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SCIENCE MEDICINES HEALTH

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Human Medicines Division

## Pharmacovigilance Risk Assessment Committee (PRAC) Minutes of the meeting on 25-28 October 2021

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 ongoing 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 outbreak) 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<sup>1</sup> 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 (see Annex II – List of participants).

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 unanimously, unless otherwise specified.

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

### 1.2. Agenda of the meeting on 25-28 October 2021

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

### 1.3. Minutes of the previous meeting on 27-30 September 2021

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 27-30 September 2021 were published on the EMA website on 21 July 2022 ([EMA/PRAC/244588/2022](#)).

## 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. Amfepramone (NAP) - EMEA/H/A-31/1501

Applicant(s): Artogodan GmbH, Temmler Pharma GmbH

PRAC Rapporteur: Anette Kirstine Stark; PRAC Co-rapporteur: Eva Jirsová

Scope: Review of the benefit-risk balance following notification by Romania 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 amfepramone-containing products reviewing the benefit-risk balance, in light of the known serious safety concerns related to the therapeutic class of anorexigens, the reported cases of cardiac-related adverse drug reactions, cases of pulmonary hypertension, and the off-label use despite the risk minimisation measures in place, and taking into account the uncertainties as to clinical relevance of this treatment. For further background, see [PRAC minutes February 2021](#), [PRAC minutes July 2021](#) and [PRAC minutes October 2021](#)<sup>2</sup>.

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

- PRAC received feedback from the ad-hoc expert group (AHEG) meeting held on 11 October 2021.
- PRAC discussed the joint assessment report issued by the Rapporteurs.
- PRAC adopted a second list of outstanding issues (LoOI), to be addressed by the MAHs in accordance with a revised timetable (EMA/PRAC/648171/2022 Rev.3).

### 3.3. Procedures for finalisation

None

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<sup>2</sup> Held 27-30 September 2021

### 3.4. Re-examination procedures<sup>3</sup>

None

### 3.5. Others

None

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

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

See also Annex I 14.1.

#### 4.1.1. Coronavirus (COVID-19) mRNA<sup>5</sup> vaccine (nucleoside-modified) - SPIKEVAX (CAP)

Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Hans Christian Siersted

Scope: Signal of capillary leak syndrome

EPITT 19743 – New signal

Lead Member State(s): DK

#### Background

COVID-19 nucleoside-modified messenger ribonucleic acid (mRNA) vaccine is indicated, as Spikevax, for active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 12 years of age and older.

During routine signal detection activities, a signal of capillary leak syndrome (CLS) was identified by Italy based on four cases retrieved from the Italian pharmacovigilance network database. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

#### Discussion

Having considered the available evidence from the ongoing monitoring of CLS in monthly summary safety reports (MSSR) for Spikevax (COVID-19 mRNA vaccine (nucleoside-modified)) and the new cases from the Italian pharmacovigilance network database, PRAC agreed that further evaluation on the signal of CLS and vaccination with Spikevax (COVID-19 mRNA vaccine (nucleoside-modified)) is warranted.

#### Summary of recommendation(s)

- The MAH should submit to EMA, within 30 days, a detailed review of cases of CLS, including a discussion on cases with a medical history of CLS together with a discussion

<sup>3</sup> Re-examination of PRAC recommendation under Article 32 of Directive 2001/83/EC

<sup>4</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>5</sup> Messenger ribonucleic acid

on the possible causal relationship between vaccination and flare-up, as well as a discussion on the pathophysiology of CLS and consideration on a possible biological plausibility associating the vaccine with development of CLS (new onset) or CLS flare up. Based on the review, the MAH should propose precautionary measures as warranted including an update of the product information and/or the RMP as applicable.

- A 30 day-timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

## 4.2. New signals detected from other sources

### 4.2.1. Olmesartan (NAP)

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Applicant(s): various

PRAC Rapporteur: Martin Huber

Scope: Signal of autoimmune hepatitis

EPITT 19258 – Related to December 2018<sup>6</sup>

Lead Member State(s): DE

#### **Background**

Olmesartan is a long-acting selective angiotensin receptor blocker (ARB) indicated for the treatment of hypertension under certain conditions.

In relation to a recommendation for olmesartan dated December 2018 on a signal of autoimmune hepatitis, four new well-documented literature cases were assessed taking into account the previously two literature cases discussed in 2018. Germany as Lead Member State (LMS) confirmed the signal needed further analysis and prioritisation by PRAC. For further background, see [PRAC minutes December 2018](#)<sup>7</sup>.

#### **Discussion**

Based on the well-documented cases confirmed by biopsy and characterised by positive dechallenge, PRAC agreed that a causal association between drug-induced autoimmune hepatitis and the use of olmesartan is a reasonable possibility. In addition, PRAC considered that this signal is also relevant for olmesartan-fixed dose combinations, namely olmesartan/amlodipine, olmesartan/hydrochlorothiazide and olmesartan/amlodipine/hydrochlorothiazide.

PRAC appointed Martin Huber as Rapporteur for the signal.

#### **Summary of recommendation(s)**

- The MAHs for olmesartan-, olmesartan/amlodipine-, olmesartan/hydrochlorothiazide- and olmesartan/amlodipine/hydrochlorothiazide-containing products should submit to EMA, within 7 days, comments on a proposed wording to update the product information with autoimmune hepatitis.
- A 21 day-timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

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<sup>6</sup> Held 26-29 November 2018

<sup>7</sup> Held 26-29 November 2018



## 4.3. Signals follow-up and prioritisation

### 4.3.1. Adalimumab - AMGEVITA (CAP); AMSPARITY (CAP); HEFIYA (CAP); HULIO (CAP); HUMIRA (CAP) - EMEA/H/C/000481/SDA/124; HYRIMOZ (CAP); IDACIO (CAP); IMRALDI (CAP); YUFLYMA (CAP)

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Applicant(s): AbbVie Deutschland GmbH & Co. KG (Humira), Amgen Europe B.V. (Amgevita), Celltrion Healthcare Hungary Kft. (Yuflyma), Fresenius Kabi Deutschland GmbH (Idacio), Mylan S.A.S (Hulio), Pfizer Europe MA EEIG (Amsparity), Samsung Bioepis NL B.V. (Imraldi), Sandoz GmbH (Hefiya, Hyrimoz)

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of acquired haemophilia

EPITT 19688 – Follow-up to June 2021

#### Background

For background information, see [PRAC minutes June 2021](#).

The MAH of Humira (adalimumab), the originator medicinal product containing adalimumab, replied to the request for information on the signal of acquired haemophilia and the responses were assessed by the Rapporteur.

#### Discussion

Having considered the available data from clinical trials, post-marketing setting, the literature, the cumulative review submitted by the MAH together with the Rapporteur's assessment, PRAC considered that given the important exposure to adalimumab and the very few cases identified, there is insufficient evidence to establish a causal association between adalimumab and acquired haemophilia at this stage.

#### Summary of recommendation(s)

- The MAHs of adalimumab-containing products should continue to monitor cases of acquired haemophilia as part of routine safety surveillance.

### 4.3.2. Coronavirus (COVID-19) mRNA<sup>8</sup> vaccine (nucleoside-modified) - COMIRNATY (CAP)

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Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Signal of myocarditis and pericarditis

EPITT 19712 – Follow-up to October 2021<sup>9</sup>

#### Background

For background information, see [PRAC minutes October 2021](#)<sup>10</sup>.

The Rapporteur performed an evaluation of the preliminary report of the study entitled: 'SARS-CoV-2 vaccination and risk of pericarditis and myocarditis: Nordic nationwide cohort study of 20 million individuals' consisting in a meta-analysis of data from Denmark, Finland,

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<sup>8</sup> Messenger ribonucleic acid

<sup>9</sup> Held 27-30 September 2021

<sup>10</sup> Held 27-30 September 2021

Norway and Sweden, taking into account an updated observed to expected (O/E) analysis based on EudraVigilance.

### **Discussion**

Considering the current EU product information of Comirnaty (COVID-19 mRNA vaccine (nucleoside-modified)), data from the preliminary study results on the known risk of myocarditis and pericarditis and the Rapporteur's assessment, PRAC agreed that the MAH of Comirnaty (COVID-19 mRNA vaccine (nucleoside-modified)) should provide a further review from clinical studies, scientific literature and other data available in public domain.

### **Summary of recommendation(s)**

- The MAH for Comirnaty (COVID-19 mRNA vaccine (nucleoside-modified)) should submit to EMA, within 15 days, a detailed review from clinical studies, scientific literature and other data available in the public domain. The MAH should include a risk estimation of myocarditis and pericarditis overall and per age group, gender and vaccine dose(s). In addition, the MAH should perform further characterisation of myocarditis and pericarditis including an estimation of the incidence of myocarditis and pericarditis, a discussion on any plausible pathophysiological mechanism(s) of myocarditis and pericarditis observed after vaccination with Comirnaty (COVID-19 mRNA vaccine (nucleoside-modified)) and data on characteristics, severity, duration and outcome of myocarditis and pericarditis after vaccination with the vaccine.

#### **4.3.3. Coronavirus (COVID-19) mRNA<sup>11</sup> vaccine (nucleoside-modified) - SPIKEVAX (CAP)**

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Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Hans Christian Siersted

Scope: Signal of myocarditis and pericarditis

EPITT 19713 – Follow-up to October 2021

### **Background**

For background information, see [PRAC minutes October 2021](#)<sup>12</sup>.

The Rapporteur performed an evaluation of the preliminary report of the study entitled: 'SARS-CoV-2 vaccination and risk of pericarditis and myocarditis: Nordic nationwide cohort study of 20 million individuals' consisting in a meta-analysis of data from Denmark, Finland, Norway and Sweden, taking into account an updated observed to expected (O/E) analysis based on EudraVigilance.

### **Discussion**

Having considered the new data from the preliminary study results on the known risk of myocarditis and pericarditis, PRAC agreed to perform an in-depth evaluation of the preliminary report.

