 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.
[30] Update of SmPC sections 4.4 and 4.5. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position.

syndrome (unmasking), overdose management with lipid emulsions, and of use in pregnancy.

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

### 6.3.6. Amitriptyline (NAP), amitriptyline, amitriptylinoxide (NAP), amitriptylinoxide (NAP) - PSUSA/00010374/202401

Applicant(s): various

PRAC Lead: Georgia Gkegka

Scope: Evaluation of a PSUSA procedure

**Background**

Amitriptyline is a tricyclic antidepressant, indicated for the treatment of major depressive disorder in adults, treatment of neuropathic pain in adults, prophylactic treatment of chronic tension type headache (CTTH) in adults, prophylactic treatment of migraine in adults, as well as for the treatment of nocturnal enuresis in children aged 6 years and above when organic pathology, including spina bifida and related disorders, have been excluded and no response has been achieved to all other non-drug and drug treatments, including antispasmodics and vasopressin-related products.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing amitriptyline or amitriptyline/amitriptylinoxide or amitriptylinoxide 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 amitriptyline or amitriptyline/amitriptylinoxide or amitriptylinoxide-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add a waring regarding drug reaction with eosinophilia and systemic symptoms (DRESS) and add it as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[31].
- In the next PSUR, the MAHs should provide a cumulative review of oral mucosal dyspigmentation and fall-related injuries associated with antidepressant use, as well as to closely monitor and report cumulative information of cases of disorientation and atrial fibrillation after amitriptyline overdose, gestational diabetes, Brugada syndrome (unmasking), overdose management with lipid emulsions, dementia and of use in pregnancy.

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

[31] 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.

### 6.3.7. Levonorgestrel, ethinylestradiol (NAP); ethinylestradiol (combination pack) (NAP) - PSUSA/00010442/202401

Applicant(s): various

PRAC Lead: Nathalie Gault

Scope: Evaluation of a PSUSA procedure

**Background**

Levonorgestrel is a synthetic progestogen similar to Progesterone used in contraception and hormone therapy. Ethinylestradiol is an oral oestrogen used as a contraceptive. Levonorgestrel/ethinylestradiol is a combination used as an oral contraceptive.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing levonorgestrel/ethinylestradiol or ethinylestradiol (combination pack) 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 levonorgestrel/ethinylestradiol or ethinylestradiol (combination pack)-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add transaminases increased as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[32].
- In the next PSUR, the MAH should continue monitoring any available evidence regarding gastro-oesophageal reflux (GERD) either for combined hormonal contraception (CHC) of hormone replacement therapy, and decrease in bone mineral density for CHCs, as well as meningioma.

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

### 6.3.8. Liothyronine (NAP) - PSUSA/00001890/202401

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

**Background**

Liothyronine or triiodothyronine (T3) is the active form of the thyroid hormone thyroxine (T4), indicated for the treatment of hypothyroidism where a fast onset of action is wanted or in case of a suspected T4/T3-conversion weakness, to treat hypothyroid phases in the context of a diagnostic or therapeutic use of radioiodine in thyroid carcinoma, for the

[32] 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.

emergency therapy of hypothyroid coma (myxoedema coma), and for the thyroid suppression test.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing liothyronine 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 liothyronine-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add a warning on biotin interference with thyroid function tests. Therefore, the current terms of the marketing authorisation(s) should be varied[33].
- In the next PSUR, the MAHs should continue to closely monitor pregnancy cases.
- The MAHs should update the RMPs as warranted, as no additional pharmacovigilance activities are considered necessary, and routine risk minimisation measures are considered sufficient, due to demotion of risks and gaps in knowledge not considered important for inclusion in the summary 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.

### 6.3.9. Macrogol 3350 combinations[34] (NAP) - PSUSA/00010705/202401

Applicant(s): various

PRAC Lead: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

**Background**

Macrogol 3350 is an iso-osmotic laxative indicated for the treatment of chronic constipation, treatment or prevention of faecal impaction, colonic lavage for the preparation of patients prior to endoscopic or radiological explorations, or colonic surgery, as warranted.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing macrogol 3350 combinations 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 macrogol 3350 combinations-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information for macrogol 3350 combination (oral use) for bowel preparation should be updated to add seizure and oesophageal rupture as

[33] Update of SmPC sections 4.4 and 4.5. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position.
[34] Oral use only

warnings and as undesirable effects with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[35].

- In the next PSUR, the MAHs should closely monitor medication errors and the safety in elderly, with a particular focus on possible complications of the adverse events, on outcome, and on distinctive elements in elderly with respect to the general population.

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.

## 6.3.10. Valproic acid; sodium valproate (NAP), valproate pivoxil (NAP), valproate semisodium (NAP), valpriomide (NAP), valproate bismuth (NAP), calcium valproate (NAP), valproate magnesium (NAP) - PSUSA/00003090/202401

Applicant(s): various

PRAC Lead: Liana Martirosyan

Scope: Evaluation of a PSUSA procedure

**Background**

Valproic acid and the relates substances are antiepileptics indicated for the treatment of epilepsy, of bipolar disorders restricted to the treatment of manic episodes when lithium is contraindicated or not tolerated, and for the prophylaxis of migraine attacks, as warranted.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing valproic acid and related substances 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 valproic acid and related substances-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add a warning regarding SCARs and angioedema, add the drug-drug interaction (DDI) between valproate and clozapine, and to add hyperpigmentation as undesirable effect with frequency 'not known', as well as to add eosinophilic in brackets to the labelled event pleural effusion. Therefore, the current terms of the marketing authorisation(s) should be varied[36].
- In the next PSUR, the MAH Sanofi should discuss the outcome of the two ongoing signals on preterm birth following in utero exposure and low birth weight following in utero exposure along with the literature, provide the signal evaluation of haemophagocytic lymphohistiocytosis, and submit a review of published epidemiological studies concerning valproic acid and new onset of type 2 diabetes mellitus.

[35] 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.
[36] Update of SmPC sections 4.4, 4.5 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position

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.

### 6.3.11. Zofenopril (NAP) - PSUSA/00003147/202401

Applicant(s): various

PRAC Lead: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

**Background**

Zofenopril is an angiotensin-converting enzyme (ACE) inhibitor indicated for the treatment of mild to moderate essential hypertension and for the treatment initiated within the first 24 hours of patients with acute myocardial infarction with or without signs and symptoms of heart failure, who are haemodynamically stable and have not received thrombolytic therapy.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing zofenopril 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 zofenopril-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add palpitations, hypotension, syncope, pruritus, urticaria and hyperkalaemia as undesirable effects with a frequency 'rare'. Therefore, the current terms of the marketing authorisation(s) should be varied[37].
- In the next PSUR, the MAH should keep under routine pharmacovigilance monitoring the risk of fractures.

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

## 6.4. Follow-up to PSUR/PSUSA procedures

See also Annex I 16.4.

### 6.4.1. Nirsevimab - BEYFORTUS (CAP) - EMEA/H/C/005304/LEG 007

Applicant: Sanofi Winthrop Industrie

PRAC Rapporteur: Kimmo Jaakkola

Scope: From PSUSA /00011026/202310:
The MAH is requested, in view of the available data regarding hypotonic-hyporesponsive episode (HHE) and apnoea case reports, either to submit a variation in accordance with

[37] 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.

Articles 16 and 17 of Regulation (EC) No 726/2004 or provide a justification for not doing so. The MAH should discuss the need for updating the product information and/or RMP. This should be provided without any delay and no later than 16th June 2024

**Background**

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

Following the evaluation of the most recently submitted PSUR(s) for the above-mentioned medicine(s), PRAC requested the MAH to submit further data on hypotonic-hyporesponsive episode (HHE) and apnoea case reports. The responses were assessed by the Rapporteur for further PRAC advice. For further background, see PRAC minutes May 2024.

**Summary of advice/conclusion(s)**

- Based on the available data, the Rapporteur's assessment and the MAH's responses, PRAC agreed that the gathered evidence is considered insufficient for confirming a causal relationship between administration of nirsevimab and subsequently occurring episodes of HHE or apnoea that would warrant amendments to the product information. PRAC agreed that more data should be collected on these events and discussed in the forthcoming PSUR, and recommended to widen the scope of the apnoea to also include other closely related reported events such as (not necessarily limited to) those covered by MedDRA SMQ Respiratory failure (Broad) and MedDRA PTs dyspnoea and neonatal dyspnoea.

## 6.5. Variation procedure(s) resulting from PSUSA evaluation

See also Annex I 16.5.

### 6.5.1. Meningococcal group A, C, W135 and Y conjugate vaccine - NIMENRIX (CAP) - EMEA/H/C/002226/II/0137

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: David Olsen

Scope: Update of section 4.8 of the SmPC in order to add 'hypersensitivity' to the list of adverse drug reactions (ADRs) with frequency uncommon, following PRAC's recommendation for procedure EMEA/H/002226/PAM/LEG/058.

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

**Summary of recommendation(s)**

- Based on the available data, the Rapporteur's assessment and the MAH's responses, PRAC agreed that the product information should be amended to add hypersensitivity and anaphylaxis as undesirable effects with frequency 'uncommon' and 'not known' respectively.

## 6.6. Expedited summary safety reviews[38]

None

# 7. Post-authorisation safety studies (PASS)

## 7.1. Protocols of PASS imposed in the marketing authorisation(s)[39]

See Annex I 17.1.

## 7.2. Protocols of PASS non-imposed in the marketing authorisation(s)[40]

See Annex I 17.2.

## 7.3. Results of PASS imposed in the marketing authorisation(s)[41]

### 7.3.1. Lenalidomide - REVLIMID (CAP) - EMEA/H/C/PSR/S/0049

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Tiphaine Vaillant

Scope: Final study report for a post-authorisation, non-interventional, retrospective, drug-utilisation study to describe the pattern of use of lenalidomide in patients with myelodysplastic syndromes (MDS)

**Background**

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

In order to fulfil the obligation to submit the results of an imposed non-interventional PASS in accordance with Article 107p of Directive 2001/83/EC, the Marketing Authorisation Holder Bristol Myers Squibb Pharma EEIG submitted on 17 June 2024 a PASS final study report to the European Medicines Agency (EMA) for lenalidomide. PRAC discussed the final study results.

**Summary of recommendation(s) and conclusions**

- Based on the review of the final report of the non-interventional PASS MDS-012 entitled 'a post-authorisation, non-interventional, retrospective, drug utilisation study to describe the pattern of lenalidomide use in patients with myelodysplastic syndromes (MDS)',

[38] 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
[39] In accordance with Article 107n of Directive 2001/83/EC
[40] 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
[41] In accordance with Article 107p-q of Directive 2001/83/EC

PRAC considered that a further RSI was necessary before a recommendation could be made on the benefit-risk balance of medicinal product(s) containing lenalidomide concerned by the PASS final report.

- PRAC endorsed the MAH's proposal to remove the study MDS-012 from the Annex II-D 'Conditions or restrictions with regard to the safe and effective use of the medicinal product' and update the RMP accordingly, following its completion. However, the MAH should further provide clarifications and justifications on the removal of the Connect® MDS/AML Disease Registry (observational category 3) from the pharmacovigilance plan in the RMP. Moreover, the MAH should further provide a justification for not discussing the risk of teratogenicity in the results of this study, while the RMP mentions this study as an additional pharmacovigilance activity to address this risk.
- The MAH should submit responses to the request for supplementary information within 30 days to EMA. A 30 days-assessment timetable will be followed.

### 7.3.2. Umeclidinium bromide, vilanterol - ANORO ELLIPTA (CAP); LAVENTAIR ELLIPTA (CAP); INCRUSE ELLIPTA (CAP); ROLUFTA ELLIPTA (CAP) - EMEA/H/C/PSR/S/0048

Applicant: GlaxoSmithKline Trading Services Limited

PRAC Rapporteur: Amelia Cupelli

Scope: Final study report for a post-authorisation safety observational cohort study to quantify the incidence and comparative safety of selected cardiovascular and cerebrovascular events in chronic obstructive pulmonary disease (COPD) patients using inhaled umeclidinium/vilanterol (UMEC/VI) combination, or inhaled UMEC versus tiotropium

**Background**

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

In order to fulfil the obligation to submit the results of an imposed non-interventional PASS in accordance with Article 107p of Directive 2001/83/EC, the Marketing Authorisation Holder GSK submitted on 24/01/2024 a PASS final study report to the European Medicines Agency (EMA) for umeclidinium bromide, umeclidinium bromide/vilanterol. PRAC discussed the final study results in addition to the MAH's responses to the request for supplementary information (RSI).

**Summary of recommendation(s) and conclusions**

- Based on the review of the final report of the non-interventional PASS entitled 'Post-authorization Safety (PAS) Observational Cohort Study to Quantify the Incidence and Comparative Safety of Selected Cardiovascular and Cerebrovascular Events in COPD Patients Using Inhaled UMEC/VI Combination, or Inhaled UMEC versus Tiotropium (Study 201038)', PRAC considered that the benefit-risk balance of Umeclidinium bromide, vilanterol containing products: Anoro Ellipta, Laventair Ellipta, Incruse Ellipta, Rolufta Ellipta remains unchanged. As this study is finalised, PRAC recommended that the terms of the marketing authorisation(s) for these products should be varied to remove the PASS from Annex II-D 'Conditions or restrictions with regard to the safe and effective use of the medicinal product' and to remove these products from the list of medicines subject to additional monitoring.

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

See also Annex I 17.4.

### 7.4.1. Dimethyl fumarate - TECFIDERA (CAP) - EMEA/H/C/002601/WS2587/0085; diroximel fumarate - VUMERITY (CAP) - EMEA/H/C/005437/WS2587/0015

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Martin Huber

Scope: Submission of the final report from study 109MS401, a multicentre, global, observational study to collect information on safety and to document the drug utilisation of Tecfidera (Dimethyl Fumarate) when used in routine medical practice in the treatment of Multiple Sclerosis (ESTEEM), listed as a category 3 study in the RMP (MEA007.6). The RMPs version 16.1 for Tecfidera and version 2.1 for Vumerity, have 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 Tecfidera, the MAH conducted a non-imposed non-interventional PASS (listed as category 3 study) to collect information on safety and to document the drug utilisation of Tecfidera (dimethyl fumarate) when used in routine medical practice in the treatment of multiple sclerosis (MS). This study was also listed in the Vumerity RMP as an additional pharmacovigilance activity, and findings from the study also impact the safety concerns of Vumerity. The Rapporteur assessed the MAH's final study report in addition to the MAH's answers to the request for supplementary information (RSI).

**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 considered that the product information of both Tecfidera and Vumerity should be updated[43] to change the frequency of the undesirable effect drug-induced liver injury (DILI) from 'not known' to 'rare'.

### 7.4.2. Tacrolimus - ADVAGRAF (CAP) - EMEA/H/C/000712/WS2519/0071/G; Tacrolimus - MODIGRAF (CAP) - EMEA/H/C/000954/WS2519/0046/G

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Eamon O'Murchu

Scope: A grouped application consisting of:

Type II (C.I.13): Submission of the final report from study F506-PV-0001 listed as a category 3 study in the RMP for Advagraf and Modigraf. This is a non-interventional post-

[42] In accordance with Article 61a (6) of Regulation (EC) No 726/2004, in line with the revised variations regulation for any submission as of 4 August 2013
[43] Update of section 4.8 of the SmPC. The package leaflet is updated accordingly.

authorization safety study (NI-PASS) of outcomes associated with the use of tacrolimus around conception, or during pregnancy or lactation using data from Transplant Pregnancy Registry International (TPRI). The RMP version 5.0 has also been submitted.

Type IB (C.I.11.z): To include the feasibility assessment of using alternative secondary-use data sources to replicate the Transplant Pregnancy Registry International (TPRI) study as a category 3 additional pharmacovigilance activity in the RMP, including the milestones for the progress report and the final report of the feasibility assessment, related to EMEA/H/C/000712/MEA/032 and EMEA/H/C/000954/MEA/024

**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 Advagraf and Modigraf (tacrolimus), the MAH conducted a non-imposed non-interventional PASS (EUPAS37025) listed as a category 3 study in the RMP on outcomes reported with the use of tacrolimus around conception, or during pregnancy or lactation using data from Transplant Pregnancy Registry International (TPRI). The Rapporteur assessed the MAH's final study report in addition to the MAH's answers to the request for supplementary information (RSI).

**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 considered that the product information should be updated in order to reflect the data from the study, where a larger number of pregnancies exposed to tacrolimus and reporting clinically relevant outcomes have been described.
- Regarding the feasibility assessment of using alternative secondary-use data sources to replicate the Transplant Pregnancy Registry International (TPRI) study, PRAC concluded that another non-interventional PASS in population-based data sources from Europe and/or North America, would not be expected to generate robust evidence on outcomes associated with use of tacrolimus during pregnancy or lactation, based on the limitations identified in the feasibility assessment and projected sample size.

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

See Annex I 17.4.1.

## 7.6. Others

See Annex I 17.6.

## 7.7. New Scientific Advice

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

### 7.8. Ongoing Scientific Advice

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

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

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

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

### 8.1. Annual reassessments of the marketing authorisation

See Annex I 18.1.

### 8.2. Conditional renewals of the marketing authorisation

See Annex I 18.1.1.

### 8.3. Renewals of the marketing authorisation

See Annex I 18.3.

## 9. Product related pharmacovigilance inspections

### 9.1. List of planned pharmacovigilance inspections

None

### 9.2. Ongoing or concluded pharmacovigilance inspections

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

### 9.3. Others

None

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

### 10.1. Safety related variations of the marketing authorisation

None

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

None

## 10.3. Other requests

### 10.3.1. Azithromycin[44] (NAP) - EMEA/H/A-31/1532

Applicant: various

PRAC Rapporteur: Kimmo Jaakkola

Scope: PRAC consultation regarding the use of azithromycin-containing products (for systemic use only) during pregnancy in the context of a referral procedure under Article 31 of Directive 2001/83/EC upon CHMP's request

**Background**

Azithromycin is a macrolide antibiotic which is active against many aerobe Gram-positive and Gram-negative bacteria including intracellular pathogens such as Chlamydia trachomatis. Azithromycin-containing products for systemic use are authorised in the European Union (EU) mainly as oral and intravenous formulations, and some as topical formulations (eye drops). Oral formulations are mainly indicated for the treatment of upper and lower respiratory tract infections, skin and soft tissue infections and uncomplicated genital infections in adults, adolescents and children while intravenous formulations are mainly indicated for treatment of community-acquired pneumonia and pelvic inflammatory disease in adults.

In the context of an evaluation of a referral procedure under Article 31 of Directive 2001/83/EC (EMEA/H/A-31/1532), CHMP requested PRAC advice on its assessment on whether the proposed updates to the product information regarding the use of azithromycin-containing products (systemic use) in pregnancy, appropriately reflect the available evidence.

**Summary of advice**

- Based on the review of the available information, PRAC concluded that, although there is a large amount of available data in pregnant women using azithromycin, it does not support different level of risk between the trimesters of pregnancy and that the data on the first trimester in view of miscarriage is inconclusive. Therefore, considering the uncertainty of the data on the risk of malformations/abortions, PRAC agreed to reflect this adequately in the product information.

## 10.4. Scientific Advice

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

[44] For systemic use only

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

## 11.1. Safety related variations of the marketing authorisation

None

## 11.2. Other requests

### 11.2.1. Brivaracetam

PRAC Lead: Guðrún Þengilsdóttir

Scope: PRAC consultation on the evaluation of initial marketing authorisation application(s) under the decentralised procedure for generic brivaracetam-containing medicinal products in order to consider the need to add the EURAP registry study as category 3 additional pharmacovigilance activity in the RMP, on request of Iceland

**Background**

Brivaracetam is an antiepileptic medicine and it is indicated as adjunctive therapy in the treatment of partial onset seizures with or without secondary generalisation in adults, adolescents and children from 2 years of age with epilepsy.

In the context of the evaluation of a marketing authorisation application in a decentralised procedure for a generic brivaracetam product, Iceland requested PRAC advice on its assessment regarding the participation in the European and International Registry of Antiepileptic Drugs in Pregnancy (EURAP) registry for generic brivaracetam-containing medicinal product as a category 3 PASS study listed in the RMP.

**Summary of advice**

- Based on the review of the available information, PRAC concluded that as the applicant is not required to perform a separate study and in line with GVP Module V, participation in the EURAP registry should not be considered a category 3 PASS study, but rather a routine pharmacovigilance activity and should be included in the RMP as such. Moreover, PRAC agreed that a harmonised approach for generic medicinal products containing brivaracetam with regard to participation in the EURAP registry should be applied. PRAC advised that marketing authorisation holders for generic brivaracetam medicinal products should be requested to participate in the EURAP registry and include this as a routine pharmacovigilance activity in the RMP. PRAC agreed that the RMS can request clarification from the Applicant on the methods that are to be used in specific MSs to encourage prescribers to register pregnant women into the EURAP as applicable, e.g. in the absence of a national coordinator for the EURAP study.
- PRAC agreed that the results of the EURAP study should continue to be reported via the PSUSA procedure, and that the MAH of the innovator product Briviact should report on all pregnancies exposed to the active substance brivaracetam from the EURAP registry in future PSURs. PRAC concluded that PSUR submissions remain not required for generic brivaracetam products.

# 12. Organisational, regulatory and methodological matters

## 12.1. Mandate and organisation of PRAC

### 12.1.1. Election of PRAC Vice-Chair

The mandate of the PRAC Vice-Chair, Martin Huber, will expire on 29 September 2024.

The election of the new vice-chair took place in accordance with the PRAC rules of procedure.

The nominations received were presented to the Committee.

The PRAC elected Liana Martirosyan as PRAC Vice-Chair for a three-year mandate starting on 30 September 2024.

The PRAC and the Agency congratulated Liana Martirosyan on her election and wished her all the best in her new role as Vice-Chair of the Committee.

### 12.1.2. PRAC membership

The Chair thanked Nathalie Gault for her contribution to PRAC as the alternate for France.

### 12.1.3. Vote by proxy

Maria Popova-Kiradjieva gave a proxy to Eva Jirsová to vote on behalf of Maria Popova-Kiradjieva for the entire duration of the meeting.

Anna Mareková gave a proxy to Maria del Pilar Rayon to vote on behalf of Anna Mareková for the entire duration of the meeting.

John Joseph Borg gave a proxy to Amelia Cupelli to vote on behalf of John Joseph Borg for the entire duration of the meeting.

Maria Teresa Herdeiro gave a proxy to Hedvig Nordeng to vote on behalf of Maria Teresa Herdeiro for the entire duration of the meeting.

Annalisa Capuano gave a proxy to Milou-Daniel Drici to vote on behalf of Annalisa Capuano for the entire duration of the meeting.

### 12.1.4. PRAC working group - Best practice guide on using PRAC plenary time efficiently and effectively – update on the implementation of quantitative goals – Q2 2024

In line with the adopted PRAC best practice guidance (BPG) on Committee efficiency (see PRAC minutes May 2016 and PRAC minutes June 2018) and the adopted implementation plan for the BPG including goals to measure compliance with the recommendations (see PRAC minutes June 2016 and PRAC minutes June 2018), PRAC was informed in writing on the quantitative measures collected for Q2 2024 of PRAC meetings post-meeting. For previous update, see PRAC minutes May 2024.

## 12.2. Coordination with EMA Scientific Committees or CMDh-v

None

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

None

## 12.4. Cooperation within the EU regulatory network

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

The EMA Secretariat presented PRAC an update on the COVID-19 vaccines and treatments, including data on the effectiveness of the existing vaccines on the new SARS Cov-2 variants. An update on the spread of the monkeypox virus, characteristics and spread of clades I and II, as well as existing vaccines and treatments was presented. PRAC noted the information.

### 12.4.2. EU Network Training Centre (EU NTC) – update on supporting capacity and capability building in the EU Medicines Regulatory Network

PRAC lead: Ulla Wändel Liminga

The EMA Secretariat presented to PRAC the EU NTC objectives and activities, with a focus on pharmacovigilance activities and training curriculum. PRAC was also provided with an overview of the EU NTC services, including information about the EU NTC Learning and development toolkit, as well as on the reimbursement and remuneration in case of training development and delivery for courses aiming at fulfilling a critical unmet learning need. PRAC noted the information.

### 12.4.3. European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) steering group – update and call for expression of interest for a PRAC representative

PRAC lead: Ulla Wändel Liminga

At the organisational, regulatory and methodological matters (ORGAM) meeting on 19 September 2024, the EMA Secretariat presented to PRAC an update of the ENCePP steering group activities, roles and composition, reiterating the critical role of the Steering Group in defining the role of ENCePP in a fast-changing environment for pharmacovigilance, pharmacoepidemiology and real-world evidence. A call for a PRAC representative in the ENCePP steering group was launched. PRAC members who are interested in taking this role can express their interest in writing.

Post-meeting note: Hedvig Nordeng was appointed as PRAC Representative in the ENCePP steering group.

### 12.4.4. PRAC strategic review and learning meeting (SRLM) under the Hungarian presidency of the European Union (EU) Council – Budapest, Hungary, 21 – 22 October 2024 - agenda

PRAC lead: Julia Pallos, Melinda Palfi

PRAC was informed on the final agenda for the 'PRAC strategic review and learning meeting (SRLM)', to be held on 21-22 October 2024 in Budapest, Hungary, under the Hungarian presidency of the Council of the European Union (EU). The topics to be discussed cover real world evidence and phenotyping in real world studies, health technology assessment, as well as educational materials and effectiveness of additional risk minimisation measures. A dedicated joint session will address the CHMP-PRAC interaction and collaboration on various aspects of the product lifecycle.

## 12.5. Cooperation with International Regulators

None

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

None

## 12.7. PRAC work plan

### 12.7.1. PRAC work plan 2024 - update

PRAC lead: Ulla Wändel Liminga, Martin Huber

The EMA Secretariat presented to PRAC a mid-year status update on the activities described in the PRAC work plan 2024. PRAC will initiate its work plan for 2025 taking into account the activities completed, progress made, priorities identified at the level of the Committee, EMA, Heads of Medicines Agencies (HMA) and EU network.

## 12.8. Planning and reporting

### 12.8.1. EU Pharmacovigilance system - quarterly workload measures and performance indicators – Q2 2024

The EMA Secretariat presented to PRAC an overview of the quarterly figures on the EMA pharmacovigilance system-related workload and performance indicators. For previous update, see PRAC minutes May 2024.

### 12.8.2. PRAC workload statistics – Q2 2024

The EMA secretariat informed PRAC in writing in post meeting about the quarterly and cumulative figures to estimate the evolution of the PRAC workload for Q2 2024, by reflecting on the number of procedures and agenda items covered at each PRAC plenary meeting. For previous update, see PRAC minutes May 2024.

## 12.9. Pharmacovigilance audits and inspections

### 12.9.1. Pharmacovigilance systems and their quality systems

None

### 12.9.2. Pharmacovigilance inspections

None

### 12.9.3. Pharmacovigilance audits

None

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

### 12.10.1. Periodic safety update reports

None

### 12.10.2. Granularity and Periodicity Advisory Group (GPAG)

PRAC lead: Jana Lukacisinova

The EMA Secretariat provided to PRAC an update on GPAG activities and the ongoing discussions on herbal products.

### 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 September 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 September 2024, the updated EURD list was adopted by CHMP and CMDh at their September 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)

## 12.11. Signal management

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

None

## 12.12. Adverse drug reactions reporting and additional monitoring

### 12.12.1. Management and reporting of adverse reactions to medicinal products

None

### 12.12.2. Additional monitoring

None

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

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

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

## 12.13. EudraVigilance database

### 12.13.1. Activities related to the confirmation of full functionality

None

## 12.14. Risk management plans and effectiveness of risk minimisations

### 12.14.1. Risk management systems

None

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

None

## 12.15. Post-authorisation safety studies (PASS)

### 12.15.1. Post-authorisation Safety Studies – imposed PASS

None

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

None

## 12.16. Community procedures

### 12.16.1. Referral procedures for safety reasons

None

## 12.17. Renewals, conditional renewals, annual reassessments

None

## 12.18. Risk communication and transparency

### 12.18.1. Public participation in pharmacovigilance

None

### 12.18.2. Safety communication

None

## 12.19. Continuous pharmacovigilance

### 12.19.1. Incident management

None

## 12.20. Impact of pharmacovigilance activities

### 12.20.1. Strategy on measuring the impact of pharmacovigilance – PRAC interest group (IG) Impact – revision of the PRAC criteria to prioritise impact research (revision 1)

PRAC lead: Liana Martirosyan

Following the lessons learnt exercise on impact research in 2023, the criteria for prioritising safety topics for impact research have been revised considering PRAC Impact Group's recommendations. The revision 1 of the document describing the prioritisation criteria including checklist to support PRAC (Co)Rapporteur's decision-making in line with the adopted process for prioritising and regulatory follow-up on impact research was adopted by PRAC via a written procedure on 06 September 2024.

### 12.20.2. Proposal for an impact study to measure the effectiveness of risk minimisation measures implemented for medicines containing nomegestrol or chlormadinone in order to minimise the risk of meningioma - DARWIN EU pilot

PRAC lead: Petar Mas

Following updating the product information to reflect the restrictions implemented for medicines containing nomegestrol or chlormadinone in order to minimise the risk of meningioma (i.e., use in the lowest effective dose and for the shortest duration possible, and only when other interventions are not appropriate) as a consequence of the referral procedure EMEA/H/A-31/1510 concluded in 2020, the PRAC Impact Group presented to PRAC a proposal for an impact study to measure RMMs' effectiveness to be conducted as pilot

study in DARWIN EU. The EMA Secretariat presented the study outline including feasibility assessment for PRAC endorsement, as well as the timelines. PRAC endorsed the proposed way forward.

## 12.21. Others

### 12.21.1. Good Pharmacovigilance Practices (GVP) module XVI - Addendum on pregnancy - update

PRAC lead: Ulla Wändel Liminga

The topic was postponed for the PRAC November 2024 plenary meeting.

### 12.21.2. Good Pharmacovigilance Practice (GVP) – status update and planning for 2025

PRAC lead: Ulla Wändel Liminga

Following the presentation of the PRAC workplan mid-year report in July 2024, PRAC members were informed about the status of the update of various GVP modules, including a proposal of the activities to be carried over for the PRAC workplan 2025. The members were invited to send their comments in writing by 07 October 2024

### 12.21.3. Committee meetings in Microsoft Teams and new tool for voting

At the organisational, regulatory and methodological matters (ORGAM) meeting on 19 September 2024, the EMA Secretariat presented to PRAC the new voting tool to be used for virtual Committee meetings starting 01 October 2024, as well as the timelines for WebEx discontinuation and transition to Microsoft Teams as a new platform for running Committee meetings. In the following period, several training and practice run sessions will be organised by EMA Secretariat in order to make sure the PRAC members and experts have the right access to the new platform before switching completely to Microsoft Teams starting 28 October 2024 (PRAC November 2024 plenary meeting). PRAC noted the information.

### 12.21.4. CHMP AR template – Revamp Project

At the organisational, regulatory and methodological matters (ORGAM) meeting on 19 September 2024, the EMA secretariat presented to PRAC the new CHMP AR/Overview template, for initial marketing authorisation applications (MAAs) and the impact on PRAC outcome and process (new RMP sections added replacing the stand-alone D94 PRAC assessment report). The PRAC members were invited to send any comment in writing by 30 September 2024. The EMA Secretariat will provide training sessions on the new process for all assessors in the next months. The new template will enter into use for new MAAs submitted from January 2025.

# 13. Any other business

None

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

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

## 14.1. New signals detected from EU spontaneous reporting systems

### 14.1.1. Lenvatinib – KISPLYX (CAP), LENVIMA (CAP)

Applicant: Eisai GmbH

PRAC Rapporteur: Mari Thorn

Scope: Signal of tumour lysis syndrome

EPITT 20108 – New signal

### 14.1.2. Lisocabtagene maraleucel – BREYANZI (CAP)

Applicant: Bristol-Myers Squibb Pharma EEIG, ATMP

PRAC Rapporteur: Gabriele Maurer

Scope: Signal of progressive multifocal leukoencephalopathy (PML)

EPITT 20109 – New signal

### 14.1.3. Sacubitril, valsartan – ENTRESTO (CAP), NEPARVIS (CAP)

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Karin Erneholm

Scope: Signal of myoclonus

EPITT 20097 – New signal

## 14.2. New signals detected from other sources

None

## 14.3. Variation procedure(s) resulting from signal evaluation

### 14.3.1. Anakinra - KINERET (CAP) - EMEA/H/C/000363/II/0093

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Karin Erneholm

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

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

Scope: Update of section 4.4 of the SmPC in order to add a new warning on 'Amyloidosis (systemic)' based on an updated safety review, following the PRAC recommendation on a signal. In addition, the MAH took the opportunity to correct a numerical error in the SmPC

# 15. Annex I – Risk management plans

## 15.1. Medicines in the pre-authorisation phase

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

### 15.1.1. Aflibercept (CAP MAA) - EMEA/H/C/006607

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

### 15.1.2. Aflibercept (CAP MAA) - EMEA/H/C/005980

Scope (pre D-180 phase): Treatment of age-related macular degeneration (AMD) and visual impairment

### 15.1.3. Aflibercept (CAP MAA) - EMEA/H/C/005899

Scope (pre D-180 phase): Treatment of age-related macular degeneration (AMD), visual impairment and retinopathy of prematurity (ROP)

### 15.1.4. Eltrombopag (CAP MAA) - EMEA/H/C/006417

Scope (pre D-180 phase): Treatment of primary immune thrombocytopenia (ITP), chronic hepatitis C virus (HCV) and acquired severe aplastic anaemia (SAA)

### 15.1.5. Filgrastim (CAP MAA) - EMEA/H/C/006400

Scope (pre D-180 phase): for the reduction in the duration of neutropenia and the incidence of febrile neutropenia

### 15.1.6. Insulin human (CAP MAA) - EMEA/H/C/006011

Scope (pre D-180 phase): Treatment of patients with diabetes mellitus who require insulin for the maintenance of glucose homeostasis

### 15.1.7. Trabectedin (CAP MAA) - EMEA/H/C/006433

Scope (pre D-180 phase): Treatment of soft tissue sarcoma and combination with PLD treatment of relapsed platinum-sensitive ovarian cancer

## 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. Alendronic acid, Colecalciferol - ADROVANCE (CAP) - EMEA/H/C/000759/WS2696/0055; Alendronic acid, Colecalciferol - FOSAVANCE (CAP) - EMEA/H/C/000619/WS2696/0058; Alendronic acid, Colecalciferol - VANTAVO (CAP) - EMEA/H/C/001180/WS2696/0045

Applicant: Organon N.V.

PRAC Rapporteur: Jan Neuhauser

Scope: Submission of an updated RMP version 8.0 following the assessment outcome from procedure WS/2467 to reclassify the risk of atypical femoral fracture from "important potential risk" to "important identified risk" and to extend the risk of "atypical femoral fracture" to "atypical fractures of long bones"

### 15.2.2. Amlodipine, Valsartan - AMLODIPINE-VALSARTAN MYLAN (CAP) - EMEA/H/C/004037/II/0021

Applicant: Mylan Pharmaceuticals Limited

PRAC Rapporteur: Karin Erneholm

Scope: Submission of an updated RMP version 4.0 in order to align the safety concerns with the latest version of RMP for Amlodipine/Valsartan available in the public domain and to bring the RMP in line with the latest RMP template

### 15.2.3. 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).

### 15.2.4. Autologous CD34+ enriched cell fraction that contains CD34+ cells transduced with retroviral vector that encodes for the human adenosine deaminase (ADA) complementary deoxyribonucleic acid (cDNA) sequence - STRIMVELIS (CAP) - EMEA/H/C/003854/II/0040, Orphan

Applicant: Fondazione Telethon ETS, ATMP

PRAC Rapporteur: Liana Martirosyan

Scope: Submission of an updated RMP version 7.0 in order to propose amendments to the STRIM-005 and STRIM-003 study protocols, as well as revised timelines for completion of both studies. In addition, the Annex II is updated accordingly

### 15.2.5. Clopidogrel - GREPID (CAP) - EMEA/H/C/001059/II/0058

Applicant: Pharmathen S.A.

PRAC Rapporteur: Carla Torre

Scope: Submission of an RMP version 0.1 following procedure EMEA/H/C/001059/IB/0057/G to be in line with the updated RMP of the reference product (Plavix).

### 15.2.6. Dulaglutide - TRULICITY (CAP) - EMEA/H/C/002825/II/0071

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Amelia Cupelli

Scope: Submission of an updated RMP version 8.1 in order to add a medullary thyroid cancer (MTC) database linkage study (Study I8F-MC-B014) as an additional pharmacovigilance activity to evaluate the important potential risk of MTC in patients exposed to long-acting glucagon-like peptide-1 receptor agonist (GLP-1 RA) therapies. In addition, the MAH took the opportunity to include an amendment to Study H9X-MC-B013 due to the removal of the United States data source

### 15.2.7. Pegcetacoplan - ASPAVELI (CAP) - EMEA/H/C/005553/II/0018, Orphan

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Kimmo Jaakkola

Scope: Submission of an updated RMP version 2.1 in order to revise the category 3 PASS Sobi.PEGCET-301 and Sobi.PEGCET-302

### 15.2.8. Rivaroxaban - RIVAROXABAN VIATRIS (CAP); NAP - EMEA/H/C/005600/WS2709/0012

Applicant(s): Viatris Limited, various

PRAC Rapporteur: Mari Thorn

Scope: To provide an updated RMP to remove the following safety concerns (classified as Missing information) in order to align with RMP version 13.4 of the reference product Xarelto:
- Patients with severe renal impairment (CrCl < 30 mL/min)
- Patients receiving concomitant systemic inhibitors of CYP 3A4 or P-gp other than azole antimycotics (e.g. ketoconazole) and HIV-protease inhibitors (e.g. ritonavir)
- Pregnant or breast-feeding women
- Long-term therapy with rivaroxaban in treatment of DVT, PE, SPAF and ACS in real-life setting
- Patients with significant liver diseases (severe hepatic impairment/Child Pugh C)
- Patients < 18 years

## 15.2.9. Tadalafil - CIALIS (CAP) - EMEA/H/C/000436/WS2697/0098; Tadalafil - TADALAFIL LILLY (CAP) - EMEA/H/C/004666/WS2697/0012

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Maria del Pilar Rayon

Scope: To provide an updated RMP version for Cialis and Tadalafil Lilly to align with the currently approved RMP version of Adcirca. There is only one RMP for all 3 tadalafil products (Adcirca, Cialis and Tadalafil Lilly), however different versions of the same RMP are officially approved in the EMA database (for Adcirca v9.2; for Cialis and Tadalafil Lilly v8.2)

## 15.2.10. Tezepelumab - TEZSPIRE (CAP) - EMEA/H/C/005588/II/0013/G

Applicant: AstraZeneca AB

PRAC Rapporteur: Eva Jirsová

Scope: A grouped application consisting of:
Type II (C.I.11.b): Submission of an updated RMP version V 3, S 1 in order to remove the SUNRISE study (D5180C00024) from the RMP due to discontinuation of the study. This is a Phase 3, randomised, double-blind, parallel-group, placebo-controlled, multicentre study to evaluate the efficacy and safety of tezepelumab 210 mg Q4W administered SC for 28 weeks using an accessorised pre-filled syringe, compared with placebo in reducing OCS use in OCS-dependent adult asthma participants. In addition, the MAH took the opportunity to implement updates to the Targeted Safety Questionnaires (TSQs) and to the Module SI of the RMP to bring it up to date.

Type IB (C.I.11.z): Submission of an updated RMP version V 3, S 1 in order to remove the DESTINATION study (D5180C00018) following procedure EMEA/H/C/005588/II/0004.

Type IB (C.I.11.z): Submission of an updated RMP version V 3, S 1 in order to propose changes to the study design and objectives for the Pregnancy PASS (D5180R00010), following procedure EMEA/H/C/005588/MEA/001.2.

Type IB (C.I.11.z): Submission of an updated RMP version V 3, S 1 in order to propose changes to the study design and objectives for the Cardiac PASS (D5180R00024), following procedure EMEA/H/C/005588/MEA/005

## 15.2.11. 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. Alectinib - ALECENSA (CAP) - EMEA/H/C/004164/II/0048

Applicant: Roche Registration GmbH

PRAC Rapporteur: Jana Lukacisinova

Scope: To update sections 4.4 and 4.6 of the SmPC to update the safety information to amend the duration of the period for which female patients of child-bearing potential must use highly effective contraceptive methods following the last dose of Alecensa, and must be informed of potential harm to the fetus in the event of pregnancy, from 3 months to 5 weeks based on the latest guidelines on contraception requirements for drugs with aneugenic potential. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet.

### 15.3.2. Amivantamab - RYBREVANT (CAP) - EMEA/H/C/005454/II/0013

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Gabriele Maurer

Scope: Extension of indication to include amivantamab in combination with lazertinib for the first-line treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with EGFR exon 19 deletions or exon 21 L858R substitution mutations (EGFRm NSCLC), based on results from study 73841937NSC3003 (MARIPOSA). This is a randomized, open-label, Phase 3 study that compares the efficacy and safety of the combination of amivantamab and lazertinib (Arm A) versus osimertinib monotherapy (Arm B) and lazertinib monotherapy (Arm C) in participants with EGFRm NSCLC. The primary objective of the MARIPOSA study was to assess the efficacy of the combination of amivantamab and lazertinib (Arm A), compared with osimertinib (Arm B), as measured by PFS assessed by BICR in adult participants with EGFRm NSCLC.
As a consequence, sections 4.1, 4.2, 4.4, 4.8, 4.9, 5.1, 5.2, 6.6 and 9 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 3.3 of the EU RMP has also been submitted. As part of the application the MAH is requesting a 1-year extension of the market protection

### 15.3.3. Andexanet alfa - ONDEXXYA (CAP) - EMEA/H/C/004108/II/0044

Applicant: AstraZeneca AB

PRAC Rapporteur: Bianca Mulder

Scope: Update of sections 4.2, 4.4, 4.8 and 5.1 of the SmPC in order to update the safety and efficacy information based on the final results from study 18-513 (ANNEXA-I), listed as a specific obligation in the Annex II; this is a phase 4 randomised controlled trial to investigate the efficacy and safety of andexanet alfa versus usual care in patients with acute intracranial haemorrhage taking apixaban, rivaroxaban or edoxaban. Consequently, the MAH proposes a switch from conditional marketing authorisation to full marketing

authorisation. The Annex II and Package Leaflet are updated accordingly. The updated RMP version 4.0 has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the PI and to bring it in line with the latest QRD template version 10.3

### 15.3.4. Atezolizumab - TECENTRIQ (CAP) - EMEA/H/C/004143/II/0087

Applicant: Roche Registration GmbH

PRAC Rapporteur: Carla Torre

Scope: Update of sections 4.2, 4.8 and 5.1 in order to include information regarding switching treatment between Tecentriq intravenous and subcutaneous (and vice versa) and to update safety information, based on primary results from study MO43576 (IMscin002); this is a phase II, randomised, multicenter, open-label cross-over study to evaluate participants and healthcare professional reported reference for subcutaneous atezolizumab compared with intravenous atezolizumab formulation in participants with non-small cell lung cancer. The RMP version 31.0 has also been submitted. In addition, the MAH took the opportunity to introduce minor formatting changes to the PI

### 15.3.5. Avacopan - TAVNEOS (CAP) - EMEA/H/C/005523/II/0015, Orphan

Applicant: Vifor Fresenius Medical Care Renal Pharma France

PRAC Rapporteur: Liana Martirosyan

Scope: Update of sections 4.5 and 5.2 of the SmPC based on final results from study CL020_168; this is an open-label, phase 1 study to evaluate the effect of repeated oral doses of avacopan on the pharmacokinetics of a single dose of simvastatin in healthy volunteers; the Package Leaflet is updated accordingly. The updated RMP version 2.0 has also been submitted. In addition, the MAH took the opportunity to implement editorial changes to the SmPC

### 15.3.6. Bimekizumab - BIMZELX (CAP) - EMEA/H/C/005316/II/0028

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Liana Martirosyan

Scope: Update of section 5.1 of the SmPC in order to update efficacy information based on the final results from study PS0015 (BE RADIANT) listed as a category 3 study in the RMP; this is a multicenter, randomized, double-blind, secukinumab-controlled, parallel-group study to evaluate the efficacy and safety of bimekizumab in adult subjects with moderate to severe chronic plaque psoriasis. In addition, the MAH has taken the opportunity to update the list of local representatives in the Package leaflet and align the PI with the latest QRD template version 10.4 as well as to update wording on polysorbates in the SmPC and the Package leaflet to align with the annex of the guideline related to excipients. The RMP version 2.1 has also been submitted

### 15.3.7. Bulevirtide - HEPCLUDEX (CAP) - EMEA/H/C/004854/II/0034, Orphan

Applicant: Gilead Sciences Ireland Unlimited Company

PRAC Rapporteur: Adam Przybylkowski

Scope: Update of section 4.8 of the SmPC in order to update safety information based on final results from study MYR204 listed as a category 3 study in the RMP; this is a multicenter, open-label, randomized Phase 2b clinical study to assess efficacy and safety of bulevirtide in combination with pegylated interferon alfa-2a in patients with chronic hepatitis delta. The RMP version 4.2 has also been submitted

## 15.3.8. Cabotegravir - APRETUDE (CAP) - EMEA/H/C/005756/II/0004

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Martin Huber

Scope: Update of sections 4.8, 5.1 and 5.2 of the SmPC to include data from clinical studies in HIV-1 uninfected adolescents (HPTN 083-01 and HPTN 084-01), updated data from the MOCHA study and updated PK data based on a population PK analysis of cabotegravir in adolescents in MOCHA, HPTN 083-01 and HPTN 084-01. In addition, the MAH took the opportunity to update section 4.2 of the SmPC to clarify the wording related to missed doses of oral PrEP and renal impairment, and to implement editorial changes in the SmPC. Furthermore, the MAH took the opportunity to align the PI with the latest QRD template version 10.4. The RMP version 1.1 has also been submitted

## 15.3.9. Cabotegravir - VOCABRIA (CAP) - EMEA/H/C/004976/II/0022

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Martin Huber

Scope: Extension of indication to include in combination with rilpivirine injection, the treatment of adolescents (at least 12 years of age and weighing at least 35 kg) for Vocabria, based on interim results from study 208580 (Phase I/II Study of the Safety, Acceptability, Tolerability, and Pharmacokinetics of Oral and Long-Acting Injectable Cabotegravir and Long-Acting Injectable Rilpivirine in Virologically Suppressed HIV-Infected Children and Adolescents). This is an ongoing Phase 1/Phase 2 multicenter, open-label, non-comparative study evaluating the safety, acceptability, tolerability, and PK of oral and LA injectable CAB and LA injectable RPV in virologically suppressed HIV-infected adolescents 12 to <18 years of age and weighing at least 35 kg who are receiving stable cART consisting of 2 or more drugs from 2 or more classes of ARV drugs. 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 4.1 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to introduce editorial changes. Furthermore, the PI is brought in line with the latest QRD template version 10.4

## 15.3.10. Canagliflozin - INVOKANA (CAP) - EMEA/H/C/002649/WS2619/0066/G; Canagliflozin, Metformin - VOKANAMET (CAP) - EMEA/H/C/002656/WS2619/0073/G

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Martin Huber

Scope: A grouped application consisting of two Type II variations, as follows:
C.I.4: Update of section 4.4 of the SmPC in order to amend an existing warning on Diabetic

Ketoacidosis based on literature. The Package Leaflet is updated accordingly.
C.I.4: Update of sections 4.6 and 5.3 of the SmPC in order to update information on pregnancy based on literature.
The RMP version 11.1 has also been submitted

## 15.3.11. 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 PFS presentation

## 15.3.12. Ceftazidime, Avibactam - ZAVICEFTA (CAP) - EMEA/H/C/004027/II/0035

Applicant: Pfizer Ireland Pharmaceuticals

PRAC Rapporteur: Rugile Pilviniene

Scope: Extension of indication to include treatment of paediatric patients from birth to less than 3-months of age in the following infections: complicated intra-abdominal infection (cIAI), complicated urinary tract infection (cUTI), including pyelonephritis, hospital-acquired pneumonia (HAP), including ventilator associated pneumonia (VAP) and in the treatment of infections due to aerobic Gram-negative organisms in patients with limited treatment options, for ZAVICEFTA, based on final results from study C3591024 and the population PK modelling/simulation analyses. Study C3591024 is a Phase 2a, 2-part, open-label, non-randomized, multicenter, single and multiple dose trial to evaluate pharmacokinetics, safety and tolerability of ceftazidime and avibactam in neonates and infants from birth to less than 3 months of age with suspected or confirmed infections due to gram-negative pathogens requiring intravenous antibiotic treatment. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2, 6.3 and 6.6 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 3.3 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the PI

## 15.3.13. Ceritinib - ZYKADIA (CAP) - EMEA/H/C/003819/II/0055

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Mari Thorn

Scope: Submission of the final report from PAES study LDK378A2303; this is a Phase III, multicenter, randomized, open-label study of oral LDK378 versus standard chemotherapy in adult patients with ALK rearranged (ALK-positive) advanced non-small cell lung cancer who have been treated previously with chemotherapy (platinum doublet) and crizotinib. The RMP (version 18.0) is updated accordingly

## 15.3.14. Dapagliflozin - EDISTRIDE (CAP) - EMEA/H/C/004161/WS2733/0068; Dapagliflozin - FORXIGA (CAP) - EMEA/H/C/002322/WS2733/0089

Applicant: AstraZeneca AB

PRAC Rapporteur: Mari Thorn

Scope: Submission of the post-treatment week 104 safety results from study D1680C00019 (T2NOW) listed as a category 3 study in the RMP. This is a randomised, placebo-controlled, double-blind, parallel-group, phase 3 trial with a 26-week safety extension period evaluating the safety and efficacy of dapagliflozin 5 and 10 mg, and saxagliptin 2.5 and 5 mg in paediatric patients with type 2 diabetes mellitus who are between 10 and below 18 years of age. The RMP version 31,s1 has also been submitted

## 15.3.15. Daratumumab - DARZALEX (CAP) - EMEA/H/C/004077/II/0072, Orphan

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Carla Torre

Scope: Extension of indication to include, in combination with bortezomib, lenalidomide and dexamethasone, the treatment of adult patients with newly diagnosed multiple myeloma, who are eligible for autologous stem cell transplant for Darzalex, based on the primary analysis results from the pivotal study 54767414MMY3014 (PERSEUS) and the results from study 54767414MMY2004 (GRIFFIN) and the D-VRd cohort of study 54767414MMY2040 (PLEIADES).
MMY3014 (PERSEUS) is a randomised, open-label, active-controlled, multicentre phase 3 study in adult subjects with newly diagnosed multiple myeloma, who are eligible for high dose therapy (as required for autologous stem cell transplant). The primary objective is to compare the efficacy of (subcutaneous) daratumumab in combination with bortezomib, lenalidomide and dexamethasone (D-VRd) versus bortezomib, lenalidomide and dexamethasone (VRd) in terms of progression free survival (PFS).
MMY2004 (GRIFFIN) is a randomised, open-label, active controlled, multicentre phase 2 study in adult subjects with newly diagnosed multiple myeloma, who are eligible for high dose therapy and autologous stem cell transplant. The primary objective is to compare the efficacy of daratumumab in combination with bortezomib, lenalidomide and dexamethasone (D-VRd) versus bortezomib, lenalidomide and dexamethasone (VRd), in terms of stringent complete response (sCR) rate.
MMY2040 (PLEIADES) is a randomised, open-label, multicentre phase 2 study to evaluate subcutaneous daratumumab in combination with standard multiple myeloma treatment regimens. The D-VRd cohort included adult subjects with newly diagnosed multiple myeloma, who were evaluated for clinical benefit in terms of very good partial response or better (VGPR) rate.
As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 10.1 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

## 15.3.16. Dengue tetravalent vaccine (live, attenuated) - DENGUE TETRAVALENT VACCINE (LIVE, ATTENUATED) TAKEDA (Art 58) - 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, randomized 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

## 15.3.17. Dostarlimab - JEMPERLI (CAP) - EMEA/H/C/005204/II/0032

Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Carla Torre

Scope: Extension of indication for JEMPERLI to include, in combination with carboplatin and paclitaxel, the treatment of adult patients with primary advanced or recurrent endometrial cancer (EC) and who are candidates for systemic therapy based on Interim Analysis 1 and 2 from study RUBY Part 1 (213361). This is a phase 3, randomized, double-blind, controlled study evaluating the efficacy and safety of dostarlimab plus carboplatin and paclitaxel in primary advanced or recurrent EC versus placebo plus carboplatin and paclitaxel.
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 4.0 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to implement editorial changes to the SmPC and to align the PI with the latest QRD template version 10.4

## 15.3.18. Dupilumab - DUPIXENT (CAP) - EMEA/H/C/004390/II/0083

Applicant: Sanofi Winthrop Industrie

PRAC Rapporteur: Kimmo Jaakkola

Scope: Extension of indication to include treatment of moderate to severe chronic spontaneous urticaria in adults and adolescents 12 years and older, who are symptomatic despite treatment with H1 antihistamines and who are intolerant to or inadequately controlled by anti-IgE therapy for Dupixent, based on the results from studies EFC16461 (CUPID) study B (pivotal) and study A (supportive); EFC16461 Study B was a 24-week, double-blind, randomized, placebo-controlled study to evaluate the efficacy and safety of dupilumab in adult and adolescent participants with CSU who remained symptomatic despite the use of H1-antihistamine and who were intolerant or incomplete responders to omalizumab and EFC16461 Study A was a 24-week, double-blind, randomized, placebo-controlled study to evaluate the efficacy and safety of dupilumab in participants with CSU who remained symptomatic despite the use of H1-antihistamine and who were naïve to omalizumab. 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 11.0 of the RMP has also been submitted

## 15.3.19. Efgartigimod alfa - VYVGART (CAP) - EMEA/H/C/005849/II/0020, Orphan

Applicant: Argenx

PRAC Rapporteur: Rhea Fitzgerald

Scope: Extension of indication to include the treatment of adult patients with chronic inflammatory demyelinating polyneuropathy (CIDP) with active disease despite treatment with corticosteroids or immunoglobulins for VYVGART, based on final results from study ARGX-113-1802; this is a pivotal study to investigate the efficacy, safety and tolerability of efgartigimod PH20 SC in adult patients with chronic inflammatory demyelinating polyneuropathy (CIDP); and based on interim results from study ARGX-113-1902; this is an open-label extension study of the ARGX-113-1802 trial to investigate the long-term safety, tolerability and efficacy of efgartigimod PH20 SC in patients with (CIDP).
As a consequence, sections 4.1, 4.2. 4.4, 4.8, 5.1 and 5.2 of the SmPC has been updated. The Package Leaflet has been updated in accordance with the SmPC. In addition, the MAH took the opportunity to implement editorial changes to the SmPC

## 15.3.20. Everolimus - VOTUBIA (CAP) - EMEA/H/C/002311/II/0089

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Martin Huber

Scope: Submission of the final report from study CRAD001M2305 listed as a category 3 study in the RMP. This is an interventional PASS study to monitor the growth and development of pediatric patients previously treated with everolimus in study CRAD001M2301 (EXIST-LT). The RMP version 15.0 has also been submitted

## 15.3.21. Faricimab - VABYSMO (CAP) - EMEA/H/C/005642/II/0011/G

Applicant: Roche Registration GmbH

PRAC Rapporteur: Carla Torre

Scope: 1.Type II (B.II.e.1.b.2)
2.Type II (B.II.b.1.c)
3.Type IB (B.II.b.2.a)
4.Type IB (B.II.b.2.a)
5.Type IB (B.II.b.2.a)
6. Type II (B.II.b.1.c)
7.Type IB (B.II.b.2.z)
8.Type IB (B.IV.1.a.1)
9.Type IA (B.II.d.1.c)

## 15.3.22. Fenofibrate, Pravastatin sodium - PRAVAFENIX (CAP) - EMEA/H/C/001243/II/0037

Applicant: Laboratoires SMB s.a.

PRAC Rapporteur: Nathalie Gault

Scope: Extension of indication to include treatment of mixed hyperlipidaemia in adult patients while on a treatment with pravastatin 40 mg monotherapy or on another moderate-intensity statin regimen for PRAVAFENIX, based on final results from the non-interventional PASS: POSE (Pravafenix Observational Study in Europe); this is a European, observational, three-year cohort comparative study on the safety of the fixed dose combination pravastatin 40 mg/fenofibrate 160 mg (Pravafenix) versus statin alone in real clinical practice. As a consequence, sections 4.1 and 4.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 4.1 of the RMP has also been submitted

## 15.3.23. Guselkumab - TREMFYA (CAP) - EMEA/H/C/004271/II/0044

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Gabriele Maurer

Scope: Extension of indication for TREMFYA to include treatment of adult patients with moderately to severely active Crohn's disease (CD) who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic treatment, based on results from GALAXI Phase 2/3 program and the GRAVITI Phase 3 study. GALAXI is a Phase 2/3, randomized, double-blind, placebo- and active-controlled, parallel-group, multicenter protocol to evaluate the efficacy and safety of guselkumab in participants with moderately to severely active CD who have demonstrated an inadequate response or failure to tolerate previous conventional or biologic therapy. GRAVITI is a Phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate the efficacy and safety of guselkumab SC induction therapy in participants with moderately to severely active CD.
As a consequence, sections 4.1, 4.2, 4.5, 4.8, 5.1, 5.2, and 5.3 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 10.1 of the RMP has also been submitted. As part of the application the MAH is requesting a 1-year extension of the market protection

## 15.3.24. Guselkumab - TREMFYA (CAP) - EMEA/H/C/004271/X/0043/G

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Gabriele Maurer

Scope: Extension application to:
- introduce a new pharmaceutical form (concentrate for solution for infusion), a new strength (200 mg) and a new route of administration (intravenous use)
- add a new strength of 200 mg for solution for injection (in pre-filled syringe / pre-filled pen) for subcutaneous use
This application is grouped with a type II variation (C.I.6.a) to include the treatment of adult patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response, lost response, or were intolerant to either conventional therapy, a biologic treatment, or a Janus kinase (JAK) inhibitor for Tremfya, based on results of a Phase 2b/3 clinical development programme (CNTO1959UCO3001) consisting of 3 separate studies, an Induction dose finding Study 1 Phase 2b, an Induction Study 2 Phase 3 and a Phase 3 Maintenance Study. These studies were randomized, double-blind, placebo-controlled, parallel-group, multicenter studies that evaluated the efficacy and safety of guselkumab in participants with moderately to severely active UC. As a consequence, sections 4.1, 4.2, 4.5, 4.8, 5.1, 5.2 and 5.3 of the SmPC of the already approved form 100 mg solution for injection are updated. The Package Leaflet and Labelling are updated in accordance. Version 10.1 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 to the PI

## 15.3.25. Herpes zoster vaccine (recombinant, adjuvanted) - SHINGRIX (CAP) - EMEA/H/C/004336/II/0076

Applicant: GlaxoSmithkline Biologicals SA

PRAC Rapporteur: Sonja Hrabcik

Scope: Update of sections 4.8 and 5.1 of the SmPC to include the final results of study ZOSTER-049, listed as a category 3 study in the RMP. This is a Phase 3b, open label, multi-country, long-term follow-up study that assessed the prophylactic efficacy, safety, and immunogenicity persistence of Shingrix in adults ≥50 years of age at the time of primary vaccination in studies ZOSTER 006 and ZOSTER-022. The study also assessed 1 or 2 additional doses of Shingrix on a 0 or 0, 2-month schedule in two subgroups of older adults. The updated RMP version 8.0 is also included. In addition, the MAH took the opportunity to implement editorial changes to the SmPC, Labelling and Package Leaflet; and to bring the PI in line with the latest QRD template version 10.4

## 15.3.26. Inotuzumab ozogamicin - BESPONSA (CAP) - EMEA/H/C/004119/II/0029, Orphan

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Gabriele Maurer

Scope: Submission of the final report from study B1931030 listed as a category 3 study in the RMP. Phase 4, open-label, randomized study of two Inotuzumab Ozogamicin dose levels in adult patients with relapsed or refractory B-cell acute lymphoblastic leukemia eligible for hematopoietic stem cell transplantation and who have risk factor(s) for veno-occlusive disease. The RMP version 3.1 has also been submitted

## 15.3.27. Linzagolix choline - YSELTY (CAP) - EMEA/H/C/005442/II/0013

Applicant: Theramex Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: Extension of indication to include treatment of endometriosis-associated pain in adult women of reproductive age for YSELTY, based on final results from studies Edelweiss 3 (18-OBE2109-003) and Edelweiss 6 (19-OBE2109-006) as well as additional supporting studies. Edelweiss 3 is a pivotal phase 3, randomised, double-blind, placebo-controlled, safety and efficacy study to evaluate linzagolix with add-back therapy as a therapy for pain associated with endometriosis, while Edelweiss 6 is an open-label extension study including patients who completed Edelweiss 3 pivotal study regardless of their previous treatment assignment and met the eligibility criteria. 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 1.1 of the RMP has also been submitted. As part of the application, the MAH is requesting a 1-year extension of the market protection

## 15.3.28. Lutetium ($^{177}$Lu) oxodotreotide - LUTATHERA (CAP) - EMEA/H/C/004123/II/0052, Orphan

Applicant: Advanced Accelerator Applications

PRAC Rapporteur: Adam Przybylkowski

Scope: Extension of indication to include the treatment of newly diagnosed, unresectable or metastatic, well-differentiated (G2 and G3), somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumours (GEP-NETs) adult patients for LUTATHERA, based on primary analysis results from study CAAA601A22301 (NETTER-2); NETTER-2

study is a Phase III, multicenter, stratified, open-label, randomized, comparator-controlled study comparing treatment with Lutathera plus octreotide LAR 30 mg (Lutathera arm) to treatment with high-dose octreotide LAR 60 mg (control arm). The main purpose of the NETTER-2 study was to determine if treatment in the Lutathera arm prolongs PFS in subjects with newly diagnosed SSTR-positive, G2 and G3 advanced GEP-NET when compared with treatment in the control arm.
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. In addition, the Marketing authorisation holder (MAH) took the opportunity to implement editorial changes in the SmPC. 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

## 15.3.29. Mavacamten - CAMZYOS (CAP) - EMEA/H/C/005457/II/0011/G

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Kimmo Jaakkola

Scope: Grouped application comprised of 2 Type II Variations as follows:

C.I.4: Update of section 4.2 of the SmPC to change the echocardiography monitoring frequency once a patient is on a stable dose of mavacamten. The proposed update is supported by the clinical data from interim Clinical study report of MAVA-LTE (CV027-003) study: "A Long-term Safety Extension Study of Mavacamten in Adults with Hypertrophic Cardiomyopathy who have completed the MAVERICK-HCM (MYK-461-006) or EXPLORER-HCM (MYK-461-005) trials", modelling & simulation results and safety data from post-approval safety database. The Package Leaflet is updated accordingly.

C.I.4: Update of section 4.2 of the SmPC to introduce the optional use of the Left ventricular outflow track (LVOT) gradient by post-exercise testing to guide dose titration for patient with specific characteristics. The proposed update is supported by the exposure-response modeling and simulation report with LVOT post-exercise gradient, based on the previously developed model with the data from the following studies: MYK-461-004 (PIONEER), MYK-461-005 (EXPLORER), MYK-461-007, MYK-461-008 (MAVA-LTE) and MYK-461-017 (VALOR).

The RMP version 4.0 has also been submitted

## 15.3.30. Melatonin - SLENYTO (CAP) - EMEA/H/C/004425/II/0028

Applicant: RAD Neurim Pharmaceuticals EEC SARL

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Extension of indication to include treatment of insomnia in children and adolescents aged 2-18 with Attention-Deficit Hyperactivity Disorder (ADHD), where sleep hygiene measures have been insufficient, based on results from phase III study NEU_CH_7911 and literature. As a consequence, sections 4.1 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

## 15.3.31. Meningococcal group B vaccine (recombinant, adsorbed) - TRUMENBA (CAP) - EMEA/H/C/004051/II/0053

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Jean-Michel Dogné

Scope: Update of sections 4.4 and 5.1 of the SmPC in order to amend an existing warning on immunocompromised individuals and to add immunogenicity data in individuals 10 years of age and above with complement deficiencies or splenic dysfunction based on final results from study B1971060 (A Phase 4, Open-Label, Single-Arm Trial to Describe the Safety, Tolerability, and Immunogenicity of Trumenba When Administered to Immunocompromised Participants ≥10 Years of Age) listed as a category 3 study in the RMP. This was an open-label, single-arm, multicenter trial in which up to 50 immunocompromised participants ≥10 years of age with asplenia (anatomic or functional) or complement deficiency have been enrolled and received bivalent rLP2086 on a 2-dose, 0- and 6-month schedule. The RMP version 8.0 has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the PI and to bring the PI in line with the latest QRD template version 10.4

## 15.3.32. Midazolam - BUCCOLAM (CAP) - EMEA/H/C/002267/II/0061

Applicant: Neuraxpharm Pharmaceuticals S.L.

PRAC Rapporteur: Liana Martirosyan

Scope: Extension of indication to include treatment of adults to Buccolam 10 mg, based on the results from study 2023-504903-10-00; this is an Interventional Study, Relative Bioavailability to investigate the pharmacokinetics of a single dose of midazolam oromucosal solution (Buccolam) compared to midazolam solution for intramuscular injection (Hypnovel) in healthy volunteers under fasting conditions. As a consequence, sections 4.1, 4.2, 4.8, 5.1, 5.2, 6.5 and 6.6 of the SmPC are updated. The Package Leaflet and Labelling are updated in accordance. Version 8.1 of the RMP has also been submitted

## 15.3.33. Mirikizumab - OMVOH (CAP) - EMEA/H/C/005122/X/0006/G

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Sonja Hrabcik

Scope: Extension application to add a new strength of 200 mg grouped with an extension of indication (C.I.6) to include treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic treatment, for Omvoh, based mainly on final results from study I6T-MC-AMAM; this is a phase 3, multicenter, randomized, double-blind, placebo- and active-controlled, treat-through study to evaluate the efficacy and safety of mirikizumab in patients with moderately to severely active Crohn's disease. As a consequence, sections 1, 2, 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2, 5.3, 6.1, 6.5, 6.6 and 8 of the SmPC are updated. The Labelling and Package Leaflet are updated in accordance. Version 1.2 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes 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.

The following Quality variations are also included as part of this application:

Type IA, A.5.b

Type II, B.II.a.3.b.5

Type IB, B.II.b.4.a

Type II, B.I.a.2.c

Type IB, B.I.a.2.z

## 15.3.34. 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.

## 15.3.35. Nusinersen - SPINRAZA (CAP) - EMEA/H/C/004312/II/0034/G, Orphan

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Mari Thorn

Scope: A grouped application consisting of:
C.I.4: Update of sections 5.1 and 5.2 of the SmPC based on final results from study CS11 (SHINE) listed as a PAES in the Annex II. The Annex II and the RMP v12.1 are updated accordingly. SHINE is a phase III, open-label extension study for patients with Spinal Muscular Atrophy (SMA) who previously participated in investigational studies of ISIS 396443.
C.I.4: Update of section 5.1 of the SmPC based on interim results from study CS5 (NURTURE, 232SM201). NURTURE is a Phase II, open-label study to assess the efficacy, safety, tolerability, and pharmacokinetics of multiple doses of nusinersen delivered

intrathecally to patients with genetically diagnosed and presymptomatic SMA.
C.I.4: Update of section 5.1 of the SmPC in order to relocate the updated information regarding immunogenicity from SmPC section 4.8 to section 5.1 as per applicable CHMP guidance. The data has been revised based on an updated integrated analysis across several studies.
C.I.4: Update of section 5.1 of the SmPC based on the outcome of a systematic literature review (SLR) and Natural History data from an International SMA registry (ISMAR)

## 15.3.36. Pegzilarginase - LOARGYS (CAP) - EMEA/H/C/005484/II/0002/G, Orphan

Applicant: Immedica Pharma AB

PRAC Rapporteur: Martin Huber

Scope: Grouped application comprising two type II variations as follows:
C.I.4 – Update of sections 4.8 and 5.1 of the SmPC in order to update efficacy and safety information based on final results from study CAEB1102-300A (SOB 003), listed as a specific obligation in Annex II. Study 300A was a Phase 3, randomized, double blind, placebo-controlled study of the efficacy and safety of pegzilarginase in adults, adolescents and children with arginase 1 deficiency (ARG1 D).
C.I.4 – Update of section 4.8 of the SmPC in order to update efficacy and safety information based on final results from study CAEB1102-102A (SOB 004), listed as a specific obligation in Annex II.
Study 102A was an open label extension study to evaluate the long-term safety, tolerability, and efficacy of pegzilarginase in adults, adolescents and children with arginase 1 deficiency (ARG1 D).
The Package Leaflet and Annex II are updated accordingly. The RMP version 1.1 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

## 15.3.37. Respiratory syncytial virus vaccine (bivalent, recombinant) - ABRYSVO (CAP) - EMEA/H/C/006027/II/0007

Applicant: Pfizer Europe Ma EEIG

PRAC Rapporteur: Liana Martirosyan

Scope: Extension of indication to include active immunization of individuals 18 through 59 years of age for ABRYSVO, based on final results from C3671023 Substudy A; this is a Phase 3 double-blinded, randomised, placebo-controlled study of safety, tolerability and immunogenicity of Abrysvo in participants ≥18 to <60 years of age at high risk of severe RSV disease due to certain chronic medical conditions. 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 1.0 of the RMP has also been submitted. In addition, the MAH took the opportunity to implement editorial changes to the SmPC. Furthermore, as part of the application the MAH is requesting a 1-year extension of the market protection

## 15.3.38. Rilpivirine - REKAMBYS (CAP) - EMEA/H/C/005060/II/0022

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Liana Martirosyan

Scope: Extension of indication to include in combination with cabotegravir injection, the treatment of adolescents (at least 12 years of age and weighing at least 35 kg) for Rekambys, based on interim results from study 208580 (Phase I/II Study of the Safety, Acceptability, Tolerability, and Pharmacokinetics of Oral and Long-Acting Injectable Cabotegravir and Long-Acting Injectable Rilpivirine in Virologically Suppressed HIV-Infected Children and Adolescents). This is an ongoing Phase 1/Phase 2 multicenter, open-label, non-comparative study evaluating the safety, acceptability, tolerability, and PK of oral and LA injectable CAB and LA injectable RPV in virologically suppressed HIV-infected adolescents 12 to <18 years of age and weighing at least 35 kg who are receiving stable cART consisting of 2 or more drugs from 2 or more classes of ARV drugs.Consequently, 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 5.1 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to update a local representative in the Package Leaflet. Furthermore, the PI is brought in line with the latest QRD template version 10.4

## 15.3.39. Sarilumab - KEVZARA (CAP) - EMEA/H/C/004254/X/0043/G

Applicant: Sanofi Winthrop Industrie

PRAC Rapporteur: Monica Martinez Redondo

Scope: Extension application to add a new strength of 175 mg/ml solution for injection in vial, grouped with an extension of indication to include treatment of active polyarticular-course juvenile idiopathic arthritis (pcJIA) in patients 2 years of age and older for KEVZARA, based on results from study DRI13925; this is a multinational, multi-center, open-label, 2 phase, 3 portions study to describe the PK profile as well as safety and efficacy of sarilumab. 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 3.0 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the PI

## 15.3.40. Somatrogon - NGENLA (CAP) - EMEA/H/C/005633/II/0016, Orphan

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Martirosyan

Scope: Extension of indication to include the long-term replacement of endogenous growth hormone of adults with growth hormone deficiency for Ngenla, based on supplemental results from study CP-4-005 and the Phase 2 supportive study CP-4-003. CP-4-005 is a Phase 3, multicenter study designed to evaluate the efficacy and safety of a Long Acting hGH Product (MOD-4023) in adult subjects with Growth Hormone Deficiency. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 4.9 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

## 15.3.41. Tislelizumab - TEVIMBRA (CAP) - EMEA/H/C/005919/II/0003

Applicant: Beigene Ireland Limited

PRAC Rapporteur: Bianca Mulder

Scope: Extension of indication to include in combination with platinum-based chemotherapy the first-line treatment of adult patients with unresectable, locally advanced or metastatic oesophageal squamous cell carcinoma (OSCC) for TEVIMBRA, based on results from study BGB-A317-306; this is a multi-regional, randomized, placebo-controlled, double-blind phase 3 study evaluating the efficacy and safety of tislelizumab in combination with chemotherapy compared to placebo in combination with chemotherapy as first-line treatment in patients with unresectable or locally advanced recurrent or metastatic OSCC. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 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 MAH took the opportunity to introduce minor editorial changes to the PI

### 15.3.42. Turoctocog alfa pegol - ESPEROCT (CAP) - EMEA/H/C/004883/II/0023

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Gabriele Maurer

Scope: Extension of indication to include children below 12 years of age for treatment and prophylaxis of bleeding with haemophilia A for Esperoct, including previously untreated patients (PUPs) based on the final results from studies 3776, 4410, 3908, 3859, 3885, 3860, 4033 and 4595. As a consequence, section 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 3.0 of the RMP has also been submitted. Furthermore, the PI is brought in line with the latest QRD template version 10.4

### 15.3.43. 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, Randomized, Observer-Blind, Multicentre Study to Evaluate the Immunogenicity and Safety of Several Doses of Antigen and MF59 Adjuvant Content in a Monovalent H5N1 Pandemic Influenza Vaccine in Healthy Paediatric 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. Albutrepenonacog alfa - IDELVION (CAP) - PSUSA/00010497/202401

Applicant: CSL Behring GmbH

PRAC Rapporteur: Bianca Mulder

Scope: Evaluation of a PSUSA procedure

### 16.1.2. Anifrolumab - SAPHNELO (CAP) - PSUSA/00010980/202401

Applicant: AstraZeneca AB

PRAC Rapporteur: Liana Martirosyan

Scope: Evaluation of a PSUSA procedure

### 16.1.3. Asparaginase[47] - SPECTRILA (CAP) - PSUSA/00010445/202401

Applicant: medac Gesellschaft fur klinische Spezialpraparate mbH

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

### 16.1.4. Ataluren - TRANSLARNA (CAP) - PSUSA/00010274/202401

Applicant: PTC Therapeutics International Limited

PRAC Rapporteur: Liana Martirosyan

Scope: Evaluation of a PSUSA procedure

### 16.1.5. Avalglucosidase alfa - NEXVIADYME (CAP) - PSUSA/00011002/202402

Applicant: Sanofi B.V.

PRAC Rapporteur: Liana Martirosyan

Scope: Evaluation of a PSUSA procedure

### 16.1.6. Avapritinib - AYVAKYT (CAP) - PSUSA/00010878/202401

Applicant: Blueprint Medicines (Netherlands) B.V.

[47] For centrally authorised products only

PRAC Rapporteur: Bianca Mulder

Scope: Evaluation of a PSUSA procedure

### 16.1.7. Baricitinib - OLUMIANT (CAP) - PSUSA/00010578/202402

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

### 16.1.8. Birch bark extract[48] - FILSUVEZ (CAP) - PSUSA/00010446/202401

Applicant: Chiesi Farmaceutici S.p.A

PRAC Rapporteur: Zane Neikena

Scope: Evaluation of a PSUSA procedure

### 16.1.9. Botulinum toxin type A[49] - NUCEIVA (CAP) - PSUSA/00010796/202401

Applicant: Evolus Pharma B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

### 16.1.10. Brexucabtagene autoleucel - TECARTUS (CAP) - PSUSA/00010903/202401

Applicant: Kite Pharma EU B.V., ATMP

PRAC Rapporteur: Bianca Mulder

Scope: Evaluation of a PSUSA procedure

### 16.1.11. Bulevirtide - HEPCLUDEX (CAP) - PSUSA/00010873/202401

Applicant: Gilead Sciences Ireland Unlimited Company

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

### 16.1.12. Ceftolozane, tazobactam - ZERBAXA (CAP) - PSUSA/00010411/202312

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

### 16.1.13. Clofarabine - EVOLTRA (CAP) - PSUSA/00000805/202312

Applicant: Sanofi B.V.

[48] For centrally authorised products only
[49] For centrally authorised products only

PRAC Rapporteur: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

### 16.1.14. Dapivirine - DAPIVIRINE VAGINAL RING 25 MG (Art 58[50]) - EMEA/H/W/002168/PSUV/0026

Applicant: International Partnership for Microbicides Belgium AISBL

PRAC Rapporteur: Jan Neuhauser;

Scope: Evaluation of a PSUR procedure

### 16.1.15. Darolutamide - NUBEQA (CAP) - PSUSA/00010843/202401

Applicant: Bayer AG

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

### 16.1.16. Darunavir - PREZISTA (CAP) - PSUSA/00000934/202312

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Liana Martirosyan

Scope: Evaluation of a PSUSA procedure

### 16.1.17. Decitabine, cedazuridine - INAQOVI (CAP) - PSUSA/00000118/202401

Applicant: Otsuka Pharmaceutical Netherlands B.V.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Evaluation of a PSUSA procedure

### 16.1.18. Defatted powder of arachis hypogaea l., semen (peanuts) - PALFORZIA (CAP) - PSUSA/00010902/202401

Applicant: Aimmune Therapeutics Ireland Limited

PRAC Rapporteur: Terhi Lehtinen

Scope: Evaluation of a PSUSA procedure

### 16.1.19. Epoetin zeta - RETACRIT (CAP); SILAPO (CAP) - PSUSA/00001241/202312

Applicants: Pfizer Europe MA EEIG (Retacrit), STADA Arzneimittel AG (Silapo), various

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

[50] 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)

### 16.1.20. Ertugliflozin - STEGLATRO (CAP); ertugliflozin, metformin hydrochloride - SEGLUROMET (CAP); ertugliflozin, sitagliptin - STEGLUJAN (CAP); - PSUSA/00010784/202312

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Bianca Mulder

Scope: Evaluation of a PSUSA procedure

### 16.1.21. Evinacumab - EVKEEZA (CAP) - PSUSA/00010945/202402

Applicant: Ultragenyx Germany GmbH

PRAC Rapporteur: Mari Thorn

Scope: Evaluation of a PSUSA procedure

### 16.1.22. Faricimab - VABYSMO (CAP) - PSUSA/00011016/202401

Applicant: Roche Registration GmbH

PRAC Rapporteur: Carla Torre

Scope: Evaluation of a PSUSA procedure

### 16.1.23. Fedratinib - INREBIC (CAP) - PSUSA/00010909/202402

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Sonja Hrabcik

Scope: Evaluation of a PSUSA procedure

### 16.1.24. Fostemsavir - RUKOBIA (CAP) - PSUSA/00010911/202402

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Liana Martirosyan

Scope: Evaluation of a PSUSA procedure

### 16.1.25. Gefapixant - LYFNUA (CAP) - PSUSA/00000132/202401

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

### 16.1.26. Glucarpidase - VORAXAZE (CAP) - PSUSA/00010968/202401

Applicant: SERB S.A.S.

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

## 16.1.27. Lisocabtagene maraleucel- BREYANZI (CAP) - PSUSA/00010990/202402

Applicant: Bristol-Myers Squibb Pharma EEIG, ATMP

PRAC Rapporteur: Gabriele Maurer

Scope: Evaluation of a PSUSA procedure

## 16.1.28. Melphalan flufenamide - PEPAXTI (CAP) - PSUSA/00011013/202402

Applicant: Oncopeptides AB

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

## 16.1.29. Meningococcal group-B vaccine (rDNA[51], component, adsorbed) - BEXSERO (CAP) - PSUSA/00010043/202401

Applicant: GSK Vaccines S.r.l

PRAC Rapporteur: Mari Thorn

Scope: Evaluation of a PSUSA procedure

## 16.1.30. Mercaptamine[52] - CYSTADROPS (CAP) - PSUSA/00010574/202401

Applicant: Recordati Rare Diseases

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

## 16.1.31. Metreleptin - MYALEPTA (CAP) - PSUSA/00010700/202401

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

## 16.1.32. Pirtobrutinib - JAYPIRCA (CAP) - PSUSA/00000155/202401

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Bianca Mulder

Scope: Evaluation of a PSUSA procedure

## 16.1.33. Pneumococcal polysaccharide conjugate vaccine (15 valent, adsorbed) - VAXNEUVANCE (CAP) - PSUSA/00010975/202401

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Gabriele Maurer

[51] Recombinant deoxyribonucleic acid
[52] Indicated for the treatment of corneal cystine crystal deposit only

Scope: Evaluation of a PSUSA procedure

### 16.1.34. Quadrivalent influenza vaccine (recombinant, prepared in cell culture) - SUPEMTEK (CAP) - PSUSA/00010886/202401

Applicant: Sanofi Pasteur

PRAC Rapporteur: Nathalie Gault

Scope: Evaluation of a PSUSA procedure

### 16.1.35. Ranolazine - RANEXA (CAP) - PSUSA/00002611/202401

Applicant: Menarini International Operations Luxembourg S.A.

PRAC Rapporteur: Mari Thorn

Scope: Evaluation of a PSUSA procedure

### 16.1.36. Regdanvimab - REGKIRONA (CAP) - PSUSA/00010964/202402

Applicant: Celltrion Healthcare Hungary Kft.

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

### 16.1.37. Remimazolam - BYFAVO (CAP) - PSUSA/00010924/202401

Applicant: Paion Pharma GmbH

PRAC Rapporteur: Eamon O'Murchu

Scope: Evaluation of a PSUSA procedure

### 16.1.38. Risdiplam - EVRYSDI (CAP) - PSUSA/00010925/202402

Applicant: Roche Registration GmbH

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

### 16.1.39. Roflumilast - DAXAS (CAP) - PSUSA/00002658/202401

Applicant: AstraZeneca AB

PRAC Rapporteur: Monica Martinez Redondo

Scope: Evaluation of a PSUSA procedure

### 16.1.40. Romosozumab - EVENITY (CAP) - PSUSA/00010824/202401

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

### 16.1.41. Salmeterol, fluticasone propionate[53] - BROPAIR SPIROMAX (CAP); SEFFALAIR SPIROMAX (CAP) - PSUSA/00010928/202401

Applicant: Teva B.V.

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

### 16.1.42. Smallpox and monkeypox vaccine (Live Modified Vaccinia Virus Ankara) - IMVANEX (CAP) - PSUSA/00010119/202401

Applicant: Bavarian Nordic A/S

PRAC Rapporteur: Gabriele Maurer

Scope: Evaluation of a PSUSA procedure

### 16.1.43. Sutimlimab - ENJAYMO (CAP) - PSUSA/00011023/202402

Applicant: Sanofi B.V.

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

### 16.1.44. Tafasitamab - MINJUVI (CAP) - PSUSA/00010951/202401

Applicant: Incyte Biosciences Distribution B.V.

PRAC Rapporteur: Mari Thorn

Scope: Evaluation of a PSUSA procedure

### 16.1.45. Talquetamab - TALVEY (CAP) - PSUSA/00000099/202402

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Barbara Kovacic Bytyqi

Scope: Evaluation of a PSUSA procedure

### 16.1.46. Tezacaftor, ivacaftor - SYMKEVI (CAP) - PSUSA/00010730/202402

Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Eamon O'Murchu

Scope: Evaluation of a PSUSA procedure

### 16.1.47. Ticagrelor - BRILIQUE (CAP) - PSUSA/00002948/202312

Applicant: AstraZeneca AB

PRAC Rapporteur: Bianca Mulder

[53] For centrally authorised products only

Scope: Evaluation of a PSUSA procedure

### 16.1.48. Upadacitinib - RINVOQ (CAP) - PSUSA/00010823/202402

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Petar Mas

Scope: Evaluation of a PSUSA procedure

### 16.1.49. Vericiguat - VERQUVO (CAP) - PSUSA/00010950/202401

Applicant: Bayer AG

PRAC Rapporteur: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

### 16.1.50. Voxelotor - OXBRYTA (CAP) - PSUSA/00010983/202402

Applicant: Pfizer Europe Ma EEIG

PRAC Rapporteur: Jo Robays

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. Lutetium ($^{177}$Lu) chloride - ENDOLUCINBETA (CAP); LUMARK (CAP); LUTETIUM ($^{177}$LU) CHLORIDE BILLEV (CAP); NAP - PSUSA/00010391/202312

Applicants: Billev Pharma ApS (Lutetium (177Lu) chloride Billev), I.D.B. Holland B.V. (Lumark), ITM Medical Isotopes GmbH (EndolucinBeta), various

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

### 16.2.2. Rasagiline - AZILECT (CAP); RASAGILINE RATIOPHARM (CAP); NAP - PSUSA/00002612/202401

Applicants: Teva B.V. (AZILECT, Rasagiline ratiopharm), various

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

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

### 16.3.1. Alitretinoin[54] (NAP) - PSUSA/00010710/202401

Applicant(s): various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

### 16.3.2. Altizide, spironolactone (NAP) - PSUSA/00002781/202401

Applicant(s): various

PRAC Lead: Barbara Kovacic Bytyqi

Scope: Evaluation of a PSUSA procedure

### 16.3.3. Amlodipine, losartan (NAP) - PSUSA/00010512/202401

Applicant(s): various

PRAC Lead: Melinda Palfi

Scope: Evaluation of a PSUSA procedure

### 16.3.4. Azelastine (NAP) - PSUSA/00000277/202312

Applicant(s): various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

### 16.3.5. Balsalazide (NAP) - PSUSA/00009074/202401

Applicant(s): various

PRAC Lead: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

### 16.3.6. Bendroflumethiazide (NAP); bendroflumethiazide, potassium chloride (NAP) - PSUSA/00010583/202401

Applicant(s): various

PRAC Lead: Eva Jirsová

Scope: Evaluation of a PSUSA procedure

### 16.3.7. Betahistine (NAP) - PSUSA/00000389/202312

Applicant(s): various

[54] Oral use only

PRAC Lead: Zane Neikena

Scope: Evaluation of a PSUSA procedure

### 16.3.8. Caffeine, drotaverine hydrochloride, metamizole sodium (NAP) - PSUSA/00001996/202401

Applicant(s): various

PRAC Lead: Anna Mareková

Scope: Evaluation of a PSUSA procedure

### 16.3.9. Celecoxib (NAP) - PSUSA/00000616/202312

Applicant(s): various

PRAC Lead: Mari Thorn

Scope: Evaluation of a PSUSA procedure

### 16.3.10. Cyproheptadine (NAP) - PSUSA/00000902/202312

Applicant(s): various

PRAC Lead: Melinda Palfi

Scope: Evaluation of a PSUSA procedure

### 16.3.11. Dapoxetine (NAP) - PSUSA/00000928/202312

Applicant(s): various

PRAC Lead: Mari Thorn

Scope: Evaluation of a PSUSA procedure

### 16.3.12. Desmopressin (NAP) - PSUSA/00000964/202312

Applicant(s): various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

### 16.3.13. Dexpanthenol (NAP) - PSUSA/00000999/202401

Applicant(s): various

PRAC Lead: Terhi Lehtinen

Scope: Evaluation of a PSUSA procedure

### 16.3.14. Doxazosin (NAP) - PSUSA/00001169/202312

Applicant(s): various

PRAC Lead: Karin Erneholm

Scope: Evaluation of a PSUSA procedure

### 16.3.15. Ferric carboxymaltose[55] (NAP) - PSUSA/00010865/202401

Applicant(s): various

PRAC Lead: Zane Neikena

Scope: Evaluation of a PSUSA procedure

### 16.3.16. Ferric derisomaltose[56] (NAP) - PSUSA/00010866/202401

Applicant(s): various

PRAC Lead: Zane Neikena

Scope: Evaluation of a PSUSA procedure

### 16.3.17. Hepatitis A vaccines (inactivated, adsorbed) (NAP) - PSUSA/00001596/202401

Applicant(s): various

PRAC Lead: Gabriele Maurer

Scope: Evaluation of a PSUSA procedure

### 16.3.18. Hydrochlorothiazide, spironolactone (NAP) - PSUSA/00001662/202401

Applicant(s): various

PRAC Lead: Barbara Kovacic Bytyqi

Scope: Evaluation of a PSUSA procedure

### 16.3.19. Iron dextran (NAP) - PSUSA/00010696/202401

Applicant(s): various

PRAC Lead: Zane Neikena

Scope: Evaluation of a PSUSA procedure

### 16.3.20. Iron sucrose[57] (NAP) - PSUSA/00010864/202401

Applicant(s): various

PRAC Lead: Zane Neikena

Scope: Evaluation of a PSUSA procedure

### 16.3.21. Levodropropizine (NAP) - PSUSA/00001853/202401

Applicant(s): various

[55] Parenteral use only
[56] Parenteral use only
[57] Parenteral use only

PRAC Lead: Melinda Palfi

Scope: Evaluation of a PSUSA procedure

### 16.3.22. Lormetazepam (NAP) - PSUSA/00001910/202312

Applicant(s): various

PRAC Lead: Sonja Hrabcik

Scope: Evaluation of a PSUSA procedure

### 16.3.23. Omega-3-acid ethyl esters (NAP) - PSUSA/00010312/202401

Applicant(s): various

PRAC Lead: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

### 16.3.24. Pentoxyverine (NAP) - PSUSA/00002345/202312

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

### 16.3.25. Povidone iodinated (NAP) - PSUSA/00002487/202401

Applicant(s): various

PRAC Lead: Nathalie Gault

Scope: Evaluation of a PSUSA procedure

### 16.3.26. Protirelin (NAP) - PSUSA/00009273/202401

Applicant(s): various

PRAC Lead: Jana Lukačišinová

Scope: Evaluation of a PSUSA procedure

### 16.3.27. Pseudoephedrine, triprolidine (NAP) - PSUSA/00003047/202312

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

### 16.3.28. Rupatadine (NAP) - PSUSA/00002673/202312

Applicant(s): various

PRAC Lead: Monica Martinez Redondo

Scope: Evaluation of a PSUSA procedure

### 16.3.29. Sodium iron gluconate[58] (NAP) - PSUSA/00010867/202401

Applicant(s): various

PRAC Lead: Zane Neikena

Scope: Evaluation of a PSUSA procedure

### 16.3.30. Tobramycin[59] [60] (NAP) - PSUSA/00009316/202312

Applicant(s): various

PRAC Lead: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

## 16.4. Follow-up to PSUR/PSUSA procedures

### 16.4.1. Burosumab - CRYSVITA (CAP) - EMEA/H/C/004275/LEG 008.1

Applicant: Kyowa Kirin Holdings B.V.

PRAC Rapporteur: Gabriele Maurer

Scope: MAH's responses to LEG 008 [Safety Review on Craniosynostosis cases] as adopted in March 2024

### 16.4.2. Dolutegravir - TIVICAY (CAP) - EMEA/H/C/002753/LEG 015.5

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Martin Huber

Scope: From EMEA/H/C/PSUSA/00010075/202101:
***Third Annual RESPOND Study Report*** (from 2023)
In view of the new data regarding diabetes mellitus and the use of INSTIs as well as new data on virologic outcomes and LeXTO, the MAH should discuss these issues as soon as corresponding publications are available(no later than 30 days after the receipt of these data).
Upcoming annual RESPOND study reports should be submitted no later than two months after they are available. Upcoming submissions should also include a discussion of the different results by the MAH

### 16.4.3. Dolutegravir, abacavir, lamivudine - TRIUMEQ (CAP) - EMEA/H/C/002754/LEG 010.5

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Martin Huber

Scope: From EMEA/H/C/PSUSA/00010075/202101:

[58] Parenteral use only
[59] Nebuliser solution only
[60] Non-centrally authorised product(s) only

***Third Annual RESPOND Study Report*** (from 2023)
In view of the new data regarding diabetes mellitus and the use of INSTIs as well as new data on virologic outcomes and LeXTO, the MAH should discuss these issues as soon as corresponding publications are available(no later than 30 days after the receipt of these data).
Upcoming annual RESPOND study reports should be submitted no later than two months after they are available. Upcoming submissions should also include a discussion of the different results by the MAH

### 16.4.4. Dolutegravir, lamivudine - DOVATO (CAP) - EMEA/H/C/004909/LEG 005.5

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: David Olsen

Scope: From EMEA/H/C/PSUSA/00010075/202101:
***Third Annual RESPOND Study Report*** (from 2023)
In view of the new data regarding diabetes mellitus and the use of INSTIs as well as new data on virologic outcomes and LeXTO, the MAH should discuss these issues as soon as corresponding publications are available(no later than 30 days after the receipt of these data).
Upcoming annual RESPOND study reports should be submitted no later than two months after they are available. Upcoming submissions should also include a discussion of the different results by the MAH

### 16.4.5. Fluciclovine ($^{18}$F) - AXUMIN (CAP) - EMEA/H/C/004197/LEG 002

Applicant: Blue Earth Diagnostics Ireland Limited

PRAC Rapporteur: Rugile Pilviniene

Scope: From EMEA/H/C/PSUSA/00010594/202305:
A Cumulative Safety Review of case reports of PET imaging interpretation errors with a focus on false positive and false negative results, as well as a discussion of related literature and further evidence available. Implementation of the self-training programme in the EU member states `

## 16.5. Variation procedure(s) resulting from PSUSA evaluation

### 16.5.1. Efavirenz, emtricitabine, tenofovir disoproxil - EFAVIRENZ/EMTRICITABINE/TENOFOVIR DISOPROXIL MYLAN (CAP) - EMA/VR/0000179367

Applicant: Mylan Pharmaceuticals Limited

PRAC Lead: Martin Huber

Scope: Update of sections 4.4 and 4.8 of the SmPC in order to amend an existing warning on Bone effects and to add 'bone mineral density decreased' to the list of adverse drug reactions (ADRs) with frequency common, based on the PRAC conclusions from the PSUSA for Emtricitabine/Tenofovir disoproxil (PSUSA/1210/202304). The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet

### 16.5.2. Fenfluramine - FINTEPLA (CAP) - EMEA/H/C/003933/II/0025, Orphan

Applicant: UCB Pharma SA

PRAC Rapporteur: Martin Huber

Scope: Update of section 4.8 of the SmPC in order to propose a combined Adverse Drug Reaction table for Dravet Syndrome and Lennox-Gastaut syndrome following PSUSA procedure EMEA/H/C/PSUSA/00010907/202306. The package leaflet is updated accordingly

### 16.5.3. Ivacaftor, tezacaftor, elexacaftor - KAFTRIO (CAP) - EMEA/H/C/005269/II/0052/G, Orphan

Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Martin Huber

Scope: Grouped application comprising two type II variations as follows:
Type II (C.I.3.b) – Update of sections 4.4 and 4.8 of the SmPC in order to amend an existing warning on rash and to add hypersensitivity to the list of adverse drug reactions (ADRs) with frequency "not known" following the outcome of procedure PSUSA/00010868/202310. The Package Leaflet is updated accordingly.
Type II (C.I.z) – Submission of post-marketing breast-feeding case reports

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

Applicant: Orexigen Therapeutics Ireland Limited

Scope: Request for re-examination of variation II/63 concluded with negative PRAC recommendation in July 2024

## 16.6. Expedited summary safety reviews[61]

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)[62]

### 17.1.1. Ketoconazole - KETOCONAZOLE HRA (CAP) - EMEA/H/C/PSA/S/0109.2

Applicant: HRA Pharma Rare Diseases

[61] 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
[62] In accordance with Article 107n of Directive 2001/83/EC

PRAC Rapporteur: Petar Mas

Scope: Substantial amendment to a prospective, multi-country, observational registry to collect clinical information on patients with endogenous Cushing's syndrome exposed to Ketoconazole (using the existing European Registry on Cushing's Syndrome (ERCUSYN)), to assess drug utilization pattern and to document the safety (e.g. hepatotoxicity, QT prolongation) and effectiveness of Ketoconazole [MAH's response to PSA/S/0109.1]

### 17.1.2. Pegzilarginase - LOARGYS (CAP) - EMEA/H/C/PSP/S/0105.1

Applicant: Immedica Pharma AB

PRAC Rapporteur: Martin Huber

Scope: MAH's response to PSP/0105 [A European, non-interventional, multicentre, registry-based post-authorisation safety study to evaluate the long-term safety of Loargys treatment in arginase 1 deficiency patients in standard clinical care] as per the request to supplementary information (RSI) adopted in May 2024

### 17.1.3. Tabelecleucel - EBVALLO (CAP) - EMEA/H/C/PSA/S/0115

Applicant: Pierre Fabre Medicament, ATMP

PRAC Rapporteur: Amelia Cupelli

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

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

### 17.2.1. Anifrolumab - SAPHNELO (CAP) - EMEA/H/C/004975/MEA 001.3

Applicant: AstraZeneca AB

PRAC Rapporteur: Liana Martirosyan

Scope: ***REVISED PROTOCOL v. 4 / Study D3461R00028****
Ttile: A non-interventional multi-database post-authorisation study to assess pregnancy-related safety data from women with Systemic Lupus Erythematosus exposed to anifrolumab

### 17.2.2. Atogepant - AQUIPTA (CAP) - EMEA/H/C/005871/MEA 002.1

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Rugile Pilviniene

Scope: ***Revised Protocol*** /Study no.: P24433
Title: Post-authorisation safety study to evaluate the utilisation and safety of atogepant in patients with migraine and significant cardiovascular or cerebrovascular disease in Europe

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

### 17.2.3. Deucravacitinib - SOTYKTU (CAP) - EMEA/H/C/005755/MEA 001.2

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Liana Martirosyan

Scope: MAH's responses to MEA 001.1 [revised protocol no PASS IM011194] as adopted in April 2024.
Long-term, observational cohort study of adults with plaque psoriasis, who are new users of deucravacitinib, non-TNFi (tumor necrosis factor inhibitor) biologics, TNFi biologics, or non-biologic systemic therapy in the real-world clinical setting (IM011194). To evaluate the long-term safety of deucravacitinib in patients with psoriasis in the real-world setting

### 17.2.4. Diroximel fumarate - VUMERITY (CAP) - EMEA/H/C/005437/MEA 001.3

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Martin Huber

Scope: ***Updated Protocol Version 6 / Study 272MS401***
A prospective observational pregnancy exposure registry to characterise how DRF may affect pregnancy and infant outcomes

### 17.2.5. Dulaglutide - TRULICITY (CAP) - EMEA/H/C/002825/MEA 006.6

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Amelia Cupelli

Scope: ***REVISED PROTOCOL / H9X-MC-B013***
Title: Dulaglutide and Potential Risks of Pancreatic Cancer and Thyroid Cancer: A Non-Interventional PASS

### 17.2.6. Eptinezumab - VYEPTI (CAP) - EMEA/H/C/005287/MEA 004.5

Applicant: H. Lundbeck A/S

PRAC Rapporteur: Liana Martirosyan

Scope: MAH's response to MEA 004.4 [REVISED PROTOCOL / PASS No. 19756N] as adopted in March 2024.
Title: Long-term cardiovascular safety and real-world use of eptinezumab - An observational, historical cohort study of patients initiating eptinezumab in routine clinical practice.
Regarding the alternative proxy as proposed by MAH to identify severe migraine patients for the subgroup analyses, there are some remaining issues:
a. The MAH is requested to discuss the validity of this proxy to define the severity of migraine and to describe any potential limitations with this regard in the protocol.
b. The MAH should specify per database which acute pain medications are used in migraine treatment and these should be used in the proxy, since this could differ per region

### 17.2.7. Etrasimod - VELSIPITY (CAP) - EMEA/H/C/006007/MEA 001

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Mari Thorn

Scope: From Initial MAA:
***PASS Protocol / Study C5041046***
Title: An Active Surveillance, Post-Authorization Safety Study to Characterize the Safety of Etrasimod in Patients with Ulcerative Colitis Using Real-World Data in the European Union (C5041046)

### 17.2.8. Hydroxycarbamide - XROMI (CAP) - EMEA/H/C/004837/MEA 006

Applicant: Nova Laboratories Ireland Limited

PRAC Rapporteur: Jo Robays

Scope: ***Protocol v1.0 / Study NOVDD-001***
Title: A comparative observational study to evaluate the safety and effectiveness of Xromi (hydroxycarbamide oral solution 100mg/ml) for the prevention of vaso-occlusive complications of sickle cell disease in children under 2 years of age

### 17.2.9. Lebrikizumab - EBGLYSS (CAP) - EMEA/H/C/005894/MEA 001

Applicant: Almirall, S.A.

PRAC Rapporteur: Liana Martirosyan

Scope: From Initial MAA:
***Protocol of study J2T-MC-B003***
Title: Observational Database Study of Pregnancy and Infant Outcomes among Women Exposed to Lebrikizumab During Pregnancy

### 17.2.10. Mogamulizumab - POTELIGEO (CAP) - EMEA/H/C/004232/MEA 001.5

Applicant: Kyowa Kirin Holdings B.V.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: MAH's response to MEA 001.4 [REVISED PROTOCOL 0.3 FOR PASS EUPAS31436] as adopted in March 2024
To Characterise the Safety of Allogeneic Hematopoietic Stem Cell Transplantation (HSCT) in Patients with Cutaneous T-Cell Lymphoma (CTCL) treated with Mogamulizumab

### 17.2.11. Neratinib - NERLYNX (CAP) - EMEA/H/C/004030/MEA 003.4

Applicant: Pierre Fabre Medicament

PRAC Rapporteur: Bianca Mulder

Scope: Revised protocol + MAH's responses to MEA 003.3 [***Amended Protocol /Study PUMA-NER-7402*** (version 4.0)] RSI as adopted in May 2024.
Title: Multicentre, multi-country, prospective, observational, post authorisation safety study to describe the incidence of discontinuation due to diarrhoea within the first 3 months of a treatment with neratinib, in adult breast cancer patients treated in extended adjuvant in a real world setting: the NERLYFE study

### 17.2.12. Niraparib, Abiraterone acetate - AKEEGA (CAP) - EMEA/H/C/005932/MEA 001.3

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Jan Neuhauser

Scope: ***Revised PASS Protocol (ver. 3)/ Study no.: PCSONCA0485***
Study title: Post authorization safety study to characterize the risk of second primary malignancies (SPM) including MDS/AML among metastatic prostate cancer patients exposed to AKEEGA

### 17.2.13. Zilucoplan - ZILBRYSQ (CAP) - EMEA/H/C/005450/MEA 001

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Karin Erneholm

Scope: From initial MAA
**DRAFT PROTOCOL** / PASS MG0026 (NI/NI, RMP)
A Multi-National Cohort Study to Assess the Implementation of the Risk Minimization Measures to Prevent Meningococcal Infection in Patients with
Generalized Myasthenia Gravis Initiating Zilucoplan, and Zilucoplan Safety in Real-World Settings

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

None

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

### 17.4.1. Baricitinib - OLUMIANT (CAP) - EMEA/H/C/004085/II/0047

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Submission of the final report from non-interventional Study I4V-MC-B012 listed as a category 3 study in the RMP. This is a post-marketing safety surveillance of baricitinib in three European registries. The RMP version 23.1 has also been submitted

### 17.4.2. Canagliflozin - INVOKANA (CAP) - EMEA/H/C/002649/WS2719/0068; Canagliflozin, metformin - VOKANAMET (CAP) - EMEA/H/C/002656/WS2719/0075

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Martin Huber

Scope: Submission of the final report from study PCSCVM003617, listed as a category 3 study in the RMP. This is a Real-World Database Study of Canagliflozin Utilization in Type 1 Diabetes Patients Over Time among European Countries. The RMP version 12.1 has also been submitted

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

### 17.4.3. Dengue tetravalent vaccine (live, attenuated) - DENGVAXIA (CAP) - EMEA/H/C/004171/II/0031

Applicant: Sanofi Pasteur

PRAC Rapporteur: Sonja Hrabcik

Scope: Submission of final study report of DNG15, listed in the RMP as category 3. DNG15 was a prospective, multinational, non-interventional, observational study aiming to assess the risk of AEs associated with CYD dengue vaccine in the real-world immunization setting

### 17.4.4. Empagliflozin - JARDIANCE (CAP) - EMEA/H/C/002677/WS2713/0089; Empagliflozin, linagliptin - GLYXAMBI (CAP) - EMEA/H/C/003833/WS2713/0062; Empagliflozin, metformin - SYNJARDY (CAP) - EMEA/H/C/003770/WS2713/0080

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Submission of the final report from study 1245-0097. This is a post-authorisation safety study (PASS) to assess the risk of urinary tract malignancies in relation to empagliflozin exposure in patients with type 2 diabetes: a multi-database European study. The RMP versions 23.0, 17.0 and 11.0 are also submitted for Jardiance, Synjardy and Glyxambi, respectively

### 17.4.5. Influenza quadrivalent vaccine (rDNA) - SUPEMTEK (CAP) - EMEA/H/C/005159/II/0020

Applicant: Sanofi Pasteur

PRAC Rapporteur: Nathalie Gault

Scope: Update of section 4.6 of the SmPC in order to update pregnancy information based on final results from study VAP00007 (non-interventional PASS); this is a Phase IV, observational retrospective post-authorization, descriptive, safety surveillance study to evaluate the safety of RIV4 in pregnant women and their offspring exposed during pregnancy or up to 28 days preceding the estimated date of conception with regards to pregnancy, birth, and neonatal/infant outcomes

### 17.4.6. Inotuzumab ozogamicin - BESPONSA (CAP) - EMEA/H/C/004119/II/0028, Orphan

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Gabriele Maurer

Scope: Submission of the final report from study B1931028; this is a non-interventional post-authorization safety study (PASS) of inotuzumab ozogamicin to characterize complications post-hematopoietic stem cell transplantation (HSCT) following inotuzumab ozogamicin treatment in adult and pediatric patients with B-cell precursor acute lymphoblastic leukemia (ALL). The RMP version 3.0 has also been submitted

### 17.4.7. Piperaquine tetraphosphate, Artenimol - EURARTESIM (CAP) - EMEA/H/C/001199/II/0040/G

Applicant: Alfasigma S.p.A.

PRAC Rapporteur: Martin Huber

Scope: C.I.13: Submission of the final report from the effectiveness evaluation survey for Eurartesim (protocol no. 3366) listed as a category 3 study in the RMP. This is a European multi-centre online survey to assess physician understanding of the revised edition of the educational material. Consequential changes to RMP version 16.1 have been implemented.

C.I.11.b: Submission of an updated RMP version 16.1 in order to delete "Severe Malaria" from the Missing Information

### 17.4.8. Pregabalin - LYRICA (CAP) - EMEA/H/C/000546/WS2708/0136; Pregabalin - PREGABALIN PFIZER (CAP) - EMEA/H/C/003880/WS2708/0057

Applicant: Upjohn EESV

PRAC Rapporteur: Liana Martirosyan

Scope: Submission of the final report from study A0081096 listed as a category 3 study in the RMP. This is a prospective randomized 12-week controlled study of visual field change in subjects with partial seizures receiving pregabalin or placebo

### 17.4.9. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/II/0104

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: Submission of the final report from study RRA-20745 listed as a category 3 study in the RMP. This is an observational post-authorization safety study (PASS) to describe the safety of ustekinumab and other Crohn's disease treatments in a cohort of patients with Crohn's disease. The RMP version 27.2 has also been submitted

### 17.4.10. Zanamivir - DECTOVA (CAP) - EMEA/H/C/004102/II/0020

Applicant: GlaxoSmithKline Trading Services Limited

PRAC Rapporteur: Mari Thorn

Scope: Submission of the final report from study 208140 listed as a category 3 PASS in the RMP. This is an observational study of the safety of zanamivir 10 mg/ml solution for infusion exposure in pregnant women with complicated influenza and their offspring. The RMP version 8.0 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. Aflibercept - EYLEA (CAP) - EMEA/H/C/002392/MEA 022.1

Applicant: Bayer AG

PRAC Rapporteur: Nathalie Gault

Scope: ***3rd Interim Study Report***

FIREFLEYE NEXT Study # 20275 (non-imposed/interventional/RMP)
An extension study to evaluate the long-term outcomes of subjects who received teatment for retinopathy of prematurity in Study 20090

### 17.5.2. Apremilast - OTEZLA (CAP) - EMEA/H/C/003746/MEA 008.6

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Monica Martinez Redondo

Scope: ***5 Year Study Report / Study BSRBR-PsA (CC-10004-PSA-012)***
Title: British Society for Rheumatology Psoriatic Arthritis Register (BSR - PsA)

### 17.5.3. Apremilast - OTEZLA (CAP) - EMEA/H/C/003746/MEA 008.5

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Monica Martinez Redondo

Scope: MAH's response to MEA 008.4 [4th interim report of the Apremilast PsA Registry in the UK - BSRBR-PsA] RSI as adopted in April 2024.
1. The MAH is requested to provide, the reason for which most patients receiving apremilast in UK for PsA are illegible for the inclusion in the study and if it is related to the inclusion criteria (CASPAR score), the calculation of this score in the patients included and not included in the study should be presented

### 17.5.4. Autologous CD34+ enriched cell fraction that contains CD34+ cells transduced with retroviral vector that encodes for the human ADA cDNA sequence - STRIMVELIS (CAP) - EMEA/H/C/003854/ANX 004.5

Applicant: Fondazione Telethon ETS, ATMP

PRAC Rapporteur: Liana Martirosyan

Scope: MAH Response to ANX 004.4 [Patient Registry / STRIM-0003] as adopted in June 2023:
Based on the PRAC Rapporteur review of the PASS interim study report, dated 21 March 2023, the PRAC considers that the risk-benefit balance of medicinal products containing the active substance Strimvelis concerned by the PASS interim report is subject to a request for supplementary information detailed in Section 12 in the Annex, before a recommendation can be made. The responses timetable to the Request for Supplementary Information will be 60 days

### 17.5.5. Beclometasone, formoterol, glycopyrronium bromide - RIARIFY (CAP) - EMEA/H/C/004836/MEA 002.1

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Jan Neuhauser

Scope: ***1st interim report / CLI-05993BA1-05 (TRIBE)***
Multinational database cohort study to assess adverse cardiovascular and cerebrovascular outcomes in patients with chronic obstructive pulmonary disease initiating a fixed triple therapy containing beclometasone dipropionate, formoterol fumarate and glycopyrronium

administered via dry powder inhaler (DPI) compared to pressurized metered dose inhaler (pMDI)

### 17.5.6. Beclometasone, formoterol, glycopyrronium bromide - TRIMBOW (CAP) - EMEA/H/C/004257/MEA 002.5

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Jan Neuhauser

Scope: ***1st interim report / CLI-05993BA1-05 (TRIBE)***
Multinational database cohort study to assess adverse cardiovascular and cerebrovascular outcomes in patients with chronic obstructive pulmonary disease initiating a fixed triple therapy containing beclometasone dipropionate, formoterol fumarate and glycopyrronium administered via dry powder inhaler (DPI) compared to pressurized metered dose inhaler (pMDI)

### 17.5.7. Beclometasone, formoterol, glycopyrronium bromide - TRYDONIS (CAP) - EMEA/H/C/004702/MEA 002.1

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Jan Neuhauser

Scope: ***First interim report / Study CLI-05993BA1-05 (TRIBE)***
Multinational database cohort study to assess adverse cardiovascular and cerebrovascular outcomes in patients with chronic obstructive pulmonary disease initiating a fixed triple therapy containing beclometasone dipropionate, formoterol fumarate and glycopyrronium administered via dry powder inhaler (DPI) compared to pressurized metered dose inhaler (pMDI)

### 17.5.8. Brexucabtagene autoleucel - TECARTUS (CAP) - EMEA/H/C/005102/ANX 002.4

Applicant: Kite Pharma EU B.V., ATMP

PRAC Rapporteur: Bianca Mulder

Scope: ***First Annual Interim Safety Report of Study KTE-EU-472-6036***
Title: Long-term, non-interventional study of recipients of Tecartus (brexucabtagene autoleucel) for treatment of adult patients with relapsed or refractory Mantle Cell Lymphoma (MCL)

### 17.5.9. Brodalumab - KYNTHEUM (CAP) - EMEA/H/C/003959/MEA 002.8

Applicant: LEO Pharma A/S

PRAC Rapporteur: Monica Martinez Redondo

Scope: **INTERIM STUDY REPORT / Study NIS-KYNTHEUM-1345 - On suicidal behaviour, serious infections, MACE and malignancy**
Title: The BRodalumab Assessment of Hazards: A Multinational Safety (BRAHMS) study in electronic healthcare databases

## 17.5.10. Covid-19 Vaccine (recombinant, adjuvanted) - NUVAXOVID (CAP) - EMEA/H/C/005808/MEA 004.7

Applicant: Novavax CZ a.s.

PRAC Rapporteur: Gabriele Maurer

Scope: From Initial MAA:
Study 2019nCoV-402:
UK Post-Authorisation Safety Study Using the Clinical Practice Research Datalink (CPRD): A surveillance study to characterise the safety profile of Nuvaxovid in adults aged 18 years and older in the real-world setting using the UK CPRD
***Second Interim report, study no. 2019nCoV-402***

## 17.5.11. Covid-19 Vaccine (recombinant, adjuvanted) - NUVAXOVID (CAP) - EMEA/H/C/005808/MEA 005.3

Applicant: Novavax CZ a.s.

PRAC Rapporteur: Gabriele Maurer

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

## 17.5.12. Dimethyl fumarate - SKILARENCE (CAP) - EMEA/H/C/002157/MEA 001.8

Applicant: Almirall S.A

PRAC Rapporteur: Mari Thorn

Scope: ***Sixth Annual Interim Results*** for a non-imposed (category 3) PASS. Study no.: M-41008-40
Study Title: An Observational Post-Authorisation Safety Study of Skilarence in European Psoriasis Registers

## 17.5.13. Drospirenone, estetrol - DROVELIS (CAP) - EMEA/H/C/005336/MEA 001.4

Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Martin Huber

Scope: ***1st Interim Study Report / Study INAS-NEES***
Title: International Active Surveillance Study: Native Estrogen Estetrol (E4) Safety Study

## 17.5.14. Drospirenone, estetrol - LYDISILKA (CAP) - EMEA/H/C/005382/MEA 001.4

Applicant: Estetra SRL

PRAC Rapporteur: Martin Huber

Scope: ***1st Interim Study Report / Study INAS-NEES***
Title: International Active Surveillance Study: Native Estrogen Estetrol (E4) Safety Study (INAS-NEES)

## 17.5.15. Lutetium ($^{177}$Lu) oxodotreotide - LUTATHERA (CAP) - EMEA/H/C/004123/MEA 001.13

Applicant: Advanced Accelerator Applications

PRAC Rapporteur: Adam Przybylkowski

Scope: MAH's response to MEA 001.12 [Study No. A-LUT-T-E02-402] as adopted in September 2023.
Title: An International, Non-Interventional, Post-Authorization Long-Term Safety Study of Lutathera, in Patients with Unresectable or Metastatic, Well-Differentiated, Somatostatin Receptor Positive, Gastroenteropancreatic Neuroendocrine Tumours (SALUS study)
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## 17.5.16. Luspatercept - REBLOZYL (CAP) - EMEA/H/C/004444/MEA 002.3

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Jo Robays

Scope: ***4th annual report / Study No. ACE-536-LTFU-001***
To evaluate the long-term safety, including TEEs (only in the β thalassaemia population with splenectomy) and progression to AML and/or other malignancies/ pre malignancies, of luspatercept in patients who have participated in Acceleron or Celgene sponsored luspatercept clinical trials

## 17.5.17. Mavacamten - CAMZYOS (CAP) - EMEA/H/C/005457/MEA 005

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Kimmo Jaakkola

Scope: From initial MAA:
PASS (RMP/non-imposed) CV027012 (DISCOVER-HCM)
Deliver Insights on Safety in Hypertrophic Cardiomyopathy and Observe Endpoints in Real-world
**First Annual Study Progress Report / CV027012 (DISCOVER-HCM)**

## 17.5.18. Octocog alfa - KOVALTRY (CAP) - EMEA/H/C/003825/MEA 005.6

Applicant: Bayer AG

PRAC Rapporteur: Gabriele Maurer

Scope: ***Study 15689*** / Annual PedNet report of 2023
Evaluation of AEs of special interest in the PedNet registry (European Paediatric Network for Haemophilia Management) (Epidemiological Study).
Submission of the annual PedNet report of 2021 containing data for Kovaltry as interim results for Study 15689, epidemiological study, category 3

## 17.5.19. Pegvaliase - PALYNZIQ (CAP) - EMEA/H/C/004744/MEA 003.7

Applicant: BioMarin International Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: MAH's response to MEA 003.6 [SECOND INTERIM REPORT for Study 165-501] RSI as adopted in March 2024.
A prospective, global observational exposure study. Title: A Multi-Center, Observational Study to Evaluate the Long Term Safety of Subcutaneous Injections of Pegvaliase in Patients with Phenylketonuria

## 17.5.20. Pegvaliase - PALYNZIQ (CAP) - EMEA/H/C/004744/MEA 005.10

Applicant: BioMarin International Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: MAH's response to MEA 005.8 [***Second Interim Report / study number: 165-504***] RSI as adopted in February 2024.
Study 165-504 - A global multicentre study to assess maternal, fetal and infant outcomes of exposure to Palynziq (pegvaliase) during pregnancy and breastfeeding

## 17.5.21. Ravulizumab - ULTOMIRIS (CAP) - EMEA/H/C/004954/MEA 009.1

Applicant: Alexion Europe SAS

PRAC Rapporteur: Kimmo Jaakkola

Scope: ***Second aHUS Registry Biennial Interim Report / PASS Study number: M07-001***
AN OBSERVATIONAL, NON-INTERVENTIONAL MULTI-CENTER, MULTI-NATIONAL STUDY OF PATIENTS WITH ATYPICAL HEMOLYTICUREMIC SYNDROME (AHUS REGISTRY).

The MAH has provided the first interim safety report of the aHUS registry study (Protocol M07-001). This study is a category 3 study, that is part of the additional pharmacovigilance activities included in the risk management plan (RMP) of ravulizumab. Based on the data presented in this report, no new safety concerns were identified.
To better contextualize the ravulizumab data regarding the safety concerns that are addressed by this PASS, the MAH should provide in the next update relevant comparisons of ravulizumab event rates to other patients in the registry (especially eculizumab only-treated patients).
The MAH has adequately fullfilled the commitment to provide the first interim safety report for aHUS registry study. However, all commitments are not fulfilled until the study is finalised.

Next Interim Report should be provided according to the RMP every 2 years until the study is finalised

## 17.5.22. Reslizumab - CINQAERO (CAP) - EMEA/H/C/003912/MEA 005.8

Applicant: Teva B.V.

PRAC Rapporteur: Gabriele Maurer

Scope: ***Updated Feasibility Assessment and Interim Safety Report*** [Study number C38072-AS-50027]
Considering the difficulties in the collection of data of a sufficient number of patients, the MAH is asked provide an updated feasibility assessment within two years and an interim safety report, when at least 200-300 study eligible patients treated with reslizumab have been accumulated in one of the databases

### 17.5.23. Rurioctocog alfa pegol - ADYNOVI (CAP) - EMEA/H/C/004195/ANX 002.4

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Bianca Mulder

Scope: MAH's response to MEA 002.3 [*Fourth Progress Report*/ PASS TAK-660-403] as adopted in April 2024.
In order to investigate the potential effects of PEG accumulation in the choroid plexus of the brain and other tissues/organs, the MAH should conduct and submit the results of a post-authorisation safety study according to an agreed protocol

### 17.5.24. Vamorolone - AGAMREE (CAP) - EMEA/H/C/005679/MEA 001

Applicant: Santhera Pharmaceuticals (Deutschland) GmbH

PRAC Rapporteur: Rhea Fitzgerald

Scope: ***Feasibility Interim Study Results / No. SNT-IV-VAM-10***
Feasibility Report for a Registry-Based Post-authorisation Safety Study (PASS) to Evaluate the Safety of Vamorolone (AGAMREE®) in Patients with Duchenne Muscular Dystrophy (DMD)

## 17.6. Others

### 17.6.1. Tozinameran - COMIRNATY (CAP) - EMEA/H/C/005735/MEA 064.3

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Liana Martirosyan

Scope: ***Justification for termination of study C4591051***
Title: A Non-Interventional Post-Approval Safety Study of Pfizer-BioNTech Bivalent COVID-19 Vaccine in the United States to ensure comprehensive understanding of real-world safety of the Pfizer-BioNTech COVID-19 bivalent Omicron-modified vaccine in large samples of general US populations

### 17.6.2. Velaglucerase alfa - VPRIV (CAP) - EMEA/H/C/001249/MEA 029.1

Applicant: Takeda Pharmaceuticals International AG Ireland Branch

PRAC Rapporteur: Martin Huber

Scope: ***Gaucher Disease Outcome Survey Annual Report 2024 + MAH's responses to MEA 029 [Gaucher Disease Outcome Survey Annual Report 2023] RSI as adopted in March 2024***

Title: Gaucher Disease Outcome Survey (GOS): An Observational, International, Multi-center, Long-term Registry of Patients with Gaucher Disease
**Request for GOS discontinuation**

## 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. Evinacumab - EVKEEZA (CAP) - EMEA/H/C/005449/S/0018 (without RMP)

Applicant: Ultragenyx Germany GmbH

PRAC Rapporteur: Mari Thorn

Scope: Annual reassessment of the marketing authorisation

## 18.2. Conditional renewals of the marketing authorisation

### 18.2.1. Adagrasib - KRAZATI (CAP) - EMEA/H/C/006013/R/0006 (without RMP)

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Kimmo Jaakkola

Scope: Conditional renewal of the marketing authorisation

### 18.2.2. Brexucabtagene autoleucel - TECARTUS (CAP) - EMEA/H/C/005102/R/0047 (with RMP)

Applicant: Kite Pharma EU B.V., ATMP

PRAC Rapporteur: Bianca Mulder

Scope: Conditional renewal of the marketing authorisation

### 18.2.3. Elranatamab - ELREXFIO (CAP) - EMEA/H/C/005908/R/0003 (without RMP)

Applicant: Pfizer Europe Ma EEIG

PRAC Rapporteur: Barbara Kovacic Bytyqi

Scope: Conditional renewal of the marketing authorisation

### 18.2.4. Loncastuximab tesirine - ZYNLONTA (CAP) - EMEA/H/C/005685/R/0018 (without RMP)

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Eva Jirsová

Scope: Conditional renewal of the marketing authorisation

### 18.2.5. Sotorasib - LUMYKRAS (CAP) - EMEA/H/C/005522/R/0018 (without RMP)

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Conditional renewal of the marketing authorisation

### 18.2.6. Spesolimab - SPEVIGO (CAP) - EMEA/H/C/005874/R/0008 (without RMP)

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Nathalie Gault

Scope: Conditional renewal of the marketing authorisation

### 18.2.7. Trastuzumab - ENHERTU (CAP) - EMEA/H/C/005124/R/0047 (without RMP)

Applicant: Daiichi Sankyo Europe GmbH

PRAC Rapporteur: Carla Torre

Scope: Conditional renewal of the marketing authorisation

## 18.3. Renewals of the marketing authorisation

### 18.3.1. Azacitidine - AZACITIDINE ACCORD (CAP) - EMEA/H/C/005147/R/0019 (without RMP)

Applicant: Accord Healthcare S.L.U.

PRAC Rapporteur: Bianca Mulder

Scope: 5-year renewal of the marketing authorisation

### 18.3.2. Azacitidine - AZACITIDINE MYLAN (CAP) - EMEA/H/C/004984/R/0019 (without RMP)

Applicant: Mylan Ireland Limited

PRAC Rapporteur: Bianca Mulder

Scope: 5-year renewal of the marketing authorisation

### 18.3.3. Bempedoic acid - NILEMDO (CAP) - EMEA/H/C/004958/R/0042 (without RMP)

Applicant: Daiichi Sankyo Europe GmbH

PRAC Rapporteur: Kimmo Jaakkola

Scope: 5-year renewal of the marketing authorisation

### 18.3.4. Bempedoic acid, Ezetimibe - NUSTENDI (CAP) - EMEA/H/C/004959/R/0047 (without RMP)

Applicant: Daiichi Sankyo Europe GmbH

PRAC Rapporteur: Kimmo Jaakkola

Scope: 5-year renewal of the marketing authorisation

### 18.3.5. Darolutamide - NUBEQA (CAP) - EMEA/H/C/004790/R/0021 (without RMP)

Applicant: Bayer AG

PRAC Rapporteur: Jan Neuhauser

Scope: 5-year renewal of the marketing authorisation

### 18.3.6. Dexmedetomidine - DEXMEDETOMIDINE ACCORD (CAP) - EMEA/H/C/005152/R/0013 (without RMP)

Applicant: Accord Healthcare S.L.U.

PRAC Rapporteur: Mari Thorn

Scope: 5-year renewal of the marketing authorisation

### 18.3.7. 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

### 18.3.8. 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

### 18.3.9. Givosiran - GIVLAARI (CAP) - EMEA/H/C/004775/R/0020 (without RMP)

Applicant: Alnylam Netherlands B.V.

PRAC Rapporteur: Martin Huber

Scope: 5-year renewal of the marketing authorisation

### 18.3.10. Insulin lispro - LYUMJEV (CAP) - EMEA/H/C/005037/R/0019 (without RMP)

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Mari Thorn

Scope: 5-year renewal of the marketing authorisation

### 18.3.11. Rituximab - RUXIENCE (CAP) - EMEA/H/C/004696/R/0017 (without RMP)

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Karin Erneholm

Scope: 5-year renewal of the marketing authorisation

### 18.3.12. Semaglutide - RYBELSUS (CAP) - EMEA/H/C/004953/R/0042 (without RMP)

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Mari Thorn

Scope: 5-year renewal of the marketing authorisation

### 18.3.13. Treprostinil sodium - TREPULMIX (CAP) - EMEA/H/C/005207/R/0020 (without RMP)

Applicant: SciPharm Sarl

PRAC Rapporteur: Zane Neikena

Scope: 5-year renewal of the marketing authorisation

## 19. Annex II – List of participants

including any restrictions with respect to involvement of members/alternates/experts following evaluation of declared interests for the 02-05 September 2024 PRAC meeting, which was held in-person. Participants marked with "a" attended the plenary session while those marked with "b" attended the ORGAM.

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 |
|---|---|---|---|---|
| Ulla Wändel Liminga [a,b] | Chair | Sweden | No interests declared | |
| Jan Neuhauser [a] | Member* | Austria | No interests declared | |
| Sonja Hrabcik [a,b] | Alternate* | Austria | No interests declared | |
| Jean-Michel Dogné [a,b] | Member | Belgium | No interests declared | |
| Jo Robays [a,b] | Alternate | Belgium | No interests declared | |
| Maria Popova-Kiradjieva [a,b] | Member* | Bulgaria | No interests declared | |
| Petar Mas [a,b] | Member | Croatia | No interests declared | |
| Barbara Kovacic Bytyqi [a,b] | Alternate | Croatia | No interests declared | |
| Elena Kaisis [a,b] | Member | Cyprus | No interests declared | |
| Panagiotis Psaras [b] | Alternate | Cyprus | No interests declared | |
| Eva Jirsová [a,b] | Member | Czechia | No interests declared | |
| Jana Lukacisinova [a,b] | Alternate | Czechia | No interests declared | |
| Marie Louise Schougaard Christiansen [a,b] | Member | Denmark | No interests declared | |
| Karin Erneholm [a,b] | Alternate | Denmark | No interests declared | |
| Maia Uusküla [a,b] | Member | Estonia | No interests declared | |
| Terhi Lehtinen [a,b] | Member | Finland | No interests declared | |
| Kimmo Jaakkola [a,b] | Alternate | Finland | No interests declared | |
| Tiphaine Vaillant [a,b] | Member | France | No interests declared | |
| Nathalie Gault [a,b] | Alternate | France | No interests declared | |

| Name | Role | Member state or affiliation | Outcome restriction following evaluation of e-DoI | Topics on agenda for which restrictions apply |
|---|---|---|---|---|
| Martin Huber [a,b] | Member (Vice-Chair) | Germany | No interests declared | |
| Gabriele Maurer [a,b] | Alternate* | Germany | No restrictions applicable to this meeting | |
| Sofia Trantza [a,b] | Member | Greece | No interests declared | |
| Georgia Gkegka [a,b] | Alternate* | Greece | No interests declared | |
| Julia Pallos [a,b] | Member | Hungary | No participation in discussion, final deliberations and voting on: | **5.1.5.** Repotrectinib - (CAP MAA) - EMEA/H/C/006005<br><br>**7.3.1.** Lenalidomide - REVLIMID (CAP) - EMEA/H/C/PSR/S/0049<br><br>**14.1.2.** Lisocabtagene maraleucel – BREYANZI (CAP)<br><br>**15.3.29.** Mavacamten - CAMZYOS (CAP) - EMEA/H/C/005457/II/0011/G<br><br>**16.1.23.** Fedratinib - INREBIC (CAP) - PSUSA/00010909/202402<br><br>**16.1.27.** Lisocabtagene maraleucel- BREYANZI (CAP) - PSUSA/00010990/202402<br><br>**17.2.3.** Deucravacitinib - |

| Name | Role | Member state or affiliation | Outcome restriction following evaluation of e-DoI | Topics on agenda for which restrictions apply |
|---|---|---|---|---|
| | | | | SOTYKTU (CAP) - EMEA/H/C/005755/MEA 001.2<br><br>**17.5.16.** Luspatercept - REBLOZYL (CAP) - EMEA/H/C/004444/MEA 002.3<br><br>**17.5.17.** Mavacamten - CAMZYOS (CAP) - EMEA/H/C/005457/MEA 005<br><br>**18.2.1.** Adagrasib - KRAZATI (CAP) - EMEA/H/C/006013/R/0006 (without RMP) |
| Melinda Palfi [a,b] | Alternate* | Hungary | No interests declared | |
| Guðrún Stefánsdóttir [a,b] | Member | Iceland | No restrictions applicable to this meeting | |
| Guðrún Þengilsdóttir [a] | Alternate | Iceland | No interests declared | |
| Rhea Fitzgerald [a,b] | Member | Ireland | No interests declared | |
| Eamon O Murchu [a,b] | Alternate | Ireland | No interests declared | |
| Amelia Cupelli [a,b] | Member | Italy | No interests declared | |
| Zane Neikena [a,b] | Member | Latvia | No interests declared | |
| Rugile Pilviniene [a] | Member | Lithuania | No interests declared | |
| Nadine Petitpain [a,b] | Member | Luxembourg | 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 |
|---|---|---|---|---|
| Anne-Cecile Vuillemin[b] | Alternate | Luxembourg | No interests declared | |
| John Joseph Borg [a] | Member* | Malta | No interests declared | |
| Liana Martirosyan [a,b] | Member | Netherlands | No interests declared | |
| Bianca Mulder [a,b] | Alternate | Netherlands | No interests declared | |
| David Olsen [a,b] | Member | Norway | No participation in discussion, final deliberations and voting on: | **16.1.15.** Darolutamide - NUBEQA (CAP) - PSUSA/00010843 /202401<br><br>**16.1.49.** Vericiguat - VERQUVO (CAP) - PSUSA/00010950 /202401<br><br>**16.3.13.** Dexpanthenol (NAP) - PSUSA/00000999 /202401<br><br>**17.5.1.** Aflibercept - EYLEA (CAP) - EMEA/H/C/00239 2/MEA 022.1<br><br>**17.5.18.** Octocog alfa - KOVALTRY (CAP) - EMEA/H/C/00382 5/MEA 005.6<br><br>**18.3.5.** Darolutamide - NUBEQA (CAP) - EMEA/H/C/00479 0/R/0021 (without RMP) |
| Pernille Harg [a,b] | Alternate* | Norway | No interests declared | |
| Adam Przybylkowski [a] | Member | Poland | No interests declared | |

| Name | Role | Member state or affiliation | Outcome restriction following evaluation of e-DoI | Topics on agenda for which restrictions apply |
|---|---|---|---|---|
| Katarzyna Ziolkowska[b] | Alternate | Poland | No interests declared | |
| Ana Sofia Diniz Martins [a] | Member | Portugal | No interests declared | |
| Carla Torre [a] | Alternate | Portugal | No interests declared | |
| Roxana Dondera [a,b] | Member | Romania | No interests declared | |
| Irina Sandu [a,b] | Alternate* | Romania | No interests declared | |
| Anna Mareková [a,b] | Member | Slovakia | No interests declared | |
| Miroslava Gocova [a,b] | Alternate* | Slovakia | No interests declared | |
| Polona Golmajer [a,b] | Member | Slovenia | No interests declared | |
| Maria del Pilar Rayon [a,b] | Member | Spain | No interests declared | |
| Monica Martinez Redondo [a,b] | Alternate | Spain | No interests declared | |
| Mari Thorn [a,b] | Alternate | Sweden | No restrictions applicable to this meeting | |
| Annalisa Capuano [a] | Member* | Independent scientific expert | No interests declared | |
| Milou-Daniel Drici [a,b] | Member | Independent scientific expert | No interests declared | |
| Maria Teresa Herdeiro [a] | Member* | Independent scientific expert | No interests declared | |
| Patricia McGettigan [a] | Member | Independent scientific expert | No restrictions applicable to this meeting | |
| Anette Kirstine Stark [a] | Member | Independent scientific expert | No interests declared | |
| Hedvig Marie Egeland Nordeng [a] | Member | Independent scientific expert | No interests declared | |
| Roberto Frontini [a] | 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 [a] | Alternate* | Healthcare Professionals' Representative | No interests declared | |
| Marko Korenjak [a] | Member | Patients' Organisation Representative | No interests declared | |
| Michal Rataj [a,b] | Alternate* | Patients' Organisation Representative | No interests declared | |
| Dennis Lex[b] | Expert | Germany | No interests declared | |
| Charlotte Backman [a,b] | Expert | Sweden | No interests declared | |
| Frederikke Hillebrand Laustsen [a,b] | Expert | Denmark | No restrictions applicable to this meeting | |
| Maria Martinez Gonzalez [a] | Expert | Spain | No interests declared | |
| Cathrine Wisbech [a] | Expert | Norway | No restrictions applicable to this meeting | |
| Rolf Gedeborg [a] | Expert | Sweden | No restrictions applicable to this meeting | |
| Mette Hjorslev Knudgaard [a] | Expert | Denmark | No interests declared | |
| Edurne Lazaro [a] | Expert | Spain | No interests declared | |
| Magdalena Wielowieyska [a] | Expert | Luxembourg | No restrictions applicable to this meeting | |
| Maria Silvia De Orbe Izquierdo [a] | Expert | Spain | No interests declared | |
| Nina Lalić [a] | Expert | Croatia | No restrictions applicable to this meeting | |
| Ivana Ljubičić [a] | Expert | Croatia | No interests declared | |

| Name | Role | Member state or affiliation | Outcome restriction following evaluation of e-DoI | Topics on agenda for which restrictions apply |
|---|---|---|---|---|
| Lara Miletić [a] | Expert | Croatia | No interests declared | |
| Lora Pavlinović [a] | Expert | Croatia | No interests declared | |
| Zvjezdana Rehorović [a] | Expert | Croatia | No restrictions applicable to this meeting | |
| Mette Hjorslev Knudgaard [a] | Expert | Denmark | No interests declared | |
| Irene Mandrup Krüger [a] | Expert | Denmark | No interests declared | |
| Line Michan | Expert | Denmark | No interests declared | |
| Lærke Nilausen [a] | Expert | Denmark | | |
| Kira Rosenkilde Underbjerg [a] | Expert | Denmark | No interests declared | |
| Aynur Sert [a] | Expert | Denmark | No interests declared | |
| Per Sindahl [a] | Expert | Denmark | No interests declared | |
| Ditte Søgaard [a] | Expert | Denmark | No interests declared | |
| Emma Stadsbjerg [a] | Expert | Denmark | No restrictions applicable to this meeting | |
| Louise Wenzel-Petersen [a] | Expert | Denmark | No interests declared | |
| Benjamin Burrus [a] | Expert | France | No interests declared | |
| Pauline Dayani [a] | Expert | France | No interests declared | |
| Camille De-Kervasdoue [a] | Expert | France | No interests declared | |
| Stéphanie Hueber [a] | Expert | France | No interests declared | |
| Tim Niehues [a] | Expert | Germany | No interests declared | |
| Magdalena Wielowieyska [a] | Expert | Luxembourg | No restrictions | |

| Name | Role | Member state or affiliation | Outcome restriction following evaluation of e-DoI | Topics on agenda for which restrictions apply |
|---|---|---|---|---|
| | | | applicable to this meeting | |
| Lisa Heltzel [a] | Expert | Netherlands | No interests declared | |
| Efe Onaghinor [a] | Expert | Netherlands | No interests declared | |
| Eva Cantarero [a] | Expert | Spain | No interests declared | |
| Maria Silvia De Orbe Izquierdo | Expert | Spain | No interests declared | |
| Natividad Galiana [a] | Expert | Spain | No restrictions applicable to this meeting | |
| Edurne Lazaro [a] | Expert | Spain | No interests declared | |
| Consuelo Mejías [a] | Expert | Spain | No restrictions applicable to this meeting | |
| Eva Segovia [a] | Expert | Spain | No interests declared | |
| Rolf Gedeborg [a] | Expert | Sweden | No restrictions applicable to this meeting | |
| Jenny Jönsson [a] | Expert | Sweden | No restrictions applicable to this meeting | |
| Kristina Magnusson-Lundqvist [a] | Expert | Sweden | No interests declared | |
| A representative from the European Commission attended the meeting | | | | |
| Observers from Health Canada (Canada), FDA and Swissmedic 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