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SCIENCE MEDICINES HEALTH

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Human Medicines Division

## Pharmacovigilance Risk Assessment Committee (PRAC) Minutes of the meeting on 02-05 May 2022

Chair: Sabine Straus – Vice-Chair: Martin Huber

### Health and safety information

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

### Disclaimers

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

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

### Note on access to documents

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

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## 1. Introduction

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

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

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

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

The Chair thanked the departing members/alternates for their contributions to the Committee

### 1.2. Agenda of the meeting on 02-05 May 2022

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 04-07 April 2022

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

Post-meeting note: the PRAC minutes of the meeting held on 04-07 April 2022 were published on the EMA website on 18 January 2023 ([EMA/PRAC/955041/2022](#)).

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

### 2.1. Newly triggered procedures

None

### 2.2. Ongoing procedures

None

## 2.3. Procedures for finalisation

None

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

### 3.1. Newly triggered procedures

None

### 3.2. Ongoing procedures

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

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

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

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

#### Background

A referral procedure under Article 31 of Directive 2001/83/EC is ongoing for the review of nomegestrol- and chlormadinone-containing product(s) following new data from two epidemiological studies conducted in France in women taking these medicines. The results showed an increase of reported cases of meningioma depending on the dose and duration of treatment and suggested that the risk may be greater in women taking nomegestrol or chlormadinone for several years. The studies also showed that after women had stopped taking nomegestrol or chlormadinone for one year or more, the risk of developing these tumours was reduced and comparable to the risk in people who never used these medicines. For further background, see [PRAC minutes October 2021](#)<sup>1</sup> and [PRAC minutes February 2022](#).

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

- PRAC discussed the joint assessment report issued by the Rapporteurs.
- PRAC adopted a further list of outstanding issues (LoOI) to be addressed by the MAHs in accordance with a revised timetable ([EMA/PRAC/522598/2021 – Rev. 2](#)).
- PRAC agreed on a further list of questions (LoQ) inviting the study authors of the EPI-PHARE<sup>2</sup> retrospective cohort studies<sup>3 4</sup> on the risk of intracranial meningioma after prolonged exposure to either nomegestrol acetate or chlormadinone acetate, to address questions on the studies.

<sup>1</sup> Held 27-30 September 2021

<sup>2</sup> Epidémiologie des produits de Santé (EPI-PHARE)

<sup>3</sup> Nguyen P, Hoisnard L, Neumann A, Zureik M, Weill A. Utilisation prolongée de l'acétate de nomégésterol et risque de méningiome intracrânien: une étude de cohorte à partir des données du SNDS. EPI-PHARE, 2021. [https://www.epi-phare.fr/app/uploads/2021/04/epi-phare\\_rapport\\_acetate\\_nomegetrol\\_avril-2021.pdf](https://www.epi-phare.fr/app/uploads/2021/04/epi-phare_rapport_acetate_nomegetrol_avril-2021.pdf)

<sup>4</sup> Nguyen P, Hoisnard L, Neumann A, Zureik M, Weill A. Utilisation prolongée de l'acétate de chlormadinone et risque de méningiome intracrânien: une étude de cohorte à partir des données du SND. EPI-PHARE, 2021. [https://www.epi-phare.fr/app/uploads/2021/04/epi-phare\\_rapport\\_acetate\\_chlormadinone\\_avril-2021-1.pdf](https://www.epi-phare.fr/app/uploads/2021/04/epi-phare_rapport_acetate_chlormadinone_avril-2021-1.pdf)

### 3.3. Procedures for finalisation

None

### 3.4. Re-examination procedures<sup>5</sup>

None

### 3.5. Others

None

## 4. Signals assessment and prioritisation<sup>6</sup>

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

See also Annex I 14.1.

#### 4.1.1. Apixaban – APIXABAN ACCORD (CAP), ELIQUIS (CAP); NAP

Applicant(s): Accord Healthcare S.L.U. (Apixaban Accord), Bristol-Myers Squibb, Pfizer EEIG (Eliquis)

PRAC Rapporteur: Menno van der Elst

Scope: Signal of masking of acquired haemophilia

EPITT 19802 – New signal

#### Background

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

During routine signal detection activities, a signal of masking of acquired haemophilia was identified by EMA, based on nine cases retrieved from EudraVigilance. The Netherlands as the Rapporteur for the CAP(s) and lead Member State for the substance confirmed that the signal needed initial analysis and prioritisation by PRAC.

#### Discussion

Having considered the available evidence from case reports in EudraVigilance, PRAC considered that cases of masked acquired haemophilia would not be considered a safety signal with the administration of apixaban but rather an aspect to be considered in clinical practice in case of bleeding under apixaban treatment. PRAC agreed that no further action is deemed warranted at this stage.

PRAC appointed Menno van der Elst as Rapporteur for the signal.

<sup>5</sup> Re-examination of PRAC recommendation under Article 32 of Directive 2001/83/EC

<sup>6</sup> 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

### Summary of recommendation(s)

- The MAHs of apixaban containing products should continue to monitor these events as part of routine safety surveillance.

## 4.2. New signals detected from other sources

None

## 4.3. Signals follow-up and prioritisation

### 4.3.1. Calcitonin gene-related peptide (CGRP) antagonists: eptinezumab – VYEPTI (CAP) - EMEA/H/C/005287/SDA/001, erenumab – AIMOVIG (CAP) - EMEA/H/C/004447/SDA/004, fremanezumab – AJOVY (CAP) - EMEA/H/C/004833/SDA/006, galcanezumab – EMGALITY (CAP) - EMEA/H/C/004648/SDA/005

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Applicant(s): Eli Lilly Nederland B.V. (Emgality), H. Lundbeck A/S (Vyepti), Novartis Europharm Limited (Aimovig), Teva GmbH (Ajoyv)

PRAC Rapporteur: Kirsti Villikka

Scope: Signal of Raynaud's phenomenon

EPITT 19766 – Follow-up to January 2022

#### Background

For background information, see [PRAC minutes January 2022](#).

The MAHs for Vyepti (eptinezumab), Aimovig (erenumab), Ajoyv (fremanezumab) and Emgality (galcanezumab) replied to the request for information on the signal of Raynaud's phenomenon and the responses were assessed by the Rapporteur.

#### Discussion

Having considered the available evidence, the data submitted by the MAHs together with the Rapporteur's assessment, PRAC agreed that there is insufficient evidence at this stage to confirm a causal association between calcitonin gene-related peptide (CGRP) antagonists and Raynaud's phenomenon. Therefore, PRAC concluded that no regulatory action is warranted at present.

### Summary of recommendation(s)

- The MAHs of CGRP inhibitors-containing products should continue to monitor cases of Raynaud's phenomenon as part of routine safety surveillance.

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

None

## 5. Risk management plans (RMPs)

### 5.1. Medicines in the pre-authorisation phase

PRAC provided CHMP with advice 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. Coronavirus (COVID-19) vaccine (recombinant protein receptor binding domain fusion heterodimer) - EMEA/H/C/006058

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Scope: Active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 16 years of age and older

#### 5.1.2. Faricimab - EMEA/H/C/005642

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Scope: Treatment of neovascular (wet) age-related macular degeneration (nAMD) and visual impairment due to diabetic macular oedema (DME)

#### 5.1.3. Lutetium (<sup>177</sup>Lu) chloride - EMEA/H/C/005859

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Scope: Radiopharmaceutical precursor intended to be used only for the radiolabelling of carrier molecules specifically developed and authorised for radiolabelling with lutetium (<sup>177</sup>Lu) chloride

#### 5.1.4. Mobocertinib - EMEA/H/C/005621

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Scope: Treatment of adult patients with epidermal growth factor receptor (EGFR) exon 20 insertion mutation-positive locally advanced or metastatic non-small cell lung cancer (NSCLC)

#### 5.1.5. Nirsevimab - EMEA/H/C/005304, PRIME

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Scope (accelerated assessment): Prevention of respiratory syncytial virus (RSV) lower respiratory tract infection disease to immunise infants from birth entering their first RSV season

#### 5.1.6. Octreotide - EMEA/H/C/005826, Orphan

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Applicant: Amryt Pharmaceuticals DAC

Scope: Treatment of acromegaly



#### 5.1.7. Relatlimab, nivolumab - EMEA/H/C/005481

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Scope: First-line treatment of advanced (unresectable or metastatic) melanoma in adults and adolescents of 12 years and older and weighing at least 40 kg

#### 5.1.8. Teclistamab - EMEA/H/C/005865, PRIME, Orphan

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Applicant: Janssen-Cilag International N.V.

Scope (accelerated assessment): Treatment of relapsed or refractory multiple myeloma

#### 5.1.9. Thalidomide - EMEA/H/C/005715

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Scope: Treatment of multiple myeloma

#### 5.1.10. Voclosporin - EMEA/H/C/005256

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Scope: Treatment of adult patients with class III, IV or V (including mixed class III/V and IV/V) lupus nephritis (LN) in combination with background immunosuppressive therapies

#### 5.1.11. Vutrisiran - EMEA/H/C/005852, Orphan

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Applicant: Alnylam Netherlands B.V.

Scope: Treatment of hereditary transthyretin-mediated amyloidosis

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

See Annex I 15.2.

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

See also Annex I 15.3.

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

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Applicant: Kite Pharma EU B.V., ATMP<sup>7</sup>

PRAC Rapporteur: Anette Kirstine Stark

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

#### 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.

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<sup>7</sup> Advanced therapy medicinal product

CAT and CHMP are evaluating a type II variation consisting of an extension of the therapeutic indication for Yescarta, a centrally authorised product containing axicabtagene ciloleucel, to include treatment of adult patients with relapsed or refractory (r/r) diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL) after first line of systemic therapy. PRAC is responsible for providing advice to CAT and CHMP on the necessary updates to the RMP to support this extension of indication. For further background, see [PRAC minutes February 2022](#).

#### **Summary of advice**

- The RMP for Yescarta (axicabtagene ciloleucel) in the context of the procedure under evaluation by CAT and CHMP could be considered acceptable provided that an update to RMP version 6.1 is submitted along with satisfactory responses to the request for supplementary information (RSI).
- PRAC considered that the concerns on the efficacy of the medicinal product in CD19 negative patients at baseline is not driven by a safety concern and should not be added in the list of safety concerns. The MAH should update the RMP accordingly.

### **5.3.2. Defibrotide - DEFITELIO (CAP) - EMEA/H/C/002393/II/0056, Orphan**

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Applicant: Gentium S.r.l.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of the final report from study 15-007 (listed as a specific obligation in Annex II): a phase 3, randomised, adaptive study of defibrotide vs. best supportive care in the prevention of hepatic veno-occlusive disease in adult and paediatric patients undergoing hematopoietic stem cell transplant (HSCT). The RMP (version 9.0) is updated accordingly. The MAH took the opportunity to bring the product information in line with the latest quality review of documents (QRD) (template 10.2). In addition, the MAH introduced some minor correction throughout the product information

#### **Background**

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

CHMP is evaluating a type II variation for Defitelio, a centrally authorised product containing defibrotide, to evaluate the results of study 15-007: a phase 3, randomised, adaptive study of defibrotide versus best supportive care in the prevention of hepatic veno-occlusive disease in adult and paediatric patients undergoing hematopoietic stem cell transplant (HSCT). PRAC is responsible for providing advice to CHMP on the necessary updates to the RMP to support this type II variation. For further background, see [PRAC minutes July 2021](#), [PRAC minutes November 2021](#)<sup>8</sup> and [PRAC minutes March 2022](#).

#### **Summary of advice**

- The RMP for Defitelio (defibrotide) in the context of the procedure under evaluation by CHMP could be considered acceptable provided that a satisfactory update to RMP version 9.0 is submitted.

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<sup>8</sup> Held 25-28 October 2021

- Considering the results of the study and the documented off label use of defibrotide in prophylaxis for veno-occlusive disease after HSCT, PRAC agreed on the importance to inform healthcare professionals not to use defibrotide in this context. PRAC agreed on the need and on the content of a direct healthcare professional communication ([DHPC](#)) along with a communication plan for its distribution.

## 6. Periodic safety update reports (PSURs)

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

See also Annex I 16.1.

#### 6.1.1. Dapagliflozin - EDISTRIDE (CAP); FORXIGA (CAP) - PSUSA/00010029/202110

Applicant(s): AstraZeneca AB

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

#### Background

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

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of Edistride and Forxiga, centrally authorised medicine(s) containing dapagliflozin 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 Edistride and Forxiga (dapagliflozin) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add tubulointerstitial nephritis as an undesirable effect with a frequency 'very rare' and to add a drug-drug interaction between dapagliflozin and lithium. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>9</sup>.
- In the next PSUR, the MAH(s) should provide data on off-label use, including a discussion on the reasons for off-label use. In addition, the MAH should provide a review of cases of nodular vasculitis and confirm whether there are any cases reported in clinical trials and in the post-marketing setting.

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

PRAC considered that the risk of tubulointerstitial nephritis and the drug-drug interaction between dapagliflozin and lithium are also relevant to fixed dose combinations containing

<sup>9</sup> Update of SmPC sections 4.5 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion

dapagliflozin/metformin and dapagliflozin/saxagliptin. In addition, PRAC considered that the drug-drug interaction between dapagliflozin and lithium is also relevant to medicinal products containing lithium (excluding diagnostic medicinal products). Further consideration will be given at the level of CMDh.

### 6.1.2. Galcanezumab - EMGALITY (CAP) - PSUSA/00010733/202109

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Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

#### **Background**

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

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Emgality, a centrally authorised medicine containing galcanezumab 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 Emgality (galcanezumab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the existing warning on serious hypersensitivity reactions to add information that such reactions may occur more than one day to four weeks after administration and be prolonged in duration. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>10</sup>.
- In the next PSUR, the MAH should present a detailed analysis of new cases of hypersensitivity reactions, with a focus on delayed reactions, together with an evaluation of the effectiveness of the current routine risk minimisation measures in place to address this risk.

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

### 6.1.3. Siponimod - MAYZENT (CAP) - PSUSA/00010818/202109

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Applicant: Novartis Europharm Limited

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

#### **Background**

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<sup>10</sup> 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

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

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Mayzent, a centrally authorised medicine containing siponimod 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 Mayzent (siponimod) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the existing warning on squamous cell carcinoma (SCC) and to add SCC as an undesirable effect with a frequency 'uncommon'. In addition, the existing warning on herpes viral infection should be amended together with the description of selected adverse reactions. Moreover, the existing warning on cryptococcal meningitis should be amended, and cryptococcal meningitis added as an undesirable effect with a frequency 'not known'. Furthermore, the physician's checklist and the patient/caregiver guide should be amended accordingly. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>11</sup>.
- In the next PSUR, the MAH should provide a detailed review of cases of lymphopenia, together with a proposal to update the product information as warranted. The MAH should also provide a cumulative review of cases of pneumonia.

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 Annex I 16.2.

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

See also Annex I 16.3.

### **6.3.1. Alfentanil (NAP) - PSUSA/00000082/202109**

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Applicant(s): various

PRAC Lead: Ronan Grimes

Scope: Evaluation of a PSUSA procedure

#### **Background**

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<sup>11</sup> Update of SmPC sections 4.4 and 4.8 as well as Annex II. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion

Alfentanil is a synthetic opioid indicated for use as an anaesthetic induction agent and as an opioid analgesic in general anaesthesia. It is also indicated as an adjuvant to regional anaesthesia, and for both short (bolus injections) and long (bolus, supplemented by increments or by infusion) surgical procedures.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing alfentanil 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 alfentanil-containing product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the existing warning on drug dependence and potential for abuse (opioid use disorder), and to add an interaction between opioids and gabapentinoids that can lead to an additive effect of the latter on central nervous system (CNS) depression. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>12</sup>.
- In the next PSUR, the MAH(s) should provide a literature review on any class effect, as well as on alfentanil. In addition, the MAH(s) should provide a discussion on any new cases of withdrawal symptoms reported after use of alfentanil for the approved indication(s).

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

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

None

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

None

#### **6.6. Expedited summary safety reviews<sup>13</sup>**

See also Annex I 16.6.

##### **6.6.1. [Coronavirus \(COVID-19\) vaccine \(Ad26.COVID-S, recombinant\) - JCOVDEN \(previously COVID-19 VACCINE JANSSEN\) \(CAP\) – EMEA/H/C/005737/MEA 014.9](#)**

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Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Tenth expedited summary safety report (SSR) for COVID-19 Vaccine Janssen (COVID-19 vaccine (Ad26.COVID-S, recombinant)) during the coronavirus disease (COVID-

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<sup>12</sup> 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

<sup>13</sup> 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

19) pandemic

### **Background**

COVID-19 vaccine (Ad26.COVID-S [recombinant]) is a monovalent vaccine composed of a recombinant, replication-incompetent human adenovirus type 26 vector that encodes a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) full-length spike (S) glycoprotein indicated, as Jcovden, a centrally authorised vaccine, for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older.

PRAC assessed the tenth expedited summary safety report (SSR) for the safety monitoring of Jcovden (COVID-19 vaccine (Ad26.COVID-S, recombinant)) as part of the safety monitoring of the vaccine. At the plenary meeting, PRAC adopted its conclusions.

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

- PRAC considered that there is no new identified information regarding safety or efficacy that warrants a regulatory action. PRAC agreed that no further SSRs are required.

## **7. Post-authorisation safety studies (PASS)**

### **7.1. Protocols of PASS imposed in the marketing authorisation(s)<sup>14</sup>**

See Annex I 17.1.

### **7.2. Protocols of PASS non-imposed in the marketing authorisation(s)<sup>15</sup>**

See Annex I 17.2.

### **7.3. Results of PASS imposed in the marketing authorisation(s)<sup>16</sup>**

See Annex I 17.3.

### **7.4. Results of PASS non-imposed in the marketing authorisation(s)<sup>17</sup>**

See also Annex I 17.4.

#### **7.4.1. Loxapine - ADASUVE (CAP) - EMEA/H/C/002400/II/0033**

Applicant: Ferrer Internacional s.a.

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Update of sections 4.2, 4.4 and 4.8 of the SmPC in order to update safety information on bronchospasm based on final results from study AMDC-204-401 EU PASS (listed as a category 3 study in the RMP): a post-authorisation observational study to evaluate the safety of Adasuve (loxapine for inhalation) in agitated persons in routine clinical care (assessed in variation II/0032 finalised in May 2021). The package leaflet and labelling are updated accordingly. In addition, the MAH took the opportunity to update the

<sup>14</sup> In accordance with Article 107n of Directive 2001/83/EC

<sup>15</sup> 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

<sup>16</sup> In accordance with Article 107p-q of Directive 2001/83/EC

<sup>17</sup> 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

list of local representatives in the package leaflet

## **Background**

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

As stated in the [RMP](#) of Adasuve (loxapine), the MAH conducted a post-authorisation observational study to evaluate the safety of Adasuve (loxapine) in agitated persons in routine clinical care and proposed to update the product information accordingly. The Rapporteur assessed the MAH's final study report together with the MAH's responses to the request for supplementary information (RSI). For further background, see [PRAC minutes December 2021](#)<sup>18</sup>.

## **Summary of advice**

- Based on the available data and the assessment of the Rapporteur, PRAC considered that further information is necessary before the ongoing variation assessing the final study report can be recommended for approval.
- PRAC considered that the available evidence is not adequate to support the proposed use of Adasuve (loxapine) in the home setting. Administration should remain in the medical setting and under the direct supervision of a healthcare professional responsible for the post-administration monitoring. In addition, a description of bronchospasm and related symptoms should be further reflected in the product information. As a consequence, the MAH should provide a revised proposal to update the product information. In addition, the MAH should continue to monitor cases of bronchospasm through routine pharmacovigilance.

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

See Annex I 17.5.

## **7.6. Others**

See Annex I 17.6.

## **7.7. New Scientific Advice**

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

## **7.8. Ongoing Scientific Advice**

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

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<sup>18</sup> Held 29 November – 02 December 2021



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

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

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

### **8.1. Annual reassessments of the marketing authorisation**

See Annex I 18.1.

### **8.2. Conditional renewals of the marketing authorisation**

See Annex I 18.2.

### **8.3. Renewals of the marketing authorisation**

See Annex I 18.3.

## **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**

#### **10.1.1. Cholic acid – ORPHACOL (CAP) - EMEA/H/C/001250/II/0044**

Applicant: Laboratoires CTRS

PRAC Rapporteur: Sofia Trantza

Scope: PRAC consultation on a variation to update sections 4.3 and 4.5 of the SmPC in order to extend the currently existing contraindication with phenobarbital in order to include primidone based on scientific literature. The package leaflet is updated accordingly. The MAH took the opportunity to submit a combined SmPC for both dosages, 50 mg and 250

mg, to introduce editorial changes and to update the contact details of the local representatives in the package leaflet

### **Background**

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

A type II variation proposing to update the product information of Orphacol (cholic acid) is under evaluation at CHMP in order to extend the currently existing contraindication between cholic acid and phenobarbital to primidone based on scientific literature. PRAC was requested to provide advice on this variation procedure.

### **Summary of advice**

- Based on the review of the available information and assessment, PRAC considered that the need for a direct healthcare professional communication (DHPC) to communicate on the drug-drug interaction (DDI) between cholic acid and primidone is not warranted in light of the current knowledge. The DDI of cholic acid and primidone is an extension of the existing DDI between cholic acid and phenobarbital, since primidone is partially metabolised to phenobarbital. Also, the concomitant use of primidone and cholic acid is already contraindicated in the product information of primidone-containing product(s). The DDI concerns a potential lack of efficacy as opposed to a new safety concern with phenobarbital antagonising the effect of cholic acid. Furthermore, PRAC agreed that there is no need to update the educational materials since the risks of DDI are not classified as important identified risks in the RMP and do not require additional risk minimisation measures.

## **10.1.2. Cholic acid – ORPHACOL (CAP) - EMEA/H/C/001250/II/0045**

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Applicant: Laboratoires CTRS

PRAC Rapporteur: Sofia Trantza

Scope: PRAC consultation on a variation to update section 4.5 of the SmPC in order to update the existing information regarding concomitant use of cholic acid (the active substance of Orphacol) and ursodeoxycholic acid based on scientific literature. The package leaflet is updated accordingly

### **Background**

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

A type II variation proposing to update the product information of Orphacol (cholic acid) is under evaluation at CHMP regarding concomitant use of cholic acid and ursodeoxycholic acid (UDCA) based on scientific literature. The PRAC was requested to provide advice on this variation procedure.

### **Summary of advice**

- Based on the review of the available information and assessment, PRAC considered that the need for a direct healthcare professional communication (DHPC) to communicate on

the drug-drug interaction (DDI) between cholic acid and UDCA is not warranted in light of the current knowledge. The DDI concerns a potential lack of efficacy as opposed to a new safety concern with UDCA inhibiting absorption of cholic acid. Considering the rarity of 3 $\beta$ -hydroxy- $\Delta$ 5-C27-steroid oxidoreductase deficiency or  $\Delta$ 4-3-oxosteroid-5 $\beta$ -reductase deficiency, the probability of concomitant use of UDCA and cholic acid is considered as very low. Furthermore, UDCA and cholic acid are niche products and further awareness to health care professionals is not considered necessary. Finally, PRAC agreed that there is no need to update the educational materials since the risks of DDI are not classified as important identified risks in the RMP and do not require additional risk minimisation measures.

### 10.1.3. **Vildagliptin - GALVUS (CAP), JALRA (CAP), XILIXARX (CAP); vildagliptin, metformin - EUCREAS (CAP), ICANDRA (CAP), ZOMARIST (CAP) - EMA/H/C/WS2253**

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Applicant(s): Novartis Europharm Limited

PRAC Rapporteur: Annika Folin

Scope: PRAC consultation on a variation to update section 4.8 of the SmPC in order to add 'cutaneous vasculitis' as a new adverse drug reaction (ADR)

#### **Background**

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

A worksharing variation proposing to update the product information of Galvus, Jalra and Xiliarx (vildagliptin) and Eucreas, Icandra and Zomarist (vildagliptin/metformin) in order to add 'cutaneous vasculitis' as an ADR is under evaluation at CHMP. PRAC was requested to provide advice on this variation.

#### **Summary of advice**

- Based on the review of the available information and assessment, PRAC supported the update of the product information to include 'cutaneous vasculitis' as an undesirable effect. PRAC also agreed with the CHMP's proposal to request the MAH to provide a justification for the proposed frequency 'not known'.

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

None

### 10.3. **Other requests**

None

### 10.4. **Scientific Advice**

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

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

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

None

### 11.2. Other requests

#### 11.2.1. Canagliflozin - CZ/H/1139/001-002/DC

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PRAC Lead: Eva Jirsová

Scope: PRAC consultation on the evaluation of an initial marketing authorisation application under the decentralised procedure for a generic canagliflozin-containing medicinal product, on request of Czechia

#### **Background**

Canagliflozin is an inhibitor of sodium-glucose transport protein 2 (SGLT2) intended, for the treatment of adults with insufficiently controlled type 2 diabetes mellitus (T2DM) as an adjunct to diet and exercise.

In the context of the evaluation of an initial marketing authorisation application under the decentralised procedure for a generic canagliflozin-containing medicinal product Czechia requested PRAC advice on its assessment.

#### **Summary of advice**

- PRAC agreed that routine pharmacovigilance activities are suitable for generic canagliflozin-containing product(s) subject to evaluation in the context of initial marketing authorisation application(s), unless a need is identified to collect data or to contribute to the planned or ongoing data collection performed by the MAH of the originator medicinal product containing canagliflozin.

## 12. Organisational, regulatory and methodological matters

### 12.1. Mandate and organisation of PRAC

#### 12.1.1. PRAC membership

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The Chair announced that Ilaria Baldelli was to step down from PRAC as the alternate for Italy after the current meeting. The Chair thanked her for her contribution to PRAC. The Chair also informed the Committee of the Commission decision ([C\(2022\) 2729 final](#)) dated 02 May 2022 appointing members and alternates of PRAC representing healthcare professionals and patients' organisations for a period of three years coming into force on 01 May 2022.

### 12.1.2. PRAC working group - Best practice guide on using PRAC plenary time efficiently and effectively – update on the implementation of quantitative goals – Q1 2022

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In line with the adopted PRAC best practice guidance (BPG) on Committee efficiency (see PRAC minutes May 2016 and PRAC minutes June 2018) and the adopted implementation plan for the BPG including goals to measure compliance with the recommendations (see PRAC minutes June 2016 and PRAC minutes June 2018), the EMA secretariat informed PRAC about the quantitative measures collected for Q1 2022 of PRAC meetings. For previous update, see [PRAC minutes February 2022](#).

### 12.1.3. Vote by proxy

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None

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

### 12.2.1. Joint PRAC/CAT recommendation on long-term safety and efficacy follow-up for patients using chimeric antigen receptor (CAR) T-cell therapy using European Society for Blood and Marrow Transplantation (EBMT) registry as data source

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Following the trilateral between the European Society for Blood and Marrow Transplantation (EBMT), MAHs and EMA, and following consultation with CAT and PRAC Rapporteurs of affected advanced medicinal products (ATMPs), the EMA Secretariat presented to PRAC proposals for the long-term efficacy follow-up of patients using ATMPs, as well as the CAT position on this topic. PRAC/CAT agreed that at this time the EBMT data submitted by the MAHs as part of the interim reports for imposed PASS/post-authorisation efficacy studies (PAES) do not fulfil the regulatory requirements for the long-term safety and effectiveness follow-up of ATMPs, as envisaged at the time of granting the marketing authorisations. Therefore, the MAHs of authorised ATMPs should redesign their long-term safety and efficacy post-marketing follow-up studies to incorporate alternative data sources for aggregate reporting to EBMT. As part of this exercise, considerations to a sufficiently large EU cohort should be given and updated protocols submitted to EMA accordingly for assessment. The joint PRAC/CAT recommendation was adopted.

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

None

## 12.4. Cooperation within the EU regulatory network

### 12.4.1. Coronavirus (COVID-19) pandemic - update

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

## 12.5. Cooperation with International Regulators

None

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

None

## **12.7. PRAC work plan**

None

## **12.8. Planning and reporting**

### **12.8.1. EU Pharmacovigilance system - quarterly workload measures and performance indicators – Q1 2022 and predictions**

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The EMA Secretariat presented to PRAC an overview of the quarterly figures on the EMA pharmacovigilance system-related workload and performance indicators. For previous update, see [PRAC minutes February 2022](#).

### **12.8.2. Marketing authorisation applications (MAA) three-year forecast report**

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The EMA Secretariat shared with PRAC an outlook of the initial marketing authorisation applications (MAAs) planned for the next three years focusing on non-COVID-19 applications. PRAC noted the information.

### **12.8.3. PRAC workload statistics – Q1 2022**

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The EMA secretariat presented to PRAC the quarterly and cumulative figures to estimate the evolution of the workload of the PRAC for Q1 2022, by reflecting on the number of procedures and agenda items covered at each PRAC plenary meeting. For previous update, see [PRAC minutes February 2022](#).

## **12.9. Pharmacovigilance audits and inspections**

### **12.9.1. Pharmacovigilance systems and their quality systems**

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None

### **12.9.2. Pharmacovigilance inspections**

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None

### **12.9.3. Pharmacovigilance audits**

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None

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

### **12.10.1. Periodic safety update reports**

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None

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

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None

## 12.10.3. PSURs repository

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None

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

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PRAC endorsed the draft revised EURD list, version May 2022, reflecting the PRAC's comments impacting on the data lock point (DLP) and PSUR submission frequencies of the substances/combinations. The PRAC endorsed the newly allocated Rapporteurs for upcoming PSUSAs in accordance with the principles previously endorsed by the PRAC (see [PRAC minutes April 2013](#)).

Post-meeting note: following the PRAC meeting of May 2022, the updated EURD list was adopted by the CHMP and CMDh at their May 2022 meetings and published on the EMA website, see: [Home> Human Regulatory>Pharmacovigilance>Periodic safety update reports>EURD list> List of Union reference dates and frequency of submission of periodic safety update reports \(PSURs\)](#)

## 12.11. Signal management

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

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None

## 12.12. Adverse drug reactions reporting and additional reporting

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

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None

### 12.12.2. Additional monitoring

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None

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

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

Post-meeting note: The updated additional monitoring list was published on the EMA website accordingly, 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**

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None

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

### **12.14.1. Risk management systems**

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None

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

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None

### **12.14.3. Risk management plan (RMP) of medicinal product(s) containing new active substance(s) - publications**

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The EMA Secretariat presented to PRAC the EMA initiative to publish RMPs<sup>19</sup> (together with all subsequent updates) of centrally authorised products containing (a) new active substance(s) according to Article 8(3) of Directive 2001/83/EC, in order to further increase the transparency of safety information to the public and stakeholders. EMA Secretariat also presented the process following a phased-approach in which the first RMPs for publication are those of COVID-19 related-medicinal products, followed by medicinal products newly authorised via the centralised procedure. PRAC supported the initiative and encouraged to deliver trainings to the EU pharmacovigilance network.

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

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

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None

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

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None

## **12.16. Community procedures**

### **12.16.1. Referral procedures for safety reasons**

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None

## **12.17. Renewals, conditional renewals, annual reassessments**

None

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<sup>19</sup> In replacement of the RMP summaries



## **12.18. Risk communication and transparency**

### **12.18.1. Public participation in pharmacovigilance**

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None

### **12.18.2. Safety communication**

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None

## **12.19. Continuous pharmacovigilance**

### **12.19.1. Incident management**

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None

## **12.20. Impact of pharmacovigilance activities**

None

## **12.21. Others**

None

## **13. Any other business**

None

## **14. Annex I – Signals assessment and prioritisation<sup>20</sup>**

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

As per the agreed criteria for new signal(s), PRAC adopted without further plenary discussion the recommendation of the Rapporteur to request MAH(s) to submit a cumulative review following standard timetables<sup>21</sup>.

#### **14.1.1. Cabozantinib – COMETRIQ (CAP), CABOMETYX (CAP)**

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Applicant: Ipsen Pharma

PRAC Rapporteur: Menno van der Elst

Scope: Signal of tumour lysis syndrome

EPITT 19794 – New signal

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<sup>20</sup> 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

<sup>21</sup> 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

Lead Member State(s): NL

## 14.2. New signals detected from other sources

None

## 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 below-mentioned medicines under evaluation for initial marketing authorisation application. Information on the medicines containing the below listed active substance(s) will be made available following the CHMP opinion on their marketing authorisation(s).

#### 15.1.1. Bevacizumab - EMEA/H/C/005534

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Scope: Treatment of metastatic carcinoma of the colon or rectum, metastatic breast cancer and recurrence of platinum-sensitive epithelial ovarian, fallopian tube or primary peritoneal cancer; first-line treatment of patients with unresectable advanced, metastatic or recurrent non-small cell lung cancer; first line treatment of patients with advanced and/or metastatic renal cell cancer

#### 15.1.2. Pemetrexed - EMEA/H/C/005848

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Scope: Treatment of malignant pleural mesothelioma and non-small cell lung cancer (NSCLC)

### 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 below-mentioned medicine(s).

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

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Applicant: Sanofi Belgium

PRAC Rapporteur: Anette Kirstine Stark

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

#### 15.2.2. Infliximab - ZESSLY (CAP) - EMEA/H/C/004647/II/0020

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Applicant: Sandoz GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of an updated RMP (version 3.0) to remove the German registry Rheumatoide Arthritis: Beobachtung der Biologika-Therapie (RABBIT) as an additional pharmacovigilance activity in alignment with the RMP of the reference product and to remove the British Association of Dermatologists Biologic and Immunomodulators Register (BADBIR) registry as an additional pharmacovigilance activity

### 15.2.3. [Nintedanib - VARGATEF \(CAP\) - EMEA/H/C/002569/II/0044](#)

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Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Georgia Gkegka

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

### 15.2.4. [Pandemic influenza vaccine \(H5N1\) \(surface antigen, inactivated, adjuvanted\) - FOCLIVIA \(CAP\) - EMEA/H/C/001208/WS2151/0068; prepandemic influenza vaccine \(H5N1\) \(surface antigen, inactivated, adjuvanted\) - AFLUNOV \(CAP\) - EMEA/H/C/002094/WS2151/0071](#)

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Applicant: Seqirus S.r.l

PRAC Rapporteur: Amelia Cupelli

Scope: Submission of an updated RMP (version 3.9) in order to align safety concerns of Aflunov (prepandemic influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted)) and Foclivia (pandemic influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted)) and to reclassify some potential risks in line with revision 2 of GVP module V on 'Risk management systems'. In addition, reference to adverse drug reaction follow-up forms for routine pharmacovigilance activity are removed

### 15.2.5. [Selexipag - UPTRAVI \(CAP\) - EMEA/H/C/003774/II/0035](#)

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Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Nathalie Gault

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

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

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

#### 15.3.1. Acalabrutinib - CALQUENCE (CAP) - EMEA/H/C/005299/X/0009/G

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Applicant: AstraZeneca AB

PRAC Rapporteur: Željana Margan Koletić

Scope: Grouped application consisting of: 1) extension application to introduce a new pharmaceutical form, film-coated tablet; 2) change of the anatomical therapeutic chemical (ATC) code for acalabrutinib from L01XE51 to L01EL02. The RMP (version 4.1) is updated accordingly

#### 15.3.2. Budesonide - JORVEZA (CAP) - EMEA/H/C/004655/II/0015, Orphan

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Applicant: Dr. Falk Pharma GmbH

PRAC Rapporteur: Zane Neikena

Scope: Update of section 4.8 of the SmPC in order to update the list of adverse drug reactions based on final results from long-term maintenance study BUL-2/EER: a double-blind, randomised, placebo-controlled, phase 3 study on the efficacy and tolerability of a 48-week treatment with two different doses of budesonide effervescent tablets vs. placebo for maintenance of clinico-pathological remission in adult patients with eosinophilic esophagitis. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet. The package leaflet and RMP (version 3.0) are updated accordingly. The MAH also submitted the final report of study BUL-6/BIO: an open-label, randomised, 3-period, 3-sequence, single dose change-over trial in 18 male and female healthy volunteers, previously assessed within procedure X/0007/G concluded in March 2020

#### 15.3.3. Bupivacaine - EXPAREL LIPOSOMAL (CAP) - EMEA/H/C/004586/II/0005

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Applicant: Pacira Ireland Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Extension of indication to extend the existing indication of treatment of somatic post-operative pain from small- to medium-sized surgical wounds to children over 6 years old or older. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 1.1) are updated accordingly

#### 15.3.4. Canakinumab - ILARIS (CAP) - EMEA/H/C/001109/II/0075

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Applicant: Novartis Europharm Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include treatment of adult patients with Schnitzler syndrome. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are

updated. The package leaflet and the RMP (version 13.0) are updated in accordance

#### **15.3.5. Casirivimab, imdevimab - RONAPREVE (CAP) - EMEA/H/C/005814/II/0002**

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Applicant: Roche Registration GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension of indication to include treatment of coronavirus (COVID-19) in hospitalised patients in adults and adolescents aged 12 years and older weighing at least 40 kg. As a consequence, sections 4.2, 4.4, 4.8, 4.9, 5.1 and 5.2 of the SmPC are updated. The package leaflet, the labelling and the RMP (version 1.1) are updated in accordance

#### **15.3.6. Coronavirus (COVID-19) vaccine (recombinant, adjuvanted) (NVX-CoV2373) - NUVAXOVID (CAP) - EMEA/H/C/005808/II/0009**

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Applicant: Novavax CZ, a.s.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include use in adolescents 12 to 17 years of age based on data from study 2019nCoV-301: a phase 3, randomised, observer-blinded, placebo-controlled study to evaluate the efficacy, safety, and immunogenicity of a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) recombinant spike protein nanoparticle vaccine (SARS-CoV-2 rS) with matrix-M adjuvant in adult participants  $\geq$  18 years with a paediatric expansion in adolescents (12 to < 18 years). As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 1.1) are updated in accordance

#### **15.3.7. Delamanid - DELTYBA (CAP) - EMEA/H/C/002552/II/0053, Orphan**

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Applicant: Otsuka Novel Products GmbH

PRAC Rapporteur: Jean-Michel Dogné

Scope: Update of section 4.8 of the SmPC in order to update the list of adverse drug reactions (ADRs) following the development of an improved methodology to identify relevant ADRs likely attributable to delamanid. The package leaflet and the RMP (version 3.6) are updated accordingly

#### **15.3.8. Dexamethasone - NEOFORDEX (CAP) - EMEA/H/C/004071/II/0017/G**

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Applicant: Laboratoires CTRS

PRAC Rapporteur: Tiphaine Vaillant

Scope: Grouped variations consisting of update of the RMP (version 4.3) with a completion of 'removal of the score line for sub-division of the 40 mg tablet and consequent deletion of the 20 mg posology' (as a category 3 activity) and to include the direct healthcare professional communication (DHPC). In addition, the MAH used the opportunity to update sections from Module 3 of the dossier with editorial changes

### 15.3.9. Dexmedetomidine - DEXDOR (CAP) - EMEA/H/C/002268/II/0035

Applicant: Orion Corporation

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of section 4.4 of the SmPC in order to add a new warning on mortality in intensive care unit patients  $\leq 65$  years old, based on results from study SPICE III: an open-label, randomised trial on early sedation with dexmedetomidine in ventilated critically ill patients and heterogeneity of treatment effect and based on the completion of post-authorisation measure (LEG 16.4) finalised in November 2021. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet. A proposal for a direct healthcare professional communication (DHPC) and a communication plan is submitted. The RMP (version 9) is updated accordingly

### 15.3.10. Dolutegravir, abacavir, lamivudine - TRIUMEQ (CAP) - EMEA/H/C/002754/X/0101/G

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Martin Huber

Scope: Grouped application consisting of: 1) extension application to introduce a new pharmaceutical form associated with a new strength (5 mg/60 mg/30 mg dispersible tablet). The new presentation is indicated for the treatment of human immunodeficiency virus (HIV) infected children weighing at least 14 kg to less than 25 kg; 2) extension of indication to include treatment of human immunodeficiency virus (HIV) infected children weighing at least 25kg for the already approved film-coated tablets. As a consequence, sections 4.1, 4.2, 5.1 and 5.2 of the SmPC are updated. The package leaflet and labelling are updated in accordance. The RMP (version 19) is updated in accordance

### 15.3.11. Elbasvir, grazoprevir - ZEPATIER (CAP) - EMEA/H/C/004126/II/0034

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Submission of the final report from study MK-5172-017 (listed as a category 3 study in the RMP): a long-term follow-up study to evaluate the durability of virologic response and/or viral resistance patterns of subjects with chronic hepatitis C who have been previously treated with Zepatier (elbasvir/grazoprevir) in a prior clinical trial (in fulfilment of MEA 002.1). The RMP (version 5.1) is updated accordingly

### 15.3.12. Emicizumab - HEMLIBRA (CAP) - EMEA/H/C/004406/II/0027

Applicant: Roche Registration GmbH

PRAC Rapporteur: Amelia Cupelli

Scope: Extension of indication to include treatment of adult and paediatric patients with haemophilia A without factor VIII (FVIII) inhibitors who have mild or moderate disease for whom prophylaxis is clinically indicated. Consequently, sections 4.1, 4.8, 5.1 and 5.2 of the SmPC are updated. In addition, section 4.2 of the SmPC is updated to make clearer that the maintenance dose for Hemlibra (emicizumab) applies from week 5 of dosing. The package leaflet and the RMP (version 4.0) are updated accordingly

### 15.3.13. Etanercept - ENBREL (CAP) - EMEA/H/C/000262/II/0246

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Eva Segovia

Scope: Update of section 5.1 of the SmPC in order to update clinical information based on final results obtained from the clinical paediatric study B1801023 (CLIPPER 2): an open label extension study to assess the long-term safety of etanercept in children and adolescents with extended oligoarticular juvenile idiopathic arthritis, enthesitis related arthritis, or psoriatic arthritis who were previously enrolled in protocol 0881A1 3338 WW(B1801014). The RMP (version 7.5) is updated accordingly

### 15.3.14. Gemtuzumab ozogamicin - MYLOTARG (CAP) - EMEA/H/C/004204/II/0024, Orphan

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Update of sections 4.8, 5.1 and 5.2 of the SmPC based on the final results from study B176103: a single-arm, open-label, phase 4 study evaluating the QT interval, pharmacokinetics, and safety of gemtuzumab ozogamicin as a single-agent regimen in patients with relapsed or refractory CD<sup>22</sup>33-positive acute myeloid leukaemia. The RMP (version 2.0) is updated in accordance. In addition, the MAH took the opportunity to introduce some editorial changes in the product information

### 15.3.15. Gilteritinib - XOSPATA (CAP) - EMEA/H/C/004752/II/0007, Orphan

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Martin Huber

Scope: Submission of the report of an integrated analysis to demonstrate the safety of long-term treatment with gilteritinib when all patients enrolled in studies 2215-CL-0101, 2215-CL-0102 and 2215-CL-0301 have completed at least 3 years of treatment with gilteritinib or have withdrawn prior to completing at least 3 years of treatment. The studies refer to: 1) study 2215-CL-0101: a phase 1/2 open-label, dose escalation study investigating the safety, tolerability, pharmacokinetics, and pharmacodynamics of ASP2215 (gilteritinib) in patients with relapsed or refractory acute myeloid leukaemia (AML); 2) study 2215-CL-0102: a phase 1 open-label, dose escalation study investigating the safety, tolerability, pharmacokinetics, and pharmacodynamics of ASP2215 in Japanese patients with relapsed or refractory AML; 3) study 2215-CL-0301: a phase 3 open-label, multicentre, randomised study of ASP2215 versus salvage chemotherapy in patients with relapsed or refractory AML with FMS-like tyrosine kinase 3 (FLT3) mutation. The RMP (version 2.0) is updated in order to address missing information regarding the safety of Xospata (gilteritinib)

### 15.3.16. Givosiran - GIVLAARI (CAP) - EMEA/H/C/004775/II/0006, Orphan

Applicant: Alnylam Netherlands B.V.

PRAC Rapporteur: Martin Huber

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<sup>22</sup> Cluster of differentiation

Scope: Update of section 4.8 of the SmPC to add 'blood homocysteine increase' as a new adverse drug reaction (ADR) and update of section 4.4 of the SmPC to add a related warning. The package leaflet and the RMP (version 1.1) are updated accordingly. In addition, the MAH took the opportunity to make editorial changes to the product information and to update the local representative details for Malta and Cyprus

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

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Update of section 4.4 of the SmPC to include information on fatal and serious cardiac arrhythmias and cardiac failure, relevant warnings and periodical monitoring of patients following a safety assessment for increased risk of sudden death/cardiac death with the use of ibrutinib. The MAH took the opportunity to correct typographical errors throughout the product information. The package leaflet and the RMP (version 11.0) are updated accordingly

#### 15.3.18. Pegcetacoplan - ASPAVELI (CAP) - EMEA/H/C/005553/II/0002, Orphan

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Kimmo Jaakkola

Scope: Update of sections 4.2, 4.8, 5.1 and 5.2 of the SmPC based on final results from study APL2-302 (Pegasus) (listed as a category 3 study in the RMP): a global, phase 3, prospective, randomised, multicentre, open-label, active-comparator-controlled study in 80 subjects. The objective was to confirm treatment efficacy and safety of pegcetacoplan monotherapy for the treatment of paroxysmal nocturnal hemoglobinuria (PNH) (in fulfilment of MEA 001). The package leaflet and the RMP (version 0.5) are updated accordingly

#### 15.3.19. Pemigatinib - PEMAZYRE (CAP) - EMEA/H/C/005266/II/0005, Orphan

Applicant: Incyte Biosciences Distribution B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Update of sections 4.4, 4.8 and 5.1 of the SmPC based on the final results from study INCB054828 (FIGHT-202) (listed as a specific obligation in the Annex II (SOB/002)): a phase 2 study investigating the efficacy and safety of pemigatinib in adults with advanced/metastatic or surgically unresectable cholangiocarcinoma including fibroblast growth factor receptor 2 (FGFR2) translocations who failed previous therapy. The RMP (version 2.0) and Annex II are updated accordingly

#### 15.3.20. Pirfenidone - ESBRIET (CAP) - EMEA/H/C/002154/II/0074

Applicant: Roche Registration GmbH

PRAC Rapporteur: Rhea Fitzgerald

Scope: Extension of indication to include treatment of 'advanced' idiopathic pulmonary fibrosis (IPF) by the deletion of the current qualifier 'mild to moderate', based on the results from study MA29957: a 52-week phase 2b, multicentre, randomised, double-blind, placebo-



controlled clinical trial in IPF-patients with advanced lung function impairment (carbon monoxide diffusion capacity (DLco) < 40% of predicted) and at high risk of grade 3 pulmonary hypertension, and additional analyses performed on the original pivotal trials for pirfenidone in IPF. As a consequence, sections 4.1, 4.8 and 5.1 of the SmPC are updated. In addition, the MAH took the opportunity to include information in section 4.4 of the SmPC related to the content of sodium. The package leaflet and the RMP (version 12.0) are updated accordingly

#### 15.3.21. [Pneumococcal polysaccharide conjugate vaccine \(20-valent, adsorbed\) - APEXXNAR \(CAP\) - EMEA/H/C/005451/II/0002](#)

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Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Jean-Michel Dogné

Scope: Update of sections 4.5, 4.8 and 5.1 of the SmPC to add information regarding the co-administration of Apexxnar (pneumococcal polysaccharide conjugate vaccine (20-valent, adsorbed)) with seasonal quadrivalent influenza vaccine (QIV) based on final study results from study B7471004 (listed as a category 3 study in the RMP): a phase 3, randomised, double-blind trial to evaluate the safety and immunogenicity of a 20-valent pneumococcal conjugate vaccine (20vPnC) when co-administered with seasonal inactivated influenza vaccine (SIIV) in adults ≥65 years of age. The package leaflet and the RMP (version 1.1) are updated accordingly

#### 15.3.22. [Relugolix, estradiol, norethisterone acetate - RYEQO \(CAP\) - EMEA/H/C/005267/II/0006](#)

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Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Martin Huber

Scope: Submission of the final report from study MVT-601-035 (listed as a category 3 study in the RMP): an international phase 3 double-blind, placebo-controlled, randomised withdrawal study of relugolix co-administered with estradiol and norethisterone in women with heavy menstrual bleeding associated with uterine fibroids to evaluate the efficacy and safety of long-term use of Ryeqo (relugolix/estradiol/norethisterone acetate). The RMP (version 1.0) is updated accordingly

#### 15.3.23. [Remdesivir - VEKLURY \(CAP\) - EMEA/H/C/005622/II/0035/G](#)

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Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Eva Jirsová

Scope: Grouped variations consisting of: 1) extension of indication for treatment of paediatric patients (at least 4 weeks of age and weighing at least 3 kg) with pneumonia requiring supplemental oxygen (low- or high-flow oxygen) or other non-invasive ventilation at start of treatment based on interim results from study GS-US-540-5823: a phase 2/3 single-arm, open-label study to evaluate the safety, tolerability, pharmacokinetics and efficacy of remdesivir in participants from birth to <18 years of age with coronavirus (COVID-19); 2) extension of indication for treatment of paediatric patients (weighing at least 40 kg) who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19 based on data from 8 adolescent patients who were

included in study GS-US-540-9012: a phase 3 randomised, double-blind placebo-controlled trial to evaluate the efficacy and safety of remdesivir treatment of COVID-19 in an outpatient setting. As a consequence, sections 4.1, 4.2, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated. The package leaflet and the RMP (version 3.2) are updated accordingly

#### **15.3.24. Remimazolam - BYFAVO (CAP) - EMEA/H/C/005246/X/0002**

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Applicant: PAION Netherlands B.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: Extension application to introduce a new pharmaceutical form associated with a new strength (50 mg powder for concentrate for solution for injection/infusion). The new presentation comes with a new indication to include the intravenous induction and maintenance of general anaesthesia (GA) in adults for Byfavo (remimazolam) 50 mg, based on final results from two pivotal trials: 1) study ONO-2745-05: a phase 2b/3, single-blind, randomised, parallel-group study assessing safety and efficacy in induction and maintenance of anaesthesia in American Society of Anesthesiologists (ASA) I/II patients (general surgery); 2) study CNS-7056-022: a phase 3, randomised, propofol controlled, parallel group, confirmatory single-blind efficacy and safety trial during induction and maintenance of anaesthesia in ASA III/IV patients. A new combined version of the SmPC, labelling and package leaflet solely for the 50 mg strength and the GA indication is provided accordingly. The RMP (version 1.1) is updated accordingly. Finally, the MAH also requested an extension of the market protection by one additional year

#### **15.3.25. Secukinumab - COSENTYX (CAP) - EMEA/H/C/003729/II/0079**

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Applicant: Novartis Europharm Limited

PRAC Rapporteur: Eva Segovia

Scope: Extension of indication to include treatment of juvenile idiopathic arthritis (enthesitis-related arthritis and juvenile psoriatic arthritis) in patients 2 years and older whose disease has responded inadequately to, or who cannot tolerate, conventional therapy. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 10.0) are updated in accordance

#### **15.3.26. Tadalafil - ADCIRCA (CAP) - EMEA/H/C/001021/X/0035/G**

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Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Grouped application consisting of: 1) extension application to introduce a new pharmaceutical form associated with a new strength (2 mg/ml oral suspension); 2) extension of indication to paediatric use from 6 months to 17 years based on study 4 (H6D-MC-LVHV [LVHV]): a 24-week placebo-controlled efficacy and safety study with an open-label long-term extension phase. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and labelling are updated accordingly. Furthermore, the product information is brought in line with the latest quality review of documents (QRD) template and editorial changes have been implemented. The RMP (version 9.1) is updated in accordance

### 15.3.27. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/II/0039

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Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Extension of indication to include treatment of active ankylosing spondylitis for Xeljanz (tofacitinib) prolonged release. 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. The RMP (version 18.1) is updated accordingly

### 15.3.28. Zanubrutinib - BRUKINSA (CAP) - EMEA/H/C/004978/II/0003

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Applicant: BeiGene Ireland Ltd

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication to include treatment of adult patients with chronic lymphocytic leukaemia (CLL) or small lymphocytic leukaemia (SLL) based on results from: 1) study BGB-3111-304: an ongoing, international, phase 3, open-label, multiple-cohort, randomised study designed to evaluate the efficacy of zanubrutinib versus bendamustine plus rituximab (B+R) in patients with previously untreated CLL/SLL; 2) study BGB-3111-305: an ongoing, international phase 3, open-label, randomised study of zanubrutinib versus ibrutinib with relapsed/refractory (R/R) CLL/SLL. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.6, 4.8, 5.1 and 5.2 of the SmPC are being updated. The package leaflet and the RMP (version 1.1) are updated in accordance. In addition, as part of the application the MAH requested a 1-year extension of the market protection

## 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 below-mentioned medicines 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. Abemaciclib - VERZENIOS (CAP) - PSUSA/00010724/202109

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Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Evaluation of a PSUSA procedure

#### 16.1.2. Adefovir - HEPSERA (CAP) - PSUSA/00000060/202109

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Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Nathalie Gault

Scope: Evaluation of a PSUSA procedure

#### 16.1.3. Amikacin<sup>23</sup> - ARIKAYCE LIPOSOMAL (CAP) - PSUSA/00010882/202109

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Applicant: Insmmed Netherlands B.V.

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

#### 16.1.4. Brolucizumab - BEOVU (CAP) - PSUSA/00010829/202110

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Applicant: Novartis Europharm Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

#### 16.1.5. Bupivacaine - EXPAREL LIPOSOMAL (CAP) - PSUSA/00010889/202110

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Applicant: Pacira Ireland Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

#### 16.1.6. Cemiplimab - LIBTAYO (CAP) - PSUSA/00010780/202109

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Applicant: Regeneron Ireland Designated Activity Company (DAC)

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

#### 16.1.7. Cenobamate - ONTOZRY (CAP) - PSUSA/00010921/202109

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Applicant: Angelini S.p.A.

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

#### 16.1.8. Chenodeoxycholic acid<sup>24 25</sup> - CHENODEOXYCHOLIC ACID LEADIANT (CAP) - PSUSA/00010590/202110

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Applicant: Leadiant GmbH

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<sup>23</sup> Centrally authorised product(s) only

<sup>24</sup> Indicated for the treatment of inborn errors of primary bile acid synthesis due to sterol 27 hydroxylase deficiency (presenting as cerebrotendinous xanthomatosis (CTX)) in infants, children and adolescents aged 1 month to 18 years and adults

<sup>25</sup> Centrally authorised product(s) only

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

#### 16.1.9. Dacomitinib - VIZIMPRO (CAP) - PSUSA/00010757/202109

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

#### 16.1.10. Daptomycin - CUBICIN (CAP) - PSUSA/00000931/202109

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Pernille Harg

Scope: Evaluation of a PSUSA procedure

#### 16.1.11. Dexamethasone<sup>26 27</sup> - NEOFORDEX (CAP) - PSUSA/00010480/202109

Applicant: Laboratoires CTRS

PRAC Rapporteur: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

#### 16.1.12. Ebola vaccine (rDNA<sup>28</sup>, replication-incompetent) - MVABEA (CAP); ZABDENO (CAP) - PSUSA/00010857/202109

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

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

#### 16.1.13. Eltrombopag - REVOLADE (CAP) - PSUSA/00001205/202109

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

#### 16.1.14. Hepatitis A (inactivated), hepatitis B (rDNA) vaccines (adsorbed) - AMBIRIX (CAP); TWINRIX ADULT (CAP); TWINRIX PAEDIATRIC (CAP) - PSUSA/00001593/202109

Applicant(s): GlaxoSmithkline Biologicals SA

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

<sup>26</sup> Indicated in symptomatic multiple myeloma only

<sup>27</sup> Centrally authorised product(s) only

<sup>28</sup> Recombinant deoxyribonucleic acid

16.1.15. Herpes zoster vaccine (recombinant, adjuvanted) – SHINGRIX (CAP) – PSUSA/00010678/202110

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Applicant: GlaxoSmithkline Biologicals SA

PRAC Rapporteur: Sonja Hrabcik

Scope : Evaluation of a PSUSA procedure

16.1.16. Idecabtagene vicleucel – ABECMA (CAP) – PSUSA/00010954/202109

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Applicant: Bristol-Myers Squibb Pharma EEIG, ATMP<sup>29</sup>

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

16.1.17. Insulin aspart - FIASP (CAP); INSULIN ASPART SANOFI (CAP); KIRSTY (CAP); NOVOMIX (CAP); NOVORAPID (CAP) - PSUSA/00001749/202109

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Applicant(s): Mylan IRE Healthcare Limited (Kirsty), Novo Nordisk A/S (Fiasp, NovoMix, NovoRapid), Sanofi-aventis groupe (Insulin Aspart Sanofi)

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

16.1.18. Lusutrombopag - MULPLEO (CAP) - PSUSA/00010755/202109

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Applicant: Shionogi B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.19. Mogamulizumab - POTEIGEO (CAP) - PSUSA/00010741/202109

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Applicant: Kyowa Kirin Holdings B.V.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Evaluation of a PSUSA procedure

16.1.20. Netupitant, palonosetron - AKYNZEO (CAP) - PSUSA/00010393/202110

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Applicant: Helsinn Birex Pharmaceuticals Limited

PRAC Rapporteur: Ilaria Baldelli

Scope: Evaluation of a PSUSA procedure

16.1.21. Ofatumumab - KESIMPTA (CAP) - PSUSA/00010927/202109

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Applicant: Novartis Ireland Limited

PRAC Rapporteur: Amelia Cupelli

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<sup>29</sup> Advanced therapy medicinal product

Scope: Evaluation of a PSUSA procedure

#### 16.1.22. Panitumumab - VECTIBIX (CAP) - PSUSA/00002283/202109

Applicant: Amgen Europe B.V.

PRAC Rapporteur: David Olsen

Scope: Evaluation of a PSUSA procedure

#### 16.1.23. Pitolisant - OZAWADE (CAP); WAKIX (CAP) - PSUSA/00010490/202109

Applicant: Bioprojet Pharma

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

#### 16.1.24. Raltegravir - ISENTRESS (CAP) - PSUSA/00010373/202109

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Nathalie Gault

Scope: Evaluation of a PSUSA procedure

#### 16.1.25. Riociguat - ADEMPAS (CAP) - PSUSA/00010174/202109

Applicant: Bayer AG

PRAC Rapporteur: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

#### 16.1.26. Selinexor - NEXPOVIO (CAP) - PSUSA/00010926/202109

Applicant: Karyopharm Europe GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

#### 16.1.27. Selumetinib - KOSELUGO (CAP) - PSUSA/00010936/202110

Applicant: AstraZeneca AB

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

#### 16.1.28. Sofosbuvir, ledipasvir - HARVONI (CAP) - PSUSA/00010306/202110

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

#### 16.1.29. Vinflunine - JAVLOR (CAP) - PSUSA/00003123/202109

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Applicant: Pierre Fabre Medicament

PRAC Rapporteur: Eva Segovia

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. Filgrastim - ACCOFIL (CAP), FILGRASTIM HEXAL (CAP), GRASTOFIL (CAP), NIVESTIM (CAP), RATIOGRASTIM (CAP), TEVAGRASTIM (CAP), ZARZIO (CAP); NAP - PSUSA/00001391/202109

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Applicants: Accord Healthcare S.L.U. (Accofil, Grastofil), Hexal AG (Filgrastim Hexal), Pfizer Europe MA EEIG (Nivestim), Ratiopharm GmbH (Ratiograstim), Sandoz GmbH (Zarzio), Teva GmbH (Tevagrastim), various

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

#### 16.2.2. Measles, mumps, rubella, varicella vaccines (live) - PROQUAD (CAP); NAP - PSUSA/00001936/202109

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

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

#### 16.2.3. Oseltamivir - TAMIFLU (CAP); NAP - PSUSA/00002225/202109

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Applicants: Roche Registration GmbH (Tamiflu), various

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

#### 16.2.4. Sodium oxybate<sup>30</sup> - XYREM (CAP); NAP - PSUSA/00010612/202110

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

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

#### 16.2.5. Teriparatide - FORSTEO (CAP), LIVOGIVA (CAP), MOVYMIA (CAP); TERROSA (CAP); NAP - PSUSA/00002903/202109

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Applicants: Eli Lilly Nederland B.V. (Forsteo), Gedeon Richter Plc. (Terrosa), STADA Arzneimittel AG (Movymia), Theramex Ireland Limited (Livogiva), various

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<sup>30</sup> Oral use only



PRAC Rapporteur: Tiphaine Vaillant  
Scope: Evaluation of a PSUSA procedure

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#### 16.2.6. **Thalidomide - THALIDOMIDE BMS (CAP); NAP - PSUSA/00002919/202110**

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Applicants: Bristol-Myers Squibb Pharma EEIG (Thalidomide BMS), various  
PRAC Rapporteur: Tiphaine Vaillant  
Scope: Evaluation of a PSUSA procedure

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

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#### 16.3.1. **Ambrosia artemisiifolia<sup>31 32 33 34</sup> (NAP) - PSUSA/00010693/202110**

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Applicant(s): various  
PRAC Lead: Brigitte Keller-Stanislowski  
Scope: Evaluation of a PSUSA procedure

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#### 16.3.2. **Carmustine<sup>35</sup> (NAP) - PSUSA/00010348/202109**

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Applicant(s): various  
PRAC Lead: Tiphaine Vaillant  
Scope: Evaluation of a PSUSA procedure

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#### 16.3.3. **Opium (NAP) - PSUSA/00010670/202109**

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Applicant(s): various  
PRAC Lead: Marie Louise Schougaard Christiansen  
Scope: Evaluation of a PSUSA procedure

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#### 16.3.4. **Sodium oxybate<sup>36</sup> (NAP) - PSUSA/00010613/202110**

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Applicant(s): various  
PRAC Lead: Ana Sofia Diniz Martins  
Scope: Evaluation of a PSUSA procedure

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#### 16.3.5. **Tolterodine (NAP) – PSUSA/00002993/202109**

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Applicant(s): various  
PRAC Lead: Annika Folin

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<sup>31</sup> Allergen for therapy

<sup>32</sup> (302)

<sup>33</sup> Sublingual use only

<sup>34</sup> Medicinal product(s) authorised via decentralised procedure

<sup>35</sup> Implant(s) only

<sup>36</sup> Intravenous use only

Scope: Evaluation of a PSUSA procedure

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

None

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

None

#### **16.6. Expedited summary safety reviews<sup>37</sup>**

##### **16.6.1. Coronavirus (COVID-19) vaccine (recombinant, adjuvanted) - NUVAXOVID (CAP) - EMEA/H/C/005808/MEA 014.1**

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Applicant: Novavax CZ, a.s.

PRAC Rapporteur: Brigitte Keller-Stanislawski

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

##### **16.6.2. Coronavirus (COVID-19) vaccine (recombinant, adjuvanted) - NUVAXOVID (CAP) - EMEA/H/C/005808/MEA 014.1**

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Applicant: Novavax CZ, a.s.

PRAC Rapporteur: Brigitte Keller-Stanislawski

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

### **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)<sup>38</sup>**

##### **17.1.1. Tisagenlecleucel - KYMRIAHA (CAP) - EMEA/H/C/PSA/S/0080.1**

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Applicant: Novartis Europharm Limited, ATMP<sup>39</sup>

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: MAH's responses to PSA/S/0080.1 [substantial amendment to a protocol previously agreed in November 2019 (PSP/S/0066.3) for registry study CCTL019B2401 to assess the

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<sup>37</sup> 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

<sup>38</sup> In accordance with Article 107n of Directive 2001/83/EC

<sup>39</sup> Advanced therapy medicinal product

long-term safety of patients with B lymphocyte malignancies treated with tisagenlecleucel] as per the request for supplementary information (RSI) adopted in January 2022

### **17.1.2. Valproate (NAP) - EMEA/H/N/PSP/J/0075.7**

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

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Submission of the third interim report for drug utilisation study (DUS) extension (DUS ext.) to assess the effectiveness of the new risk minimisation measures and to further characterise the prescribing patterns for valproate and related substances, in Europe, using databases in Germany, France, Netherlands, Spain, Sweden and United Kingdom; together with an updated protocol (version 8) as a MAH's response to PSP/J/0075.6 [second interim report for a DUS to assess the effectiveness of the new risk minimisation measures (RMMs) and to further characterise the prescribing patterns for valproate as required in the outcome of the referral procedure under Article 31 of Directive 2001/83/EC on valproate-containing products completed in February 2018 (EMEA/H/A-31/1454)]

## **17.2. Protocols of PASS non-imposed in the marketing authorisation(s)<sup>40</sup>**

### **17.2.1. Botulinum toxin type A - NUCEIVA (CAP) - EMEA/H/C/004587/MEA 002.3**

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Applicant: Evolus Pharma B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Amendment to a previously agreed protocol for study EV-010: a non-interventional PASS for Nuceiva (botulinum toxin type A) in the treatment of moderate-to-severe glabellar lines

### **17.2.2. Brexucabtagene autoleucel - TECARTUS (CAP) - EMEA/H/C/005102/MEA 005.2**

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Applicant: Kite Pharma EU B.V., ATMP<sup>41</sup>

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to MEA 005.1 [protocol for study KT-EU-472-5966: a prescriber survey to assess prescribers' understanding of the risks of Tecartus (KTE-X19) to evaluate the effectiveness of risk minimisation activities, namely healthcare professional (HCP) educational materials and patient alert card (PAC) [final study report expected in September 2023] (from initial opinion/marketing authorisation(s) (MA))] as per the request for supplementary information (RSI) adopted in December 2021

### **17.2.3. Canagliflozin - INVOKANA (CAP) - EMEA/H/C/002649/MEA 009.5**

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Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Martin Huber

Scope: MAH's response to MEA 009.4 [amendment to a previously agreed protocol for a

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<sup>40</sup> 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

<sup>41</sup> Advanced therapy medicinal product

drug utilisation study (DUS) to evaluate the drug utilisation patterns of canagliflozin-containing medicines including off-label usage in type 1 diabetes mellitus (T1DM) and the risk of diabetic ketoacidosis (DKA) using EU databases on market uptake and exposure within the European Union] as per the request for supplementary information (RSI) adopted in December 2021

#### 17.2.4. Canagliflozin, metformin - VOKANAMET (CAP) - EMEA/H/C/002656/MEA 008.5

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to MEA 008.4 [amendment to a previously agreed protocol for a drug utilisation study (DUS) to evaluate the drug utilisation patterns of canagliflozin-containing medicines including off-label usage in type 1 diabetes mellitus (T1DM) and the risk of diabetic ketoacidosis (DKA) using EU databases on market uptake and exposure within the European Union] as per the request for supplementary information (RSI) adopted in December 2021

#### 17.2.5. Darbepoetin alfa - ARANESP (CAP) - EMEA/H/C/000332/MEA 092.3

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Martin Huber

Scope: Amendment to a previously agreed protocol for study 20190404 (listed as a category 3 study in the RMP): a retrospective cohort study to assess the use of erythropoiesis stimulating agents (ESAs) in subjects receiving myelosuppressive chemotherapy in Europe

#### 17.2.6. Dimethyl fumarate - TECFIDERA (CAP) - EMEA/H/C/002601/MEA 007.4

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Martin Huber

Scope: MAH's response to MEA 007.3 [amendment to a protocol previously agreed in November 2017 for study 109MS401 (ESTEEM): 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 relapsing multiple sclerosis] as per the request for supplementary information (RSI) adopted in September 2021

#### 17.2.7. Diroximel fumarate - VUMERITY (CAP) - EMEA/H/C/005437/MEA 002

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Martin Huber

Scope: Protocol for study SE-VUM-12146 (listed as category 3 study in the RMP): an observational study utilising data from 'big data' multiple sclerosis registries to evaluate the long-term safety of Vumerity (diroximel fumarate) and Tecfidera (dimethyl fumarate) (from initial opinion/marketing authorisation(s) (MA))

#### 17.2.8. Empagliflozin - JARDIANCE (CAP) - EMEA/H/C/002677/MEA 004.5

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Eva Segovia

Scope: Amendment to a previously agreed protocol as a response to MEA 010.4 [fifth monitoring interim report for study 1245.97: a non-interventional PASS assessing the risk of urinary tract malignancies in relation to empagliflozin exposure in patients with type 2 diabetes mellitus (T2DM): a multi-database European study [final clinical study report (CSR) expected in June 2021]] as per the request for supplementary information (RSI) adopted in October 2021

#### 17.2.9. Empagliflozin, metformin - SYNJARDY (CAP) - EMEA/H/C/003770/MEA 006.7

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Eva Segovia

Scope: Amendment to a previously agreed protocol as a response to MEA 006.6 [fifth monitoring interim report for study 1245.97: a non-interventional PASS assessing the risk of urinary tract malignancies in relation to empagliflozin exposure in patients with type 2 diabetes mellitus (T2DM): a multi-database European study (final clinical study report (CSR) expected in June 2021)] as per the request for supplementary information (RSI) adopted in October 2021

#### 17.2.10. Filgotinib - JYSELECA (CAP) - EMEA/H/C/005113/MEA 016

Applicant: Galapagos N.V.

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Protocol for study GLPG0634-CL-413: a non-interventional, PASS of filgotinib in patients with moderately to severely active ulcerative colitis (a European multi registry-based study)

#### 17.2.11. Mepolizumab - NUCALA (CAP) - EMEA/H/C/003860/MEA 015

Applicant: GlaxoSmithKline Trading Services Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Protocol for study 218065: a PASS to describe real-world safety and effectiveness of mepolizumab in paediatric eosinophilic granulomatosis with polyangiitis (EGPA) patients in Europe

#### 17.2.12. Natalizumab - TYSABRI (CAP) - EMEA/H/C/000603/MEA 064.2

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Amendment to a previously agreed protocol for study 101MS411 (listed as a category 3 study in the RMP): an observational study utilising data from the US Tysabri outreach unified commitment to health (TOUCH) prescribing programme and selected EU

multiple sclerosis (MS) registries to estimate the risk of progressive multifocal leukoencephalopathy (PML) and other serious opportunistic infections among patients who were exposed to a MS disease modifying treatment prior to treatment with Tysabri (natalizumab)

#### **17.2.13. Neratinib - NERLYNX (CAP) - EMEA/H/C/004030/MEA 002.4**

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Applicant: Pierre Fabre Medicament

PRAC Rapporteur: Menno van der Elst

Scope: Amendment to a previously agreed protocol for study PUMA-NER-6202: a randomised study to characterise the incidence and severity of diarrhoea in patients with early stage epidermal growth factor receptor 2 + (HER2+) breast cancer treated with neratinib and intensive loperamide prophylaxis versus neratinib and intensive loperamide prophylaxis plus a bile acid sequestrant in the first month of treatment

#### **17.2.14. Ofatumumab - KESIMPTA (CAP) - EMEA/H/C/005410/MEA 002.1**

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Applicant: Novartis Ireland Limited

PRAC Rapporteur: Amelia Cupelli

Scope: MAH's response to MEA 002 [protocol for study OMB157G2407 (listed as category 3 study in the RMP): pregnancy outcomes intensive monitoring (PRIM) to evaluate pregnancy and infant outcomes in patients taking Kesimpta (ofatumumab)] as per the request for supplementary information (RSI) adopted in December 2021

#### **17.2.15. Risankizumab - SKYRIZI (CAP) - EMEA/H/C/004759/MEA 001.5**

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Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Amendment to a previously agreed protocol for study P19-633: a post-marketing registry-based prospective cohort study of long-term safety of risankizumab in real world setting in Denmark and Sweden [final study report expected in December 2031] together with a statistical analysis plan (SAP)

#### **17.2.16. Risdiplam - EVRYSDI (CAP) - EMEA/H/C/005145/MEA 007.2**

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Applicant: Roche Registration GmbH

PRAC Rapporteur: Jan Neuhauser

Scope: MAH's response to MEA 007.1 [protocol for study BN42833 - Risdiplam pregnancy surveillance study: a phase 4, non-interventional surveillance study [final study report expected in Q4/2031] (from initial opinion/marketing authorisation (MA))] as per the request for supplementary information (RSI) adopted in February 2022

#### **17.2.17. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/MEA 008.5**

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Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: MAH's response to MEA 008.4 [updated protocol for study A3921312 (listed as a category 3 study in the RMP): a prospective non-interventional comparative active surveillance PASS of serious infection, malignancy, cardiovascular and other safety events of interest among patients treated with tofacitinib for moderately to severely active rheumatoid arthritis (RA) within the British Society for Rheumatology Biologics Register-Rheumatoid Arthritis (BSRBR-RA) following on the recommendation of the signal on major adverse cardiovascular events (MACE) and malignancies excluding non-melanoma skin cancer (NMSC) (EPITT 19382) finalised in June 2021] as per the request for supplementary information adopted in December 2021

#### **17.2.18. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/MEA 009.5**

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Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: MAH's response to MEA 009.4 [updated protocol for study A3921314 (listed as a category 3 study in the RMP): a prospective non-interventional comparative active surveillance PASS of serious infection, malignancy, cardiovascular and other safety events of interest among patients treated with tofacitinib for moderately to severely active rheumatoid arthritis (RA) within the Swedish (ARTIS) register following on the recommendation of the signal on major adverse cardiovascular events (MACE) and malignancies excluding non-melanoma skin cancer (NMSC) (EPITT 19382) finalised in June 2021] as per the request for supplementary information adopted in December 2021

#### **17.2.19. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/MEA 010.5**

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Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: MAH's response to MEA 010.4 [updated protocol for study A3921316 (listed as a category 3 study in the RMP): a prospective non-interventional comparative active surveillance PASS of serious infection, malignancy, cardiovascular and other safety events of interest among patients treated with Xeljanz (tofacitinib) for moderately to severely active rheumatoid arthritis (RA) within the Spanish registry of adverse events of biological therapies and biosimilars in rheumatoid diseases (BIOBADASER) following on the recommendation of the signal on major adverse cardiovascular events (MACE) and malignancies excluding non-melanoma skin cancer (NMSC) (EPITT 19382) finalised in June 2021] as per the request for supplementary information adopted in December 2021

#### **17.2.20. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/MEA 011.5**

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Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: MAH's response to MEA 011.4 [updated protocol for study A3921317 (listed as a category 3 study in the RMP): a prospective non-interventional comparative active surveillance PASS of serious infection, malignancy, cardiovascular and other safety events of interest among patients treated with Xeljanz (tofacitinib) for moderately to severely active rheumatoid arthritis (RA) within the German registry Rheumatoide Arthritis: Beobachtung der Biologika-Therapie (RABBIT) following on the recommendation of the

signal on major adverse cardiovascular events (MACE) and malignancies excluding non-melanoma skin cancer (NMSC) (EPITT 19382) finalised in June 2021] as per the request for supplementary information adopted in December 2021

#### [17.2.21. Tofacitinib - XELJANZ \(CAP\) - EMEA/H/C/004214/MEA 013.4](#)

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Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: MAH's response to MEA 013.3 [protocol for study A3921344 (listed as a category 3 study in the RMP): an active surveillance, post-authorisation study to characterise the safety of tofacitinib in patients with moderately to severely active ulcerative colitis (UC) in the real-world setting using data from the Swedish Quality Register for Inflammatory Bowel Disease (SWIBREG) registry] as per the request for supplementary information (RSI) adopted in December 2021

#### [17.2.22. Tofacitinib - XELJANZ \(CAP\) - EMEA/H/C/004214/MEA 018](#)

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Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Protocol for study A3921407: a PASS surveillance programme among patients treated with tofacitinib for polyarticular course juvenile idiopathic arthritis and juvenile psoriatic arthritis (PsA) within the German Biologics in Paediatric Rheumatology Registry (BIKER) and within the Juvenile Arthritis Methotrexate/Biologics long-term Observation (JuMBO) biological register (from X/0024/G)

#### [17.2.23. Tofacitinib - XELJANZ \(CAP\) - EMEA/H/C/004214/MEA 019](#)

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Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Protocol for study A3921408: a PASS surveillance programme among patients treated with tofacitinib for polyarticular course juvenile idiopathic arthritis and juvenile psoriatic arthritis (PsA) within the Swedish juvenile idiopathic arthritis (JIA) clinical registry (from X/0024/G)

#### [17.2.24. Tofacitinib - XELJANZ \(CAP\) - EMEA/H/C/004214/MEA 020](#)

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Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Protocol for study A3921409: a PASS surveillance programme among patients treated with tofacitinib for polyarticular course juvenile idiopathic arthritis and juvenile psoriatic arthritis (PsA) within the UK juvenile idiopathic arthritis (JIA) biologics register (from X/0024/G)

#### [17.2.25. Tozinameran - COMIRNATY \(CAP\) - EMEA/H/C/005735/MEA 047](#)

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Applicant: BioNTech Manufacturing GmbH



PRAC Rapporteur: Menno van der Elst

Scope: Protocol for study C4591038 (listed as a category 3 study in the RMP): a post conditional approval active surveillance study among individuals in Europe receiving the Pfizer BioNTech coronavirus disease 2019 (COVID-19) vaccine to investigate natural history of post-vaccination myocarditis and pericarditis

### **17.3. Results of PASS imposed in the marketing authorisation(s)<sup>42</sup>**

#### **17.3.1. Lumacaftor, ivacaftor– ORKAMBI (CAP) - EMEA/H/C/PSR/S/0039**

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Applicant: Vertex Pharmaceuticals

PRAC Rapporteur: Rhea Fitzgerald

Scope: Final report for study VX-14 809-108: an observational PASS to evaluate the utilisation patterns and long-term effects of lumacaftor and ivacaftor combination therapy in patients with cystic fibrosis

#### **17.3.2. Rivaroxaban – XARELTO (CAP) - EMEA/H/C/PSR/S/0027**

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Applicant: Bayer AG

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Final study report comprising the pharmaco-epidemiological study programme of rivaroxaban use and potential adverse outcomes in routine clinical practice in the United Kingdom, Germany, the Netherlands and Sweden

### **17.4. Results of PASS non-imposed in the marketing authorisation(s)<sup>43</sup>**

#### **17.4.1. Alglucosidase alfa - MYOZYME (CAP) - EMEA/H/C/000636/II/0090**

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Applicant: Genzyme Europe BV

PRAC Rapporteur: Nathalie Gault

Scope: Submission of the final report from non-interventional study AGLU06909/LTS13930: a prospective safety sub-registry to assess anaphylaxis and severe allergic reactions, and severe cutaneous and systemic immune complex mediated reactions with alglucosidase alfa treatment (Pompe registry report 2020 (in fulfillment of MEA024.15 and MEA025.15))

#### **17.4.2. Apremilast - OTEZLA (CAP) - EMEA/H/C/003746/II/0038**

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Applicant: Amgen Europe B.V.

PRAC Rapporteur: Eva Segovia

Scope: Submission of the final study report (CSR) from PsOBest registry (listed as a category 3 study in the RMP): an observational study to assess the long-term safety and effectiveness of apremilast in routine clinical practice in Germany. The RMP (version 14.0) is updated accordingly

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<sup>42</sup> In accordance with Article 107p-q of Directive 2001/83/EC

<sup>43</sup> 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. Etanercept - ENBREL (CAP) - EMEA/H/C/000262/II/0244

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Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Eva Segovia

Scope: Submission of the final report from study B1801310 (BIKER) (listed as a category 3 study in the RMP): an observational PASS of etanercept and methotrexate in the treatment of juvenile idiopathic arthritis (JIA) using data obtained from participants in the German Biologics JIA registry (BIKER) to monitor long-term safety and effectiveness of etanercept in the treatment of JIA in regular clinical practice

#### 17.4.4. Hepatitis B surface antigen - HEPLISAV B (CAP) - EMEA/H/C/005063/II/0014

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Applicant: Dynavax GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Submission of the final report from study HBV25 (listed as a category 3 study in the RMP): a post-marketing observational surveillance study comparing the occurrence of acute myocardial infarction (AMI) in recipients of Heplisav B (hepatitis B surface antigen) with recipients of another hepatitis B vaccine. As a consequence, the MAH proposed the removal of AMI as an important potential risk from the list of safety concerns. The RMP (version 1.2) is updated accordingly

#### 17.4.5. Infliximab - REMICADE (CAP) - EMEA/H/C/000240/II/0231

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Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of the final report of the Remicade (infliximab) Anti-Rheumatic Therapy in Sweden (ARTIS) register study. The RMP (version 20.1) is updated accordingly and with revisions agreed in previous procedures

#### 17.4.6. Talimogene laherparepvec - IMLYGIC (CAP) - EMEA/H/C/002771/II/0051

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Applicant: Amgen Europe B.V., ATMP<sup>44</sup>

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Submission of the final report from study 20180062 (listed as a category 3 study in the RMP) - an observational research study report (ORSR): a multinational, non-interventional, cross-sectional survey study for patients aged  $\geq 18$  years who have received Imlygic (talimogene laherparepvec) at least once in the 3 months prior to completing the survey to evaluate the effectiveness of patient-directed additional risk minimisation measures

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

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Applicant: Takeda Pharmaceuticals International AG

PRAC Rapporteur: Martin Huber

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<sup>44</sup> Advanced therapy medicinal product

Scope: Submission of final physician data study results for study EUPASS 14255: an evaluation of the effectiveness of risk minimisation measures - a survey among healthcare professionals (HCPs) and patient/caregivers to assess their knowledge and attitudes on prescribing and home administration conditions of velaglucerase alfa (Vpriv) in 6 European countries

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

### **17.5.1. Avelumab - BAVENCIO (CAP) - EMEA/H/C/004338/MEA 002.4**

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Applicant: Merck Europe B.V.

PRAC Rapporteur: Anette Kirstine Stark

Scope: Third yearly progress update report for study MS100070-0031 (listed as a category 3 study in the RMP): a non-interventional cohort study to assess characteristics and management of patients with Merkel cell carcinoma (MCC) in Germany [final study report expected in Q1/2024]

### **17.5.2. Coronavirus (COVID-19) vaccine (ChAdOx1-S [recombinant]) - VAXZEVRIA (CAP) - EMEA/H/C/005675/MEA 006.4**

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Applicant: AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

Scope: Semi-annual report (period covered 01 June 2021 to 30 November 2021) for study COVID-19 vaccines International Pregnancy Exposure Registry (C-VIPER) (listed as a category 3 study in the RMP): a pregnancy registry of women exposed to Vaxzevria (AZD1222 – COVID-19 vaccine) immediately before or during pregnancy (from initial opinion/marketing authorisation(s) (MA))

### **17.5.3. Damoctocog alfa pegol - JIVI (CAP) - EMEA/H/C/004054/MEA 003.3**

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Applicant: Bayer AG

PRAC Rapporteur: Menno van der Elst

Scope: Twelfth annual European Haemophilia Safety Surveillance (EUHASS) report for study 14149 (listed as a category 3 study in the RMP): evaluation of cases with adverse events (AEs) of special interest in the EUHASS registry

### **17.5.4. Elasomeran - SPIKEVAX (CAP) - EMEA/H/C/005791/MEA 003.5**

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Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Fourth interim report for a study (listed as a category 3 study in the RMP): a post authorisation safety of Spikevax (elasomeran) in the US - an enhanced pharmacovigilance study to provide additional evaluation of adverse events of special interest (AESI) and emerging validated safety signals [final clinical study report (CSR) expected in June 2023] (from initial opinion/marketing authorisation (MA)) and MAH's response to MEA 003.3 as

per the response for supplementary information (RSI) adopted in November 2021

#### **17.5.5. [Elasomeran - SPIKEVAX \(CAP\) - EMEA/H/C/005791/MEA 005.3](#)**

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Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Interim report for a study (listed as a category 3 study in the RMP): Moderna mRNA-1273 observational pregnancy outcome study to evaluate outcomes of pregnancies in females exposed to Spikevax (elasomeran) during pregnancy [final clinical study report (CSR) expected in June 2024]

#### **17.5.6. [Lenvatinib - LENVIMA \(CAP\) - EMEA/H/C/003727/MEA 014.4](#)**

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Applicant: Eisai GmbH

PRAC Rapporteur: Annika Folin

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

#### **17.5.7. [Levofloxacin - QUINSAIR \(CAP\) - EMEA/H/C/002789/ANX 004.6](#)**

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Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Fourth annual interim report for a post-marketing, open-label, observational safety study of Quinsair (nebulised levofloxacin hemihydrate) in patients with cystic fibrosis and chronic *Pseudomonas aeruginosa* infection, using data collected through European cystic fibrosis registries [final clinical study report (CSR) expected in June 2022]

### **17.6. Others**

#### **17.6.1. [Alemtuzumab - LEMTRADA \(CAP\) - EMEA/H/C/003718/ANX 010.3](#)**

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Applicant: Sanofi Belgium

PRAC Rapporteur: Anette Kirstine Stark

Scope: MAH's response to ANX 010.1 [feasibility report for a drug utilisation study (DUS) to assess compliance with the therapeutic indication and effectiveness of measures to minimise the risk of cardiovascular and cerebrovascular adverse events in close temporal association with Lemtrada (alemtuzumab) infusion and immune-mediated adverse reactions, as requested in the conclusions of the referral procedure under Article 20 of Regulation (EC) No 726/2004 (EMEA/H/A-20/1483) finalised in 2019] as per the request for supplementary information (RSI) adopted in December 2021

#### **17.6.2. [Avatrombopag - DOPTELET \(CAP\) - EMEA/H/C/004722/MEA 002.4](#)**

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Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Eva Segovia

Scope: MAH's response to MEA 002.3 [feasibility assessment for study AVA-CLD-402: evaluation of the feasibility of conducting a PASS of Doptelet (avatrombopag) in patients with severe chronic liver disease (CLD) and of the use of potential European electronic health care databases] as per the request for supplementary information (RSI) adopted in June 2021

### **17.6.3. Avatrombopag - DOPTelet (CAP) - EMEA/H/C/004722/MEA 003.1**

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Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Eva Segovia

Scope: MAH's response to MEA 003 [feasibility assessment for a study to further characterise the long-term safety profile of avatrombopag in patients with primary chronic immune thrombocytopenia in European patient registers and electronic healthcare databases as requested in the conclusions of variation II/0004/G finalised in December 2020] as per the request for supplementary information (RSI) adopted in July 2021

### **17.6.4. Zanubrutinib - BRUKINSA (CAP) - EMEA/H/C/004978/MEA 002**

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Applicant: BeiGene Ireland Ltd

PRAC Rapporteur: Menno van der Elst

Scope: Protocol for study LTE1 (listed as a category 3 study in the RMP): a phase 3, open-label study to evaluate the long-term safety and efficacy of zanubrutinib, as monotherapy or in combination, in patients with B-cell malignancies who are or were previously enrolled in a BeiGene parent study and who are still benefiting or may benefit from treatment with zanubrutinib, or who are willing to have long-term survival follow-up

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

Based on the review of the available pharmacovigilance data for the medicines 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. Idebenone - RAXONE (CAP) - EMEA/H/C/003834/S/0029 (with RMP)**

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Applicant: Santhera Pharmaceuticals (Deutschland) GmbH

PRAC Rapporteur: Amelia Cupelli

Scope: Annual reassessment of the marketing authorisation

## **18.2. Conditional renewals of the marketing authorisation**

### **18.2.1. Avapritinib - AYVAKYT (CAP) - EMEA/H/C/005208/R/0017 (with RMP)**

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Applicant: Blueprint Medicines (Netherlands) B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Conditional renewal of the marketing authorisation

### **18.2.2. Imlifidase - IDEFIRIX (CAP) - EMEA/H/C/004849/R/0007 (without RMP)**

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Applicant: Hansa Biopharma AB

PRAC Rapporteur: Menno van der Elst

Scope: Conditional renewal of the marketing authorisation

### **18.2.3. Larotrectinib - VITRAKVI (CAP) - EMEA/H/C/004919/R/0024 (without RMP)**

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Applicant: Bayer AG

PRAC Rapporteur: Rugile Pilviniene

Scope: Conditional renewal of the marketing authorisation

### **18.2.4. Tafasitamab - MINJUVI (CAP) - EMEA/H/C/005436/R/0003 (without RMP)**

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Applicant: Incyte Biosciences Distribution B.V.

PRAC Rapporteur: Annika Folin

Scope: Conditional renewal of the marketing authorisation

## **18.3. Renewals of the marketing authorisation**

### **18.3.1. Alectinib - ALECENSA (CAP) - EMEA/H/C/004164/R/0039 (without RMP)**

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Applicant: Roche Registration GmbH

PRAC Rapporteur: Jana Lukacisinova

Scope: 5-year renewal of the marketing authorisation

### **18.3.2. Buprenorphine, naloxone - ZUBSOLV (CAP) - EMEA/H/C/004407/R/0019 (without RMP)**

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Applicant: Accord Healthcare S.L.U.

PRAC Rapporteur: Martin Huber

Scope: 5-year renewal of the marketing authorisation

### **18.3.3. Fluticasone furoate, umeclidinium, vilanterol - ELEBRATO ELLIPTA (CAP) - EMEA/H/C/004781/R/0026 (with RMP)**

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Applicant: GlaxoSmithKline Trading Services Limited

PRAC Rapporteur: Annika Folin

Scope: 5-year renewal of the marketing authorisation

**18.3.4. Fluticasone furoate, umeclidinium, vilanterol - TRELEGY ELLIPTA (CAP) - EMEA/H/C/004363/R/0023 (with RMP)**

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Applicant: GlaxoSmithKline Trading Services Limited

PRAC Rapporteur: Annika Folin

Scope: 5-year renewal of the marketing authorisation

**18.3.5. Guselkumab - TREMFYA (CAP) - EMEA/H/C/004271/R/0033 (without RMP)**

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Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: 5-year renewal of the marketing authorisation

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

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Applicant: Instituto Grifols, S.A.

PRAC Rapporteur: Amelia Cupelli

Scope: 5-year renewal of the marketing authorisation

**18.3.7. Lutetium (<sup>177</sup>Lu) oxodotreotide - LUTATHERA (CAP) - EMEA/H/C/004123/R/0032 (without RMP)**

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Applicant: Advanced Accelerator Applications

PRAC Rapporteur: Adam Przybylkowski

Scope: 5-year renewal of the marketing authorisation

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

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Applicant: Mundipharma Corporation (Ireland) Limited

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: 5-year renewal of the marketing authorisation

**18.3.9. Niraparib - ZEJULA (CAP) - EMEA/H/C/004249/R/0034 (without RMP)**

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Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Jan Neuhauser

Scope: 5-year renewal of the marketing authorisation

**18.3.10. Ritonavir - RITONAVIR MYLAN (CAP) - EMEA/H/C/004549/R/0015 (without RMP)**

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Applicant: Mylan Pharmaceuticals Limited

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: 5-year renewal of the marketing authorisation

**18.3.11. Tacrolimus - TACFORIUS (CAP) - EMEA/H/C/004435/R/0010 (without RMP)**

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Applicant: Teva B.V.

PRAC Rapporteur: Ronan Grimes

Scope: 5-year renewal of the marketing authorisation

**18.3.12. Tivozanib - FOTIVDA (CAP) - EMEA/H/C/004131/R/0021 (without RMP)**

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Applicant: EUSA Pharma (Netherlands) B.V.

PRAC Rapporteur: Rugile Pilviniene

Scope: 5-year renewal of the marketing authorisation

**18.3.13. Trastuzumab - ONTRUZANT (CAP) - EMEA/H/C/004323/R/0040 (with RMP)**

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Applicant: Samsung Bioepis NL B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

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 May 2022 meeting.

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Sabine Straus	Chair	The Netherlands	No interests declared	Full involvement
Jan Neuhauser	Member	Austria	No interests declared	Full involvement
Sonja Hrabcik	Alternate	Austria	No interests declared	Full involvement
Jean-Michel Dogné	Member	Belgium	No interests declared	Full involvement
Maria Popova-Kiradjieva	Member	Bulgaria	No interests declared	Full involvement
Nikica Mirošević Skvrce	Member	Croatia	No interests declared	Full involvement
Željana Margan Koletić	Alternate	Croatia	No interests declared	Full involvement
Panagiotis Psaras	Alternate	Cyprus	No interests declared	Full involvement
Eva Jirsová	Member	Czechia	No interests declared	Full involvement
Anette Kirstine Stark	Member	Denmark	No interests declared	Full involvement
Marie Louise Schougaard Christiansen	Alternate	Denmark	No interests declared	Full involvement
Maia Uusküla	Member	Estonia	No interests declared	Full involvement
Krõõt Aab	Alternate	Estonia	No interests declared	Full involvement
Kirsti Villikka	Member	Finland	No interests declared	Full involvement
Kimmo Jaakkola	Alternate	Finland	No interests declared	Full involvement
Tiphaine Vaillant	Member	France	No interests declared	Full involvement
Nathalie Gault	Alternate	France	No interests declared	Full involvement
Martin Huber	Member (Vice-Chair)	Germany	No interests declared	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Brigitte Keller-Stanislawski	Alternate	Germany	No interests declared	Full involvement
Sofia Trantza	Member	Greece	No interest declared	Full involvement
Georgia Gkegka	Alternate	Greece	No interest declared	Full involvement
Julia Pallos	Member	Hungary	No participation in final deliberations and voting on:	<p>4.1.1. Apixaban – APIXABAN ACCORD (CAP), ELIQUIS (CAP)</p> <p>5.1.7. Relatlimab, nivolumab - EMEA/H/C/005481</p> <p>16.2.6. Thalidomide - THALIDOMIDE BMS (CAP); NAP - PSUSA/00002919/202110</p> <p>16.1.16. Idecabtagene vicleucel – ABECMA (CAP) – PSUSA/00010954/202109</p>
Guðrún Stefánsdóttir	Member	Iceland	No participation in final deliberations and voting on:	<p>16.1.22. Panitumumab - VECTIBIX (CAP) - PSUSA/00002283/202109</p> <p>16.2.1. Filgrastim - ACCOFIL (CAP), FILGRASTIM HEXAL (CAP), GRASTOFIL (CAP), NIVESTIM (CAP), RATIOGRASTIM (CAP), TEVAGRASTIM (CAP), ZARZIO (CAP); NAP - PSUSA/00001391/202109</p> <p>17.2.5. Darbepoetin alfa - ARANESP (CAP) - EMEA/H/C/000332/MEA 092.3</p>

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				17.4.2. Apremilast - OTEZLA (CAP) - EMEA/H/C/003746/II/0038  17.4.6. Talimogene laherparepvec - IMLYGIC (CAP) - EMEA/H/C/002771/II/0051
Rhea Fitzgerald	Member	Ireland	No interests declared	Full involvement
Amelia Cupelli	Member	Italy	No interests declared	Full involvement
Ilaria Baldelli	Alternate	Italy	No interests declared	Full involvement
Zane Neikena	Member	Latvia	No interests declared	Full involvement
Rugile Pilviniene	Member	Lithuania	No interests declared	Full involvement
Lina Seibokiene	Alternate	Lithuania	No participation in discussion, final deliberations and voting on:	17.3.2. Rivaroxaban – XARELTO (CAP) - EMEA/H/C/PSR/S/0027
Anne-Cécile Vuillemin	Alternate	Luxembourg	No interests declared	Full involvement
John Joseph Borg	Member	Malta	No interests declared	Full involvement
Menno van der Elst	Member	The Netherlands	No interests declared	Full involvement
Liana Gross-Martirosyan	Alternate	The Netherlands	No interests declared	Full involvement
David Olsen	Member	Norway	No participation in final deliberations and voting on:	16.1.25. Riociguat - ADEMPAS (CAP) - PSUSA/00010174/202109  17.3.2. Rivaroxaban – XARELTO (CAP) - EMEA/H/C/PSR/S/0027  17.5.3.

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				Damoctocog alfa pegol - JIVI (CAP) - EMEA/H/C/004054/MEA 003.3  18.2.3. Larotrectinib - VITRAKVI (CAP) - EMEA/H/C/004919/R/0024 (without RMP)
Karen Pernille Harg	Alternate	Norway	No interests declared	Full involvement
Adam Przybylkowski	Member	Poland	No interests declared	Full involvement
Katarzyna Ziolkowska	Alternate	Poland	No interests declared	Full involvement
Ana Diniz Martins	Member	Portugal	No interests declared	Full involvement
Marcia Sofia Sanches de Castro Lopes Silva	Alternate	Portugal	No interests declared	Full involvement
Roxana Dondera	Member	Romania	No interests declared	Full involvement
Alexandra - Maria Spurni	Alternate	Romania	No interests declared	Full involvement
Marek Juracka	Member	Slovakia	No interests declared	Full involvement
Anna Mareková	Alternate	Slovakia	No interests declared	Full involvement
Polona Golmajer	Member	Slovenia	No interests declared	Full involvement
Eva Segovia	Member	Spain	No interests declared	Full involvement
Maria del Pilar Rayon	Alternate	Spain	No interests declared	Full involvement
Ulla Wändel Liminga	Member	Sweden	No interests declared	Full involvement
Annika Folin	Alternate	Sweden	No interests declared	Full involvement
Annalisa Capuano	Member	Independent scientific expert	No interests declared	Full involvement
Milou Daniel Drici	Member	Independent scientific expert	No interests declared	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Maria Teresa Herdeiro	Member	Independent scientific expert	No interests declared	Full involvement
Patricia McGettigan	Member	Independent scientific expert	No interests declared	Full involvement
Daniel Morales	Member	Independent scientific expert	No interests declared	Full involvement
Hedvig Nordeng	Member	Independent scientific expert	No interests declared	Full involvement
Roberto Frontini	Member	Healthcare Professionals' Representative	No restrictions applicable to the meeting	Full involvement
Christelle Bizimungu	Expert	Belgium	No restrictions applicable to this meeting	Full involvement
Laurence de Fays	Expert	Belgium	No interests declared	Full involvement
Hanna Belcik Christensen	Expert	Denmark	No restrictions applicable to this meeting	Full involvement
Julia Maslovskaja	Expert	Estonia	No interests declared	Full involvement
Helve Vestman	Expert	Estonia	No interests declared	Full involvement
Samuel Crommelynck	Expert	France	No restrictions applicable to this meeting	Full involvement
Vincent Gazin	Expert	France	No interests declared	Full involvement
Marie-Caroline Pesquidous	Expert	France	No restrictions applicable to this meeting	Full involvement
Youssef Shaim	Expert	France	No restrictions applicable to this meeting	Full involvement
Faustine Vidil	Expert	France	No interests declared	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Nicole Bick	Expert	Germany	No interests declared	Full involvement
Dennis Lex	Expert	Germany	No restrictions applicable to this meeting	Full involvement
Eleanor Carey	Expert	Ireland	No restrictions applicable to this meeting	Full involvement
Eamon O'Murchu	Expert	Ireland	No interests declared	Full involvement
Liene Luce	Expert	Latvia	No interests declared	Full involvement
Ieva Rutkovska	Expert	Latvia	No interests declared	Full involvement
Lisa Heltzel	Expert	The Netherlands	No interests declared	Full involvement
Fernanda Inês Carvalho Pereira Ribeiro Vaz	Expert	Portugal	No interests declared	Full involvement
Carla Torre	Expert	Portugal	No restrictions applicable to this meeting	Full involvement
Consuelo Mejías Pavón	Expert	Spain	No interests declared	Full involvement
Charlotte Backman	Expert	Sweden	No interests declared	Full involvement

A representative from the European Commission attended the meeting

Meeting run with support from relevant EMA staff

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

## 20. Annex III - List of acronyms and abbreviations

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

[Home>Committees>PRAC>Agendas, minutes and highlights](#)

## 21. Explanatory notes

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

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

(Items 2 and 3 of the PRAC minutes)

A referral is a procedure used to resolve issues such as concerns over the safety or benefit-risk balance of a medicine or a class of medicines. In a referral, EMA is requested to conduct a scientific assessment of a particular medicine or class of medicines on behalf of the European Union (EU). For further detailed information on safety related referrals please see:

[http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general\\_content\\_000150.jsp&mid=WC0b01ac05800240d0](http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000150.jsp&mid=WC0b01ac05800240d0)

### **Signals assessment and prioritisation**

(Item 4 of the PRAC minutes)

A safety signal is information on a new or incompletely documented adverse event that is potentially caused by a medicine and that warrants further investigation. Signals are generated from several sources such as spontaneous reports, clinical studies and the scientific literature. The evaluation of safety signals is a routine part of pharmacovigilance and is essential to ensuring that regulatory authorities have a comprehensive knowledge of a medicine's benefits and risks.

The presence of a safety signal does not mean that a medicine has caused the reported adverse event. The adverse event could be a symptom of another illness or caused by another medicine taken by the patient. The evaluation of safety signals is required to establish whether or not there is a causal relationship between the medicine and the reported adverse event.

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

### **Risk Management Plans (RMPs)**

(Item 5 of the PRAC minutes)

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

### **Assessment of Periodic Safety Update Reports (PSURs)**

(Item 6 of the PRAC minutes)

A PSUR is a report providing an evaluation of the benefit-risk balance of a medicine, which is submitted by marketing authorisation holders at defined time points following a medicine's authorisation.

PSURs summarises data on the benefits and risks of a medicine and includes the results of all studies carried out with this medicine (in the authorised and unauthorised indications).

### **Post-authorisation Safety Studies (PASS)**

(Item 7 of the PRAC minutes)

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

### **Product related pharmacovigilance inspections**

(Item 9 of the PRAC minutes)

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

More detailed information on the above terms can be found on the EMA website:

<https://www.ema.europa.eu/en>