Considering the current EU product information of Spikevax (COVID-19 mRNA vaccine (nucleoside-modified)), data from the preliminary study results on the known risk of myocarditis and pericarditis and the Rapporteur's assessment, PRAC agreed that the MAH of

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<sup>11</sup> Messenger ribonucleic acid

<sup>12</sup> Held 27-30 September 2021

Spikevax (COVID-19 mRNA vaccine (nucleoside-modified)) should provide a further review from clinical studies, scientific literature and other data available in public domain.

#### **Summary of recommendation(s)**

- The MAH for Spikevax (COVID-19 mRNA vaccine (nucleoside-modified)) should submit to EMA, within 15 days, a detailed review from clinical studies, scientific literature and other data available in the public domain. The MAH should include a risk estimation of myocarditis and pericarditis overall and per age group, gender and vaccine dose(s). In addition, the MAH should perform further characterisation of myocarditis and pericarditis including an estimation of the incidence of myocarditis and pericarditis, a discussion on any plausible pathophysiological mechanism(s) of myocarditis and pericarditis observed after vaccination with Spikevax (COVID-19 mRNA vaccine (nucleoside-modified)) and data on characteristics, severity, duration and outcome of myocarditis and pericarditis after vaccination with the vaccine.

#### **4.3.4. Coronavirus (COVID-19) mRNA<sup>13</sup> vaccine (nucleoside-modified) - COMIRNATY (CAP) – EMEA/H/C/005735/SDA/038, SPIKEVAX (CAP) - EMEA/H/C/005791/SDA/044; coronavirus (COVID-19) vaccine (Ad26.COV2-S, recombinant) - COVID-19 VACCINE JANSSEN (CAP) – EMEA/H/C/005737/SDA/031; coronavirus (COVID-19) vaccine (ChAdOx1-S [recombinant]) - VAXZEVRIA (CAP) - EMEA/H/C/005675/SDA/088**

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Applicant(s): AstraZeneca AB (Vaxzevria), BioNTech Manufacturing GmbH (Comirnaty), Janssen-Cilag International N.V. (Covid-19 vaccine Janssen), Moderna Biotech Spain, S.L. (Spikevax)

PRAC Rapporteur (lead): Menno van der Elst

Scope: Signal of multisystem inflammatory syndrome

EPITT 19732 – Follow-up to September 2021<sup>14</sup>

#### **Background**

For background information, see [PRAC minutes September 2021](#).

The MAHs replied to the request for information on the signal of multisystem inflammatory syndrome (MIS) and the responses were assessed by the Rapporteur.

#### **Discussion**

Having considered the available data from the cumulative reviews submitted by the MAHs together with the Rapporteur's assessment, PRAC agreed that there is insufficient evidence to support a causal association between COVID-19 vaccines and MIS at this stage.

#### **Summary of recommendation(s)**

- The MAHs for Comirnaty (COVID-19 mRNA vaccine (nucleoside-modified)), Spikevax (COVID-19 mRNA vaccine (nucleoside-modified)), COVID-19 vaccine Janssen (COVID-19 vaccine (Ad26.COV2-S [recombinant])) and Vaxzevria (COVID-19 vaccine (ChAdOx1-S [recombinant])) should continue to closely monitor cases of MIS.

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<sup>13</sup> Messenger ribonucleic acid

<sup>14</sup> Held 14 October 2021

- The MAHs should implement a dedicated questionnaire to retrieve an appropriate level of information to facilitate the assessment of cases of suspected MIS.
- In the next monthly summary safety reports (MSSRs) and PSURs, MAHs should report any cases of MIS together with information on prior or current severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, laboratory markers of inflammation, measures of disease activity, duration of fever and information excluding differential diagnoses.

#### 4.3.5. Ertapenem - INVANZ (CAP) - EMEA/H/C/000389/SDA/026; NAP

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Applicant(s): Merck Sharp & Dohme B.V., various

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Signal of toxic encephalopathy in patients with renal impairment

EPITT 19498 – Follow-up to July 2021

##### **Background**

For background information, see [PRAC minutes July 2021](#).

The MAH for Invanz (ertapenem) replied to the request for information on the signal of toxic encephalopathy in patients with renal impairment and the responses were assessed by the Rapporteur.

##### **Discussion**

Based on the available evidence ascertained from EudraVigilance and the literature, the review submitted by the MAH together with the Rapporteur's assessment, PRAC considered that there is a reasonable possibility of causality concerning events of encephalopathy in association with ertapenem and that recovery in patients with renal impairment may be prolonged. Therefore, PRAC agreed that an update of the product information is warranted to add encephalopathy as a warning and as an undesirable effect with a frequency 'not known'.

##### **Summary of recommendation(s)**

- The MAHs for ertapenem-containing products should submit to EMA or relevant National Competent Authorities (NCAs) of the EU Member States as applicable, within 60 days, a variation to amend<sup>15</sup> the product information with encephalopathy.
- In the next PSUR, the MAH for Invanz (ertapenem) should include a cumulative review of cases of peripheral neuropathy.

For the full PRAC recommendation, see [EMA/PRAC/605613/2021 Corr](#) published on 10 December 2021 on the EMA website.

#### 4.3.6. Ibrutinib - IMBRUVICA (CAP)

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Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Signal of sudden death/cardiac death with ibrutinib and concomitant angiotensin-

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<sup>15</sup> Update of SmPC sections 4.4 and 4.8

converting enzyme (ACE) inhibitors<sup>16</sup> from a clinical trial<sup>17</sup>

EPITT 19726 – Follow-up to September 2021<sup>18</sup>

### **Background**

For background information, see [PRAC minutes September 2021](#).

The MAH replied to the request for information on the signal of sudden death/cardiac death with ibrutinib and concomitant angiotensin-converting enzyme (ACE) inhibitors<sup>19</sup> from the FLAIR study<sup>20</sup> and the responses were assessed by the Rapporteur.

### **Discussion**

Having considered the available evidence from the review submitted by the MAH together with the Rapporteur's assessment, PRAC agreed that the risk of sudden or cardiac death associated with ibrutinib and the concomitant use of ACE inhibitors does not seem to be plausible, and hence, there is insufficient evidence to establish a causal association at this stage.

### **Summary of recommendation(s)**

- The MAHs of Imbruvica (ibrutinib) should continue to monitor cases of sudden death/cardiac death with ibrutinib and concomitant ACE inhibitors as part of routine safety surveillance.

## **4.3.7. Labetalol (NAP)**

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Applicant(s): various

PRAC Rapporteur: Karen Pernille Harg

Scope: Signal of nipple pain and suppressed lactation

EPITT 19639 – Follow-up to May 2021

### **Background**

For background information, see [PRAC minutes May 2021](#).

The MAH Aspen Pharma replied to the further request for information on the signal of nipple pain and suppressed lactation and the responses were assessed by the Rapporteur.

### **Discussion**

Having considered the available evidence in databases including EudraVigilance, the literature, data submitted by the MAH together with the Rapporteur's assessment, PRAC agreed that there is sufficient evidence to establish a causal association between labetalol and nipple pain and Raynaud's phenomenon of the nipple. Therefore, PRAC agreed that an update of the product information is warranted to add nipple pain and Raynaud's phenomenon of the nipple as an undesirable effect with a frequency 'not known'. In addition,

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<sup>16</sup> Benazepril, captopril, cilazapril, enalapril, enalaprilat, fosinopril, imidapril, lisinopril, perindopril, quinapril, ramipril, trandolapril, zofenopril and combinations

<sup>17</sup> Study 2013-001944-76 (FLAIR): a phase 3 study evaluating first-line treatment with ibrutinib+rituximab versus fludarabine, cyclophosphamide and rituximab in patients with chronic lymphocytic leukaemia who are up to 75 years of age

<sup>18</sup> Held 30 August-02 September 2021

<sup>19</sup> Benazepril, captopril, cilazapril, enalapril, enalaprilat, fosinopril, imidapril, lisinopril, perindopril, quinapril, ramipril, trandolapril, zofenopril and combinations

<sup>20</sup> Study 2013-001944-76 (FLAIR): a phase 3 study evaluating first-line treatment with ibrutinib+rituximab versus fludarabine, cyclophosphamide and rituximab in patients with chronic lymphocytic leukaemia who are up to 75 years of age

PRAC agreed that the assessed data on suppressed lactation are not sufficiently strong to warrant changes to the product information at this stage.

#### **Summary of recommendation(s)**

- The MAHs for labetalol-containing products should submit to relevant National Competent Authorities (NCAs) of the EU Member States, within 60 days, a variation to amend<sup>21</sup> the product information with nipple pain and Raynaud's phenomenon of the nipple.
- The MAHs should continue to monitor cases of suppressed lactation as part of routine safety surveillance.

For the full PRAC recommendation, see [EMA/PRAC/605613/2021 Corr](#) published on 10 December 2021 on the EMA website.

#### **4.3.8. Lenvatinib – KISPLYX (CAP) - EMEA/H/C/004224/SDA/016; LENVIMA (CAP) - EMEA/H/C/003727/SDA/018**

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Applicant(s): Eisai GmbH

PRAC Rapporteur: Annika Folin

Scope: Signal of colitis

EPITT 19691 – Follow-up to June 2021

#### **Background**

For background information, see [PRAC minutes June 2021](#).

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

#### **Discussion**

Having considered the available data from non-clinical and clinical studies, literature and EudraVigilance, the review submitted by the MAH together with the Rapporteur's assessment, and taking also into account the plausible biological mechanism, PRAC agreed that there is sufficient evidence for a causal association between lenvatinib and colitis. Therefore, PRAC agreed that an update of the product information is warranted to add colitis as an undesirable effect with a frequency 'uncommon'.

#### **Summary of recommendation(s)**

- The MAH for Kisplyx and Lenvima (lenvatinib) should submit to EMA, within 60 days, a variation to amend<sup>22</sup> the product information.

For the full PRAC recommendation, see [EMA/PRAC/605613/2021](#) published on 22 November 2021 on the EMA website.

#### **4.3.9. Propylthiouracil (NAP)**

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Applicant(s): various

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<sup>21</sup> Update of SmPC section 4.8. The package leaflet is to be updated accordingly

<sup>22</sup> Update of SmPC section 4.8. The package leaflet is to be updated accordingly

PRAC Rapporteur: Krõõt Aab

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

EPITT 19692 – Follow-up to July 2021

### **Background**

For background information, see [PRAC minutes July 2021](#).

The MAHs for propylthiouracil-containing products replied to the request for information on the signal of drug reaction with eosinophilia and systemic symptoms (DRESS) and the responses were assessed by the Rapporteur.

### **Discussion**

Having considered the available data from EudraVigilance, the literature, reviews submitted by the MAHs together with the Rapporteur's assessment, PRAC agreed that there is insufficient evidence at this stage to conclude on a causal relationship between DRESS and propylthiouracil.

### **Summary of recommendation(s)**

- The MAHs of propylthiouracil-containing products should continue to monitor cases of DRESS as part of routine safety surveillance.

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

See also Annex I 14.4.

### **4.4.1. Everolimus - AFINITOR (CAP) - EMEA/H/C/001038/II/0076**

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Applicant: Novartis Europharm Limited

PRAC Rapporteur: Martin Huber

Scope: Update of section 4.8 of the SmPC to include lymphoedema as an adverse drug reaction based on post-marketing data and related to the outcome of a signal procedure (EPITT 18197) adopted in February 2015. 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.

In relation to a recommendation dated February 2015 on a signal of lymphoedema (EPITT 18197) and a PSUR single assessment (PSUSA) procedure concluded in October 2015, the MAH submitted a variation based on a literature article by *Halamkova et al.*<sup>23</sup> to update the product information regarding lymphoedema. PRAC is responsible for adopting an outcome based on the assessment report from the PRAC Rapporteur, to be further considered at the level of CHMP, responsible for adopting an opinion on this variation. For further background, see [PRAC minutes February 2015](#) and [PRAC minutes October 2015](#).

### **Summary of outcome(s)**

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<sup>23</sup> Halamkova et al. Everolimus-related unilateral abdominal lymphedema in a renal cancer patient: A case report. *Medicine (Baltimore)*.2020;99(42):e22634

- Based on the available data and the Rapporteur's assessment, PRAC supported the update<sup>24</sup> to the product information<sup>25</sup> to add lymphoedema as an undesirable effect with a frequency 'common'.

## 5. Risk management plans (RMPs)

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

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

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

See also Annex I 15.1.

#### 5.1.1. [Betulae cortex dry extract \(5-10 : 1\); extraction solvent: n-heptane 95% \(w/w\) - EMEA/H/C/005035, Orphan](#)

Applicant: Amryt Pharmaceuticals DAC

Scope: Treatment to achieve accelerated healing of wounds associated with dystrophic and junctional epidermolysis bullosa (EB) in patients from birth onwards

#### 5.1.2. [Coronavirus \(COVID-19\) vaccine \(recombinant, adjuvanted\) \(NVX-CoV2373\) - EMEA/H/C/005808](#)

Scope: Prevention of coronavirus disease-2019 (COVID-19)

#### 5.1.3. [Dengue tetravalent vaccine \(live, attenuated\) - EMEA/H/W/005362](#)

Scope (accelerated assessment): Prevention of dengue disease

#### 5.1.4. [Dengue tetravalent vaccine \(live, attenuated\) - EMEA/H/C/005155](#)

Scope (accelerated assessment): Prevention of dengue disease

#### 5.1.5. [Pneumococcal polysaccharide conjugate vaccine \(20-valent, adsorbed\) - EMEA/H/C/005451](#)

Scope: Prevention of invasive disease and pneumonia caused by *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F and 33F

#### 5.1.6. [Regdanvimab - EMEA/H/C/005854](#)

Scope: Treatment of coronavirus disease-2019 (COVID-19) caused by severe acute

<sup>24</sup> Update of SmPC sections 4.3, 4.4 and 4.8. The package leaflet is updated accordingly

<sup>25</sup> Update of SmPC section 4.8. The package leaflet is updated accordingly



respiratory syndrome coronavirus 2 (SARS-CoV-2)

#### 5.1.7. Rimegepant - EMEA/H/C/005725

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Scope: Management of migraine

#### 5.1.8. Somatrogen - EMEA/H/C/005633, Orphan

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Applicant: Pfizer Europe MA EEIG

Scope: Long-term treatment of paediatric patients with growth disturbance due to insufficient secretion of growth hormone

#### 5.1.9. Tebentafusp - EMEA/H/C/004929, Orphan

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Applicant: Immunocore Ireland Limited

Scope (accelerated assessment): Treatment of uveal melanoma

#### 5.1.10. Valoctocogene roxaparvovec - EMEA/H/C/005830, Orphan

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Applicant: BioMarin International Limited, ATMP

Scope (accelerated assessment): Treatment of severe haemophilia A

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

See also Annex I 15.2.

#### 5.2.1. Aflibercept - EYLEA (CAP) - EMEA/H/C/002392/II/0075

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Applicant: Bayer AG

PRAC Rapporteur: Nathalie Gault

Scope: Submission of an updated RMP (version 30.1) to include a follow-up questionnaire on intraocular pressure (IOP) increase and timing of IOP increase report submission. In addition, the MAH proposed to simplify the educational material consisting of a prescriber guide and injection video based on collected data and following consultation with a panel of ophthalmologists, as per the conclusions of variation II/0068 concluded in March 2021

#### Background

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

PRAC is evaluating a type II variation procedure for Eylea, a centrally authorised medicine containing aflibercept, to update the RMP to include a follow-up questionnaire on intraocular pressure (IOP) increase and to propose a simplification of the educational material consisting of a prescriber guide and injection video based on collected data and following consultation with a panel of ophthalmologists, as requested in the conclusions of variation II/0068 concluded in March 2021. For further background, see [PRAC minutes March 2021](#) and [PRAC minutes September 2021](#).

## Summary of advice

- The RMP version 30.3 for Eylea (afibercept) in the context of the variation procedure under evaluation by PRAC is acceptable.
- PRAC supported the shortened list of safety concerns in line with revision 2 of GVP module V on 'Risk management systems', by removing important identified and potential risks that do not need any further characterisation nor any additional risk minimisation measures. Nevertheless, these safety concerns will continue to be monitored in future PSURs. PRAC also supported the revised prescriber guide and prescriber video. Moreover, PRAC agreed that key elements on breastfeeding were not necessary and should not be included in the list of safety concerns nor in the educational material. As a result, Annex II-D on 'Conditions or restrictions with regard to the safe and effective use of the medicinal product' was updated accordingly.

### 5.2.2. Pregabalin - LYRICA (CAP) - EMEA/H/C/000546/WS1919/0109; PREGABALIN PFIZER (CAP) - EMEA/H/C/003880/WS1919/0038

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Applicant: Upjohn EESV

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Submission of an updated RMP (version 13.2) to include results from recently completed PASS, namely: 1) study A0081359: a population-based cohort study of pregabalin to characterize pregnancy outcomes; 2) study A0081106: a 12-month open-label study to evaluate the safety and tolerability of pregabalin as adjunctive therapy in paediatric subjects 1 month to 16 years of age with partial onset seizures and paediatric and adult subjects 5 to 65 years of age with primary generalized tonic-clonic seizures; 3) study A0081042: a double-blind, placebo-controlled, parallel-group, multicentre study of the efficacy and safety of pregabalin as adjunctive therapy in children 1 month through <4 years of age with partial onset seizures; 4) study A0081105: a randomized, double-blind, placebo-controlled, parallel group, multicentre trial of pregabalin as adjunctive therapy in paediatric and adult subjects with primary generalized tonic-clonic seizures. In addition, information on study A0081096: a prospective randomized 12-week controlled study of visual field change in subjects with partial seizures receiving pregabalin or placebo has been updated as well as study A0081365: a phase 4, randomised, double-blind, double-dummy, placebo- and active-controlled, single-dose, six-way crossover study to evaluate the potential for abuse with pregabalin. In light of the results from the pregnancy outcomes study (study A0081359), section 4.6 of the SmPC is updated on the risks of pregabalin treatment during pregnancy. In addition, section 4.4 of the SmPC is updated to highlight that pregabalin should not be used during pregnancy unless clearly necessary and women of childbearing potential use effective contraception

## Background

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

PRAC is evaluating a worksharing type II variation procedure for Lyrica and Pregabalin Pfizer, centrally authorised medicines containing pregabalin, to update the RMP to reflect the introduction of results from recently completed PASS studies and evaluate results from non-interventional studies, such as the population-based cohort study of pregabalin to

characterize pregnancy outcomes part of the current procedure ('pregabalin pregnancy outcomes study'). PRAC is responsible for adopting an outcome based on the assessment report from the PRAC Rapporteur, to be further considered at the level of CHMP, responsible for adopting an opinion on this variation. For further background, see [PRAC minutes October 2020](#)<sup>26</sup> and [PRAC minutes June 2021](#).

#### **Summary of advice**

- The RMP for Lyrica and Pregabalin Pfizer (pregabalin) in the context of the variation procedure under evaluation by PRAC could be considered acceptable provided that an update to RMP version 13.2 is submitted at the next regulatory opportunity.
- Based on the study data assessed, PRAC supported the updates to the product information<sup>27</sup> to add a warning on women of childbearing potential/contraception to state that in the first trimester of pregnancy pregabalin may cause major birth defects in the unborn child, In addition, the product information is amended to include that women of childbearing potential have to use effective contraception during treatment and that pregabalin has been shown to cross the placenta in rats and may cross the human placenta.

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

See also Annex I 15.3.

#### **5.3.1. Coronavirus (COVID-19) mRNA<sup>28</sup> vaccine (nucleoside-modified) - COMIRNATY (CAP) - EMEA/H/C/005735/X/77**

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Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Extension application to add a new strength (0.1 mg/mL) indicated for children from 5 to 11 years of age. The RMP (version 3.0) is updated accordingly

#### **Background**

Nucleoside-modified messenger ribonucleic acid (mRNA) vaccine is indicated, as Comirnaty, for active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in people aged 12 years and older.

CHMP is evaluating an extension application (line extension) for Comirnaty, a centrally authorised vaccine as a COVID-19 mRNA<sup>29</sup> vaccine to add a new strength for children from 5 to 11 years of age. At an extraordinary meeting convened remotely on 23 November 2021, PRAC reviewed the risk management plan (RMP) submitted within this procedure. PRAC is responsible for providing advice to CHMP on the necessary updates to the RMP to support the procedure.

#### **Summary of advice**

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<sup>26</sup> Held 28 September - 01 October 2020

<sup>27</sup> Update of SmPC sections 4.4 and 4.6. The package leaflet is updated accordingly

<sup>28</sup> Messenger ribonucleic acid

<sup>29</sup> Messenger ribonucleic acid

- The RMP version 3.0 for Comirnaty (nucleoside-modified mRNA vaccine) under evaluation by PRAC in the context of the extension application procedure is considered acceptable.
- PRAC considered that that the proposed post-authorisation pharmacovigilance plan is sufficient to identify and characterise the risks of the medicinal product. PRAC also considered that routine risk minimisation measures are sufficient to minimise the risks of the medicinal product in the proposed indication(s) in light of the current knowledge.

## 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. Avelumab - BAVENCIO (CAP) - PSUSA/00010635/202103

Applicant: Merck Europe B.V.

PRAC Rapporteur: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

#### Background

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

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Bavencio, a centrally authorised medicine containing avelumab 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 Bavencio (avelumab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the existing adverse reaction information on immunogenicity and to further detail the risk of diabetic ketoacidosis in the package leaflet, including information on its symptoms. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>30</sup>.
- In the next PSUR, the MAH should further characterise and provide new information on the effect of prior and concomitant antibiotic use on the efficacy of immune checkpoint inhibitors (ICIs).

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

<sup>30</sup> Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion

6-monthly to yearly and the list of Union reference dates (EURD list) will be updated accordingly.

### 6.1.2. Cemiplimab - LIBTAYO (CAP) - PSUSA/00010780/202103

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Applicant: Regeneron Ireland Designated Activity Company (DAC)

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

#### **Background**

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

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Libtayo, a centrally authorised medicine containing cemiplimab 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 Libtayo (cemiplimab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include in the package leaflet the risk of diabetic ketoacidosis and its symptoms. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>31</sup>.
- In the next PSUR, the MAH should provide a review of cases of vitiligo.

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. Dimethyl fumarate<sup>32</sup> - TECFIDERA (CAP) - PSUSA/00010143/202103

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Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

#### **Background**

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

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

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

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<sup>31</sup> Update of the package leaflet. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion

<sup>32</sup> Indicated for the treatment of multiple sclerosis only

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Tecfidera (dimethyl fumarate) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include alopecia as an undesirable effect with a frequency 'common'. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>33</sup>.
- In the next PSUR, the MAH should review all available data on patients switching from fingolimod to dimethyl fumarate with regard to lymphopenia and efficacy and discuss potential safety concerns in this patient population. The MAH should also provide detailed reviews of cases of lymphocytopenia, potential malignancies, pulmonary embolism and alopecia. In addition, the MAH should include a review of cases of pregnancy reported with the concomitant use of dimethyl fumarate. Finally, the MAH should present a literature review addressing the nuclear factor erythroid 2-related factor (NRF2) and skin cancers together with a discussion on the potential role of dimethyl fumarate in this patho-mechanism.

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

#### 6.1.4. Dupilumab - DUPIXENT (CAP) - PSUSA/00010645/202103

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Applicant: sanofi-aventis groupe

PRAC Rapporteur: Kimmo Jaakkola

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 Dupixent, a centrally authorised medicine containing dupilumab 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 Dupixent (dupilumab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add dry eye as an undesirable effect with a frequency 'uncommon'. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>34</sup>.
- In the next PSUR, the MAH should include an updated cumulative review of cases of Steven-Johnson syndrome (SJS)/severe cutaneous adverse reactions (SCAR) as well as reviews of cases of helminthic infections and of cutaneous T-cell lymphoma (CTLC). In addition, the MAH should provide a detailed review of pregnancy reported with

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<sup>33</sup> Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion

<sup>34</sup> Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion

concomitant use of dupilumab. Finally, the MAH should provide a review of cases of hypersensitivity.

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

#### 6.1.5. Ipilimumab - YERVOY (CAP) - PSUSA/00009200/202103

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Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

##### **Background**

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

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Yervoy, a centrally authorised medicine containing ipilimumab 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 Yervoy (ipilimumab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the existing warning on immune-related endocrinopathy when ipilimumab is used as monotherapy to reflect information on type 1 diabetes mellitus and diabetic ketoacidosis. In addition, the posology and method of administration is updated to add information on diabetes grades. Furthermore, the undesirable effect section dedicated to ipilimumab as monotherapy is updated to add pneumonia, diabetes mellitus (including diabetic ketoacidosis) and myelitis with a frequency 'uncommon', 'rare' and 'not known' respectively. Myelitis is also added as an undesirable effect with a frequency 'rare' when ipilimumab is used in combination with nivolumab or used in combination with nivolumab and chemotherapy. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>35</sup>.

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

#### 6.1.6. Ocrelizumab - OCREVUS (CAP) - PSUSA/00010662/202103

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Applicant: Roche Registration GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

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<sup>35</sup> Update of SmPC sections 4.2, 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

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 Ocrevus, a centrally authorised medicine containing ocrelizumab 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 Ocrevus (ocrelizumab) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- The MAH should submit to EMA, within 180 days, cumulative reviews of cases of colitis ulcerative, colitis, inflammatory bowel disease and Crohn's disease, including data from spontaneous reports, literature and clinical trials, along with a discussion on a possible biological mechanism. Also, the MAH should provide a literature review of cases of alopecia and alopecia areata and appendicitis and discuss the need for risk minimisation measures. This should include a proposal to amend the product information as warranted. Finally, the MAH should include a literature review of cases of appendicitis together with a discussion on the need for risk minimisation measures as warranted.

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

## **6.1.7. Vandetanib - CAPRELSA (CAP) - PSUSA/00009327/202104**

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Applicant: Genzyme Europe BV

PRAC Rapporteur: Tiphaine Vaillant

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 Caprelsa, a centrally authorised medicine containing vandetanib 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 Caprelsa (vandetanib) in the approved indication(s) remains unchanged.



- Nevertheless, the product information should be updated to include the risk of wound healing complications as a warning. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>36</sup>.
- In the next PSUR, the MAH should closely monitor cases of fistula. In addition, the MAH should provide detailed reviews on new cases of pulmonary hypertension, pulmonary arterial hypertension, tubulointerstitial nephritis and myocarditis.

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)

### 6.2.1. Bimatoprost - LUMIGAN (CAP); NAP - PSUSA/00000413/202103

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Applicants: Allergan Pharmaceuticals Ireland (Lumigan), various

PRAC Rapporteur: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

#### Background

Bimatoprost is a synthetic prostamide indicated for the reduction of elevated intraocular pressure (IOP) in chronic open-angle glaucoma and ocular hypertension in adults (as monotherapy or as adjunctive therapy to beta-blockers).

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

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

- Based on the review of the data on safety and efficacy, the benefit-risk balance of bimatoprost-containing products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add prostaglandin analogue periorbitopathy (PAP) as a warning and as an undesirable effect with a frequency 'very common'. Therefore, the current terms of the marketing authorisations should be varied<sup>37</sup>.

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

PRAC considered the risk of PAP is also relevant to bimatoprost/timolol-containing products as a fixed dose combination (FDC). Further consideration will be given at the level of CHMP

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<sup>36</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

<sup>37</sup> Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion

and CMDh.

### 6.2.2. Enoxaparin - INHIXA (CAP); NAP - PSUSA/00010833/202104

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Applicants: Techdow Pharma Netherlands B.V. (Inhixa), various

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

#### **Background**

Enoxaparin is a low molecular weight heparin indicated in the prophylaxis of venous thromboembolic disease in moderate and high-risk surgical patients, in particular those undergoing orthopaedic or general surgery including cancer surgery and in medical patients with an acute illness (such as acute heart failure, respiratory insufficiency, severe infections or rheumatic diseases) and reduced mobility at increased risk of venous thromboembolism. It is also indicated for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), excluding PE likely to require thrombolytic therapy or surgery, as well as in the treatment of unstable angina and non-ST-segment elevation myocardial infarction (NSTEMI), in combination with oral acetylsalicylic acid and of acute ST-segment elevation myocardial infarction (STEMI) including patients to be managed medically or with subsequent percutaneous coronary intervention (PCI).

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

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

- Based on the review of the data on safety and efficacy, the benefit-risk balance of enoxaparin-containing products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add acute generalised exanthematous pustulosis (AGEP) as a warning and as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisations should be varied<sup>38</sup>.
- In the next PSUR, the MAHs should provide a cumulative review of cases of severe cutaneous adverse reactions (SCARs), except for AGEP, including post-marketing, clinical trials and literature data along with a discussion on the need for an update of the product information as warranted.

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

### 6.2.3. Esomeprazole - NEXIUM CONTROL (CAP); NAP - PSUSA/00001269/202103

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Applicants: GlaxoSmithKline Dungarvan Ltd (Nexium Control), various

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<sup>38</sup> Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion

PRAC Rapporteur: Rugile Pilviniene

Scope: Evaluation of a PSUSA procedure

### **Background**

Esomeprazole is a proton pump inhibitor (PPI) indicated for the short-term treatment of reflux symptoms (e.g. heartburn and acid regurgitation) in adults. It is also indicated for the treatment of gastroesophageal reflux disease (GERD), for the prevention of relapse of GERD in patients with healed oesophagitis, for the healing/prevention of *Helicobacter pylori*-associated ulcers in combination with appropriate antibiotics, for the healing/prevention of ulcers associated with non-steroidal anti-inflammatory drug (NSAID) therapy, for the treatment of pathological hypersecretory conditions including Zollinger-Ellison syndrome. In addition, it is indicated in the prevention of re-bleeding in patients following therapeutic endoscopy for acute bleeding gastric or duodenal ulcers, for the prevention of re-bleeding of gastric or duodenal ulcers following treatment with intravenous esomeprazole (oral) as well as for the prevention of gastric and/or duodenal ulcers associated with low-dose aspirin therapy in patients at risk.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of Nexium Control, a centrally authorised medicine(s) containing esomeprazole, and nationally authorised medicine(s) containing esomeprazole and issued a recommendation on their marketing authorisations.

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

- Based on the review of the data on safety and efficacy, the benefit-risk balance of esomeprazole-containing products in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisations should be maintained.
- In the next PSUR, the originator MAHs for esomeprazole-containing-products should provide a cumulative review of cases of drug rash with eosinophilia and systemic symptoms (DRESS) and acute generalized exanthematous pustulosis (AGEP), including post-marketing, clinical trials and literature data, along with a discussion on the need for an update of the product information as warranted.

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

Submission of PSURs for products referred to in Articles 10(1), 10a, 14, 16a of Directive 2001/83/EC as amended is not required any longer and the EURD list should be updated accordingly.

#### **6.2.4. Voriconazole - VFEND (CAP); NAP - PSUSA/00003127/202102**

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Applicants: Pfizer Europe MA EEIG (Vfend), various

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

### **Background**

Voriconazole is a triazole antifungal agent indicated in adults and children aged 2 years and above for the treatment of invasive aspergillosis, candidaemia in non-neutropenic patients, fluconazole-resistant serious invasive Candida infections including *Candida krusei* and for the treatment of serious fungal infections caused by *Scedosporium spp* and *Fusarium spp*. It is also indicated in other serious fungal infections in patients intolerant of, or refractory to, other therapy, for the prevention of breakthrough of fungal infections in febrile high-risk patients and as prophylaxis in patients who are at high risk of developing invasive fungal infections, such as haematopoietic stem cell transplant (HSCT) recipients.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of Vfend, a centrally authorised medicine(s) containing voriconazole, and nationally authorised medicines containing voriconazole and issued a recommendation on their marketing authorisations.

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

- Based on the review of the data on safety and efficacy, the benefit-risk balance of voriconazole-containing products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to refine the existing warning on squamous cell carcinoma of the skin (SCC) to reflect cutaneous SCC in situ or Bowen's disease and to add it as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisations should be varied<sup>39</sup>.
- In the next PSUR, the MAHs should closely monitor the risk of melanoma and propose risk minimisation measures (RMM) as appropriate. In addition, the MAHs should provide a detailed analysis of data related to cardiac failure and cardiomyopathy and propose RMM as appropriate.

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

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

See also Annex I 16.3.

### **6.3.1. Dobutamine (NAP) - PSUSA/00001151/202103**

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Applicant(s): various

PRAC Lead: Nathalie Gault

Scope: Evaluation of a PSUSA procedure

#### **Background**

Dobutamine is a synthetic catecholamine indicated for the treatment of patients with hypoperfusion states in whom cardiac output is insufficient to meet circulatory demands and when inotropic support is required for the treatment of patients in whom abnormally increased ventricular filling pressures introduce a risk of pulmonary congestion and oedema.

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<sup>39</sup> Update of SmPC sections 4.4 and 4.8. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing dobutamine 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 dobutamine-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include stress cardiomyopathy (Takotsubo syndrome) as a warning and as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>40</sup>.
- In the next PSUR, the MAHs should monitor cases of 'drug ineffective'.

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

### **6.3.2. Metamizole (NAP) - PSUSA/00001997/202103**

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Applicant(s): various

PRAC Lead: Melinda Palfi

Scope: Evaluation of a PSUSA procedure

#### **Background**

Metamizole is a non-opioid pyrazolone derivative indicated for the treatment of severe or resistant pain including colicky pain, tumour pain, post-operative or post-traumatic pain, dysmenorrhoea, gingivitis, headache, toothache, pains due to infection, pneumonia and rheumatic conditions. It is also indicated for the treatment of high fever not responding to general therapeutic measure.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing metamizole 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 metamizole-containing medicinal product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add drug reaction with eosinophilia and systemic symptoms (DRESS) to the existing warning on severe cutaneous reactions and as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>41</sup>.

The frequency of PSUR submission should be revised from yearly to three-yearly and the

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<sup>40</sup> Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position

<sup>41</sup> Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position

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

PRAC considered that the risk of DRESS is also relevant for medicinal product(s) containing fixed dose combinations containing metamizole, namely caffeine/isometheptene/metamizole, caffeine/metamizole, caffeine/drotaverine hydrochloride/metamizole sodium, hyoscine butylbromide/metamizole, metamizole sodium/triacetonamide tosilate, fempiverinium bromide/metamizole sodium/pitofenone hydrochloride and metamizole sodium/pitofenone hydrochloride. Further consideration is to be given at CMDh.

### 6.3.3. Ondansetron (NAP) - PSUSA/00002217/202102

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Applicant(s): various

PRAC Lead: Polona Golmajer

Scope: Evaluation of a PSUSA procedure

#### **Background**

Ondansetron is a selective 5-HT<sub>3</sub> (5-hydroxytryptamine-3) receptor antagonist indicated in patients for the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy (chemotherapy/radiotherapy-induced nausea and vomiting (CINV/RINV)) and the management of post-operative nausea and vomiting (PONV). In the paediatric population, ondansetron is indicated for the management of CINV in children aged  $\geq 6$  months and for the prevention and treatment of PONV in children aged  $\geq 1$  month.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing ondansetron 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 ondansetron-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add myocardial ischemia as a warning and as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>42</sup>.
- In the next PSUR, the MAH(s) should provide cumulative reviews on cases off myocardial infarction and acute coronary syndrome (ACS). The MAHs should discuss the need to update the product information as warranted.

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

### 6.3.4. Spironolactone (NAP) - PSUSA/00002780/202103

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Applicant(s): various

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<sup>42</sup> Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position

PRAC Lead: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

### **Background**

Spironolactone is a non-selective competitive receptor antagonist of aldosterone indicated for the treatment of essential hypertension, congestive heart failure (alone or in combination with standard therapy), including severe heart failure (NYHA<sup>43</sup> class III-IV), management of hirsutism, adjunctive therapy in diuretic-induced hypokalaemia/hypomagnesaemia, for the diagnosis of hyperaldosteronism, for the short-term preoperative treatment of patients with primary hyperaldosteronism, as well as for conditions in which secondary hyperaldosteronism may be present, including liver cirrhosis accompanied by oedema and/or ascites, nephrotic syndrome, and other oedematous conditions (alone or in combination with standard therapy).

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing spironolactone 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 spironolactone-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add prostate specific antigen (PSA) increase in use of spironolactone during abiraterone treatment in prostate cancer patients as a warning. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>44</sup>.

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 information on PSA increase in spironolactone- and abiraterone-treated prostate cancer patients is also relevant for inclusion in product information of medicinal product(s) containing spironolactone as fixed dose combinations (FDC). Further consideration is to be given at CMDh.

#### **6.3.5. Terlipressin (NAP) - PSUSA/00002905/202104**

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Applicant(s): various

PRAC Lead: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

### **Background**

Terlipressin is a synthetic analogue of the nonapeptide vasopressin indicated for the treatment of bleeding oesophageal varices (BOV), hepatorenal syndrome (HRS) and for the

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<sup>43</sup> New York Heart Association

<sup>44</sup> Update of SmPC section 4.4. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position

treatment of bleeding in connection with surgery particularly from gastrointestinal and urogenital tracts.

PRAC is currently reviewing the benefit-risk balance of nationally authorised medicines containing terlipressin, in the framework of the assessment of a PSUR single assessment (PSUSA) procedure due for PRAC recommendation at the December 2021 PRAC meeting.

#### **Summary of conclusions**

- The PRAC Rapporteur presented the preliminary assessment of the currently ongoing PSUSA procedure, which is due to complete at the following PRAC meeting.
- Further discussion and adoption of a recommendation is planned at the December 2021 PRAC meeting.

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

See also Annex I 16.4.

### **6.4.1. Fentanyl - EFFENTORA (CAP) - EMEA/H/C/000833/LEG 019.1**

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Applicant: Teva B.V.

PRAC Rapporteur: Martin Huber

Scope: MAH's response to LEG 019 [review of the current labelling for fentanyl transmucosal route of administration regarding off-label use, misuse and accidental exposure as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00001369/202004) adopted in January 2021] as per the request for supplementary information (RSI) adopted in July 2021

#### **Background**

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

Following the evaluation of the most recently submitted PSUR(s) for the above-mentioned medicine(s), PRAC requested the MAH to submit a thorough review of their current labelling to ensure the risks for off-label use, misuse and accidental exposure are appropriately mitigated and to propose corrective actions as appropriate. For further background, see [PRAC minutes January 2021](#) and [PRAC minutes July 2021](#). The initial responses together with the responses to the successive request for supplementary information (RSI) were assessed by the Rapporteur for further PRAC advice.

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

- Based on the available data and the Rapporteur's assessment, PRAC agreed with the inclusion and/or reinforcement of warning(s) in the product information/labelling to inform patients and caregivers about the risks related to off-label use, misuse and accidental exposure. PRAC agreed with reflecting that Effentora (fentanyl) must only be used by patients already taking other opioids for chronic cancer pain and accidental use can cause serious harm and be fatal.
- The MAH should submit to EMA, within 60 days, a variation to update the product information accordingly. The MAH should also further consider the impact of the



proposed warnings regarding labelling and multilingual packaging on the legibility and readability of information on packaging.

#### 6.4.2. Fentanyl - INSTANYL (CAP) - EMEA/H/C/000959/LEG 030.1

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Applicant: Takeda Pharma A/S

PRAC Rapporteur: Tiphaine Vaillant

Scope: MAH's response to LEG 030 [review of the current labelling for fentanyl transmucosal route of administration regarding off-label use, misuse and accidental exposure as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00001369/202004) adopted in January 2021] as per the request for supplementary information (RSI) adopted in July 2021

##### **Background**

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

Following the evaluation of the most recently submitted PSUR(s) for the above-mentioned medicine(s), PRAC requested the MAH to submit a thorough review of their current labelling to ensure the risks for off-label use, misuse and accidental exposure are appropriately mitigated and to propose corrective actions as appropriate. For further background, see [PRAC minutes January 2021](#) and [PRAC minutes July 2021](#). The initial responses together with the responses to the successive request for supplementary information (RSI) were assessed by the Rapporteur for further PRAC advice.

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

- Based on the available data and the Rapporteur's assessment, PRAC agreed with the inclusion and/or reinforcement of warning(s) in the product information/labelling to inform patients and caregivers about the risks related to off-label use, misuse and accidental exposure. PRAC agreed with reflecting that Instanyl (fentanyl) must only be used by patients already taking other opioids for chronic cancer pain and that accidental use can cause serious harm and be fatal.
- The MAH should submit to EMA, within 60 days, a variation to update the product information accordingly. The MAH should also further consider the impact of the proposed warnings regarding labelling and multilingual packaging on the legibility and readability of information on packaging.

#### 6.4.3. Fentanyl - PECFENT (CAP) - EMEA/H/C/001164/LEG 021.1

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Applicant: Kyowa Kirin Holdings B.V.

PRAC Rapporteur: Martin Huber

Scope: MAH's response to LEG 021 [review of the current labelling for fentanyl transmucosal route of administration regarding off-label use, misuse and accidental exposure as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00001369/202004) adopted in January 2021] as per the request for supplementary information (RSI) adopted in July 2021

## Background

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

Following the evaluation of the most recently submitted PSUR(s) for the above-mentioned medicine(s), PRAC requested the MAH to submit a thorough review of their current labelling to ensure the risks for off-label use, misuse and accidental exposure are appropriately mitigated and to propose corrective actions as appropriate. For further background, see [PRAC minutes January 2021](#) and [PRAC minutes July 2021](#). The initial responses together with the responses to the successive request for supplementary information (RSI) were assessed by the Rapporteur for further PRAC advice.

## Summary of advice/conclusion(s)

- Based on the available data and the Rapporteur's assessment, PRAC agreed with the inclusion and/or reinforcement of warning(s) in the product information/labelling to inform patients and caregivers about the risks related to off-label use, misuse and accidental exposure. PRAC agreed with reflecting that Pecfent (fentanyl) must only be used by patients already taking other opioids for chronic cancer pain and accidental use can cause serious harm and be fatal.
- The MAH should submit to EMA, within 60 days, a variation to update the product information accordingly. The MAH should also further consider the impact of the proposed warnings regarding labelling and multilingual packaging on the legibility and readability of information on packaging.

### 6.4.4. [Infliximab - REMICADE \(CAP\) - EMEA/H/C/000240/LEG 159.2](#)

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Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: MAH's response to LEG 0159.1 [review on administration of live vaccines, including a literature review on postnatal clearance of tumour necrosis factor alfa (TNF $\alpha$ ) inhibitors in the newborn, particularly of infliximab and of cases of disseminated BCG vaccinations associated with administration of BCG after birth as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00010759/201908) adopted in April 2020] as per the conclusions adopted in May 2021

## Background

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

Following the evaluation of the most recently submitted PSUR for the above-mentioned medicine(s), PRAC requested the MAH to provide a review on administration of live vaccines to infants after in utero infliximab exposure. For further background, see [PRAC minutes April 2020](#), [PRAC minutes December 2020](#)<sup>45</sup> and [PRAC minutes May 2021](#). The initial responses together with the responses to the successive request for supplementary information (RSI) were assessed by the Rapporteur for further PRAC advice.

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<sup>45</sup> Held 23-26 November 2020

### Summary of advice/conclusion(s)

- Based on the available data and the Rapporteur's assessment, PRAC supported to update the product information<sup>46</sup> regarding administration of live vaccines to infant exposed to infliximab during pregnancy. PRAC also agreed with the proposed update to the patient reminder card. In addition, PRAC supported the dissemination of a direct healthcare professional communication (DHPC) on the use of live vaccines after pregnancy exposure or after breastfeeding.
- The MAH should submit to EMA, within 60 days, a variation accordingly together with a proposed DHPC and a communication plan.

#### 6.4.5. Methotrexate - JYLAMVO (CAP) - EMEA/H/C/003756/LEG 002.2

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Applicant: Therakind (Europe) Limited

PRAC Rapporteur: Martin Huber

Scope: MAH's response to LEG 002.1 [comprehensive review of the value of performing liver biopsies as a diagnostic tool to monitor hepatotoxicity of methotrexate in non-oncologic indications as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00002014/201910) adopted in May 2020] as per the request for supplementary information (RSI) adopted in June 2021

### Background

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

Following the evaluation of the most recently submitted PSUR(s) for the above-mentioned medicine(s), PRAC requested the MAH to submit a review of the value of performing liver biopsies as a diagnostic tool to monitor hepatotoxicity of methotrexate in non-oncologic indications. For further background, see [PRAC minutes May 2020](#), [PRAC minutes January 2021](#) and [PRAC minutes June 2021](#). The initial responses together with the responses to the successive request for supplementary information (RSI) were assessed by the Rapporteur for further PRAC advice.

### Summary of advice/conclusion(s)

- Based on the available data and the Rapporteur's assessment, PRAC agreed with the refined warning on liver function tests.
- The MAH should submit a variation to EMA, within 60 days, to amend the product information<sup>47</sup> accordingly.

#### 6.4.6. Methotrexate - NORDIMET (CAP) - EMEA/H/C/003983/LEG 003.2

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Applicant: Nordic Group B.V.

PRAC Rapporteur: Martin Huber

Scope: MAH's response to LEG 003.1 [comprehensive review of the value of performing liver biopsies as a diagnostic tool to monitor hepatotoxicity of methotrexate in non-

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<sup>46</sup> Update of sections 4.4, 4.5 and 4.6. The package leaflet is to be updated accordingly

<sup>47</sup> SmPC section 4.4. The package leaflet is to be updated accordingly

oncologic indications as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00002014/201910) adopted in May 2020] as per the request for supplementary information (RSI) adopted in June 2021

### **Background**

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

Following the evaluation of the most recently submitted PSUR(s) for the above-mentioned medicine(s), PRAC requested the MAH to submit a review of the value of performing liver biopsies as a diagnostic tool to monitor hepatotoxicity of methotrexate in non-oncologic indications. For further background, see [PRAC minutes May 2020](#), [PRAC minutes January 2021](#) and [PRAC minutes June 2021](#). The initial responses together with the responses to the successive request for supplementary information (RSI) were assessed by the Rapporteur for further PRAC advice.

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

- Based on the available data and the Rapporteur's assessment, PRAC agreed with the refined warning on liver function tests.
- The MAH should submit a variation to EMA, within 60 days, to amend the product information<sup>48</sup> accordingly.

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

See also Annex I 16.5.

### **6.5.1. Emicizumab - HEMLIBRA (CAP) - EMEA/H/C/004406/II/0026**

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Applicant: Roche Registration GmbH

PRAC Rapporteur: Amelia Cupelli

Scope: Update of section 4.8 of the SmPC to include new data related to hypersensitivity as per the outcome of the last PSUR single assessment (PSUSA) procedure (PSUSA/00010668/202011) adopted in June 2021. The package leaflet is updated in accordance

### **Background**

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

Following the evaluation of the most recently submitted PSUR(s) for the above-mentioned medicine(s), the MAH submitted to EMA a variation to update the product information in line with the conclusions of the PSUR single assessment (PSUSA) procedure. For background information, see [PRAC minutes June 2021](#). PRAC is responsible for adopting an outcome based on the assessment report from the PRAC Rapporteur, to be further considered at the level of CHMP, responsible for adopting an opinion on this variation.

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<sup>48</sup> SmPC section 4.4. The package leaflet is to be updated accordingly

### Summary of recommendation(s)

- Based on the available data and the Rapporteur's assessment, PRAC agreed with the proposed amendments<sup>49</sup> to the product information in order to add urticaria and rash as undesirable effects with a frequency 'common' and angioedema with a frequency 'uncommon'.

#### 6.5.2. Fampridine - FAMPYRA (CAP) - EMEA/H/C/002097/II/0049

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Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Update of section 4.8 of SmPC to include new symptoms of trigeminal neuralgia as per the outcome of the last PSUR single assessment (PSUSA) procedure (PSUSA/00001352/202001) finalised in September 2020. The package leaflet is updated accordingly. The MAH introduced further editorial updates including an update of the product information in line with the latest quality review of documents (QRD) template (version 10.2) and an update of the contact details of the local representatives

### Background

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

Following the evaluation of the most recently submitted PSUR(s) for the above-mentioned medicine(s), the MAH submitted to EMA a variation to update the product information in line with the conclusions of the PSUR single assessment (PSUSA) procedure. For background information, see [PRAC minutes September 2020](#)<sup>50</sup> and [PRAC minutes July 2021](#). PRAC is responsible for adopting an outcome based on the assessment report from the PRAC Rapporteur, to be further considered at the level of CHMP, responsible for adopting an opinion on this variation.

### Summary of recommendation(s)

- Based on the available data and the Rapporteur's assessment, PRAC agreed with the proposed amendments<sup>51</sup> to the product information in order to amend the existing undesirable effect of trigeminal neuralgia with a frequency 'uncommon' to reflect that it includes both de novo symptoms and exacerbation of existing trigeminal neuralgia.

#### 6.5.3. Macitentan - OPSUMIT (CAP) - EMEA/H/C/002697/II/0042, Orphan

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Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Eva Segovia

Scope: Update of Annex II of the product information and of the RMP (version 12.1) in line with the outcome of the last PSUR single assessment (PSUSA) procedure (PSUSA/00010115/202010) adopted in June 2021 to remove the controlled distribution system and prescriber kit (prescribing check list and healthcare professional (HCP) brochure) as additional risk minimisation measures (aRMM) while the patient alert card is

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<sup>49</sup> Update of SmPC section 4.8. The package leaflet is updated accordingly

<sup>50</sup> Held 31 August – 03 September 2020

<sup>51</sup> Update of SmPC section 4.8. The package leaflet is updated accordingly

kept as an aRMM. In addition, the RMP is updated to remove off-label use from the list of safety concerns, elderly patients aged over 75 years, patients with moderate to severe hepatic impairment and patients with severe renal impairment and/or undergoing dialysis as missing information. The MAH took the opportunity to include in the RMP updated specific follow-up questionnaires forms (in line with internal company template. Finally, the MAH the opportunity to bring the product information in line with the latest quality review of documents (QRD) template (version 10.2)

### **Background**

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

Following the evaluation of the most recently submitted PSUR(s) for the above-mentioned medicine(s), the MAH to submitted to EMA a variation to update Annex II of the product information and the RMP in line with the conclusions of the PSUR single assessment (PSUSA) procedure. For background information, see [PRAC minutes June 2021](#). PRAC is responsible for adopting an outcome based on the assessment report from the PRAC Rapporteur, to be further considered at the level of CHMP, responsible for adopting an opinion on this variation.

### **Summary of recommendation(s)**

- Based on the available data and the Rapporteur's assessment, PRAC considered that in line with other endothelin receptor antagonists (ERAs) currently approved in EU, the patient card for Opsumit (macitentan) as an additional risk minimisation measure should be further refined to focus only on the risks of hepatotoxicity and teratogenicity as important identified risks. Therefore, the MAH should submit to EMA responses to the request for supplementary information (RSI).

## **6.6. Expedited summary safety reviews<sup>52</sup>**

See also Annex I 16.6.

### **6.6.1. Coronavirus (COVID-19) vaccine (Ad26.COVID-19, recombinant) - COVID-19 VACCINE JANSSEN (CAP) – EMEA/H/C/005737/MEA 014.6**

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Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Seventh expedited monthly summary safety report (MSSR) for COVID-19 Vaccine Janssen (COVID-19 vaccine (Ad26.COVID-19, recombinant)) during the coronavirus disease (COVID-19) pandemic

#### **Background**

COVID-19 vaccine (Ad26.COVID-19 [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 COVID-19 vaccine Janssen, a centrally authorised vaccine, for

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<sup>52</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

active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older.

PRAC assessed the seventh monthly summary safety report (MSSR) for COVID-19 vaccine Janssen (COVID-19 vaccine (Ad26.COVID-19-S, [recombinant])) as part of the safety monitoring of the vaccine. At an extraordinary meeting held on 04 November 2021, PRAC adopted its conclusions.

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

- In the next MSSR<sup>53</sup>, the MAH should provide cumulative reviews and data. In particular, the MAH should include further analyses on cases of encephalitis including cases of acute disseminated encephalomyelitis (ADEM) and propose to update the product information as warranted. In addition, the MAH should provide updated cumulative reviews of cases of vasculitis and of rhabdomyolysis. A discussion on the need to update the product information and/or RMP should also be included.
- In the next PSUR, the MAH should provide an in-depth review of autoimmune hepatitis. In addition, the MAH should include a cumulative review of cases of neuralgic amyotrophy. Furthermore, the MAH should include a cumulative review focused on serious hypertension. A discussion on the need to update the product information should be provided, as warranted.

#### **6.6.2. Coronavirus (COVID-19) vaccine (ChAdOx1-S [recombinant]) - VAXZEVRIA (CAP) - EMEA/H/C/005675/MEA 027.6**

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Applicant: AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

Scope: Seventh expedited monthly summary safety report (MSSR) for Vaxzevria (COVID-19 vaccine (ChAdOx1-S [recombinant])) during the coronavirus disease (COVID-19) pandemic

#### **Background**

Coronavirus (COVID-19) vaccine (ChAdOx1-S [recombinant]) is a monovalent vaccine composed of a single recombinant, replication-deficient chimpanzee adenovirus (ChAdOx1) vector encoding the S glycoprotein of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) indicated, as Vaxzevria, 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 seventh monthly summary safety report (SSR)<sup>54</sup> for Vaxzevria (COVID-19) vaccine (ChAdOx1-S [recombinant]) as part of the safety monitoring of the vaccine. At an extraordinary meeting held on 04 November 2021, PRAC adopted its conclusions.

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

- The MAH should submit to EMA, within 15 days, a variation to include in the product information<sup>55</sup> cerebral venous sinus thrombosis (CVST) without thrombocytopenia as a warning and as an undesirable effect with a frequency 'not known'.

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<sup>53</sup> Submission date on 15 November 2021

<sup>54</sup> First bi-monthly SSR

<sup>55</sup> SmPC sections 4.4 and 4.8. The package leaflet is to be updated accordingly



- In the next SSR<sup>56</sup>, the MAH should provide cumulative reviews and data. In particular, the MAH should include updated reviews of acute macular outer retinopathy (AMOR), acute macular neuro-retinopathy (AMN) and paracentral acute middle maculopathy (PAMM) as well as of CVST without thrombocytopenia. In addition, the MAH should provide an in-depth discussion of all relevant data from post-marketing sources, clinical trials, pre-clinical data and relevant literature related to pulmonary embolism and deep vein thrombosis (DVT) without thrombocytopenia.
- In the next PSUR, the MAH should provide reviews of thrombosis, thrombocytopenia, CVST without thrombocytopenia, myocarditis and pericarditis, AMOR/AMN/PAMM, capillary leak syndrome, encephalitis, neuralgic amyotrophy and autoimmune hepatitis. The MAH should provide a proposal to update the product information as warranted.

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

### 7.1. Protocols of PASS imposed in the marketing authorisation(s)<sup>57</sup>

See also Annex I 17.1.

#### 7.1.1. Selumetinib - KOSELUGO (CAP) - EMEA/H/C/PSP/S/0095

Applicant: AstraZeneca AB

PRAC Rapporteur: Annika Folin

Scope: Protocol for a PASS of paediatric patients initiating selumetinib: a multiple-country prospective cohort study

#### Background

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

In order to fulfil the specific obligation to conduct a PASS ([Annex II-E](#)) imposed in accordance with Article 107n(3) of Directive 2001/83/EC, the MAH AstraZeneca AB submitted to EMA a protocol version 1.0 for a study entitled: 'a PASS of paediatric patients initiating selumetinib: a multiple-country prospective cohort study' for review by PRAC in order to confirm the long-term safety of selumetinib in the treatment of symptomatic, inoperable plexiform neurofibroma (PN) in paediatric patients with neurofibromatosis type 1 (NF1) aged 3 years and above. PRAC is responsible for evaluating the PASS protocol.

#### Endorsement/Refusal of the protocol

- Having considered the protocol version 1.0 in accordance with Article 107n of Directive 2001/83/EC, PRAC objected to the draft protocol for the above-listed medicinal product(s). PRAC agreed that the PASS is non-interventional, but the study design does not fulfil the study objectives at this stage.
- The MAH should provide further clarifications on the target enrolment of patients and describe the probable distribution of age and stage of Tanner of the population expected to be included in the study. In addition, the MAH should consider severe hepatic

<sup>56</sup> Submission date on 15 December 2021

<sup>57</sup> In accordance with Article 107n of Directive 2001/83/EC



impairment and hypersensitivity to the active substance or to any of the excipients as additional exclusion criteria. Furthermore, the MAH previously agreed to obtain structured information on choking events via follow-up questionnaires of the nested prospective cohort. The MAH should update the protocol accordingly.

- The MAH should submit a revised PASS protocol within 30 days to EMA. A 30 days-assessment timetable will be followed.

## 7.2. Protocols of PASS non-imposed in the marketing authorisation(s)<sup>58</sup>

See Annex I 17.2.

## 7.3. Results of PASS imposed in the marketing authorisation(s)<sup>59</sup>

See also Annex I 17.3.

### 7.3.1. Valproate (NAP) - EMEA/H/N/PSR/J/0036

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

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Results for a joint survey among healthcare professionals (HCP) to assess knowledge of HCP and behaviour with regards to pregnancy prevention programme (PPP) as well as receipt/use of a direct healthcare professional communication (DHPC) and educational materials and survey among patients to assess knowledge of the patients with regards to PPP as well as receipt/use of educational materials, 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)]

#### Background

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

Further to the conclusions dated 2018 of the referral procedure under Article 31 of Directive 2001/83/EC ([EMEA/H/A-31/1454](#)) conducted by PRAC for valproate-containing medicines, MAHs were required as a condition to the marketing authorisation(s) ([Annex IV](#)) to conduct a survey among healthcare professionals (HCP) to assess knowledge of HCP and behaviour with regards to pregnancy prevention programme (PPP) as well as receipt/use of a direct healthcare professional communication (DHPC) and educational materials and survey among patients to assess knowledge of the patients with regards to PPP as well as receipt/use of educational materials.

The MAH Sanofi-Aventis Recherche & Développement on behalf of a consortium submitted to EMA the final results version 1.0 of the 'surveys among HCP and Patients to assess their knowledge and behaviour with respect to the new risk minimisation measures (RMM) for valproate use in Europe'. PRAC discussed the final study results. PRAC is responsible for evaluating the PASS final results.

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<sup>58</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>59</sup> In accordance with Article 107p-q of Directive 2001/83/EC

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

- Based on the review of the final report of the registry study and the assessment from the Rapporteur, PRAC considered that a request for supplementary information (RSI) was necessary before a final recommendation could be issued.
- PRAC agreed that several aspects require further clarification and improvements, such as implementation of the additional RMM (aRMM) to ensure all eligible HCPs within the target groups receive relevant materials. In addition, knowledge on valproate risks, teratogenicity and neurodevelopment disorders (NDD) should be further improved among HCPs and patients.
- PRAC also agreed that a qualitative study (as a category 3 study in the RMP) is necessary to investigate barriers and reasons why certain measures part of the PPP are not always followed in clinical practice. Therefore, the MAH should provide a study synopsis including timelines, high level description of methodology, with a discussion on sampling techniques, and a proposal to include more countries with a special focus on EU Member States (MS) with major differences across healthcare systems, to obtain a representative sample of HCPs and patients.
- The MAH should submit responses to the RSI within 180 days to EMA. A 60 day-assessment timetable will be followed.

#### **7.4. Results of PASS non-imposed in the marketing authorisation(s)<sup>60</sup>**

See Annex I 17.4.

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

See Annex I 17.5.

#### **7.6. Others**

See Annex I 17.6.

#### **7.7. New Scientific Advice**

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

#### **7.8. Ongoing Scientific Advice**

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

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

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

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<sup>60</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 04 August 2013

## **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**

None

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

None

### **10.3. Other requests**

#### **10.3.1. Tirbanibulin – KLISYRI (CAP) - EMEA/H/C/005183/ANX 001**

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Applicant: Almirall S.A.

PRAC Rapporteur: Michal Radik; PRAC Co-Rapporteur: Rhea Fitzgerald

Scope: PRAC consultation on an interventional imposed PASS protocol for study M-14789-41 (listed as a category 1 study in Annex II): a phase 4, multicentre, randomized, evaluator-blinded, active-controlled study to determine the incidence of squamous cell carcinoma and evaluate the long-term safety and efficacy of tirbanibulin 10 mg/g ointment and diclofenac sodium 3% gel for the treatment of adult patients with actinic keratosis on the face or scalp

### **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 procedure evaluating a protocol for a study imposed to the MAH of Klisyri (tirbanibulin) is under evaluation at CHMP. In 2021, CHMP adopted a positive opinion with a condition in Annex II to further investigate the risk of progression of actinic keratosis (AK) to squamous cell carcinoma (SCC) in adult patients with non-hyperkeratotic, non-hypertrophic actinic keratosis (AK) treated with tirbanibulin. The MAH submitted a protocol for study M-14789-41<sup>61</sup>, an interventional study to determine the incidence of SCC and evaluate the long-term safety of tirbanibulin. PRAC was requested to provide advice on this procedure.

### **Summary of advice**

- Based on the review of the available information and assessment, PRAC advised to choose a different comparator from diclofenac such as 0.5% 5-fluorouracil (5FU), 3.75% imiquimod, methyl-aminolevulinate photodynamic therapy (MAL-PDT) or 5-aminolevulinic acid photodynamic therapy (ALA-PDT). PRAC also advised that the trial design should be in line with the authorised conditions of use as the study should give insight into the safety profile in the authorised indication and posology.

## **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. Fentanyl (NAP) - FR/H/PSUFU/00001369/202004**

Applicant(s): Angelini farmaceutica S.A., Aurobindo, Gedeon Richter PLC, Grünenthal, Kyowa Mylan, Sandoz, Stada, Teva B.V., Yes Pharmaceuticals

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<sup>61</sup> A phase 4, multi-centre, randomized, evaluator-blinded, active-controlled study to determine the incidence of squamous cell carcinoma and evaluate the long-term safety of tirbanibulin 10 mg/g ointment and diclofenac sodium 3% gel for the treatment of adult patients with actinic keratosis on the face or scalp

PRAC Lead: Tiphaine Vaillant

Scope: Further PRAC consultation on a PSUR follow-up (PSU FU) procedure evaluating off-label use, misuse and accidental exposure, as discussed at PRAC and agreed by CMDh following the conclusion of the PSUR single assessment (PSUSA) procedure (PSUSA/00001369/202004) concluded in January 2021, following advice in July 2021, on request of France

### **Background**

Fentanyl is a potent opioid analgesic indicated for analgesia through various routes of administration and pharmaceutical forms. With respect to the transmucosal route of administration, fentanyl-containing products are indicated for the treatment of breakthrough pain (BTP) in adults with cancer who are already receiving maintenance opioid therapy for chronic cancer pain.

Based on the assessment of the recent PSUR single assessment (PSUSA) procedure for fentanyl for transmucosal route of administration (PSUSA/00001369/202004) concluded in January 2021, PRAC considered that a thorough review of the current labelling should be performed to ensure that the risks of off-label use, misuse and accidental exposure are appropriately mitigated. For background, see [PRAC minutes January 2021](#) and [PRAC minutes July 2021](#).

On request of CMDh, MAH(s) for nationally approved fentanyl for transmucosal route of administration-containing product(s) submitted the requested reviews for evaluation within a worksharing periodic safety update follow-up (PSU FU) procedure. In the context of the ongoing evaluation of the PSU FU procedure (FR/H/PSUFU/00001369/202004), France, as lead Member State (LMS), requested PRAC advice on its assessment.

### **Summary of advice**

- Based on the available data and the LMS's assessment, PRAC supported the inclusion and/or reinforcement of warning(s) in the product information/labelling to inform patients and caregivers about the risks relating to off-label use, misuse and accidental exposure. PRAC advised that the product information/labelling for fentanyl-containing products for transmucosal use mention that the medicinal product(s) must only be used by patients already taking other opioids for chronic cancer pain and accidental use can cause serious harm and be fatal.

#### **11.2.2. Methotrexate<sup>62</sup> (NAP) - DE/H/PSUFU/00002014/201910**

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Applicant(s): Addenda Pharma, Especialidades Farmacéuticas Centrum S.A., Gebro Pharma, medac, Morningside Healthcare Limited, Mylan, Nordic Group, Orion Pharma, Pfizer, Remedica, Rompharm, Sandoz, Teva

PRAC Lead: Martin Huber

Scope: Further PRAC consultation on a PSUR follow-up (PSU FU) procedure evaluating comprehensive reviews of the value of performing liver biopsies as a diagnostic tool to monitor hepatotoxicity of methotrexate in non-oncologic indications, as discussed at PRAC and agreed by CMDh following the conclusion of the PSUSA procedure (PSUSA/00002014/201910) concluded in May 2020, following advice in January 2021, on

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<sup>62</sup> In non-oncology indication(s)

request of Germany

## Background

Methotrexate is a folic acid antagonist indicated<sup>63</sup> for the treatment of autoimmune disease such as active rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), psoriasis and severe psoriatic arthritis.

Based on the assessment of the recent PSUR single assessment (PSUSA) procedure for methotrexate (PSUSA/00002014/201910) concluded in May 2020, PRAC considered that reviews of the value of performing liver biopsies as a diagnostic tool to monitor hepatotoxicity of methotrexate in non-oncologic indication(s) should be further assessed.

On request of CMDh, MAH(s) for nationally approved methotrexate-containing product(s) submitted the requested safety reviews for evaluation within a worksharing periodic safety update follow-up (PSU FU) procedure. In the context of the ongoing evaluation of the PSU FU procedure (DE/H/PSUFU/00002014/201910), Germany, as lead Member State (LMS), requested PRAC to further advice on its assessment. For further background, see [PRAC minutes May 2020](#), [PRAC minutes January 2021](#) and [PRAC minutes June 2021](#).

## Summary of advice

- Based on the review of the available information and evidence, PRAC supported the LMS assessment. PRAC agreed with the refined warning<sup>64</sup> on liver function tests. In addition, PRAC supported the inclusion of recommendation in the product information regarding elderly patients to ensure the latter are monitored closely by a physician so that possible side effects can be detected as early as possible.

## 12. Organisational, regulatory and methodological matters

### 12.1. Mandate and organisation of PRAC

#### 12.1.1. PRAC membership

The Chair announced that Anna Marekova has been appointed as the new alternate for Slovakia<sup>65</sup>, replacing Marek Juracka who took over the role of member. The Chair also announced that Milena Radoha-Bergoc has been appointed as the new alternate for Slovenia<sup>66</sup>, replacing Polona Golmajer who took over the role of member. In addition, the Chair announced that Elena Kaisis has been appointed as the new member for Cyprus<sup>67</sup>, replacing Panagiotis Psaras who took over the role of alternate, replacing Christina Sylvia Chrysostomou. Finally, the Chairperson announced that Ruta Kerpauskiene stepped down as alternate for Lithuania<sup>68</sup> and the position remains vacant until further notice. The Chair thanked Ruta Kerpauskiene for her contribution to PRAC.

<sup>63</sup> In non-oncology indication(s)

<sup>64</sup> SmPC section 4.4 and package leaflet

<sup>65</sup> Mandate effective as of 29 October 2021

<sup>66</sup> Mandate effective as of 03 November 2021

<sup>67</sup> Mandate effective as of 09 November 2021

<sup>68</sup> On 17 October 2021

### 12.1.2. PRAC working group - Best practice guide on using PRAC plenary time efficiently and effectively – update on the implementation of quantitative goals – Q3 2021

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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 updated PRAC at the organisational, regulatory and methodological matters (ORGAM) meeting on 11 November 2021, on the quantitative measures collected for Q3 2021 of PRAC meetings. For previous update, see [PRAC minutes September 2021](#).

### 12.1.3. Vote by proxy

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None

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

### 12.2.1. Advanced therapy medicinal products (ATMP) - Impact of tocilizumab shortages on the use of chimeric antigen receptor-T (CAR-T) cell-based ATMPs in the EU

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The EMA Secretariat presented to PRAC a recommendation from the Committee for Advanced Therapies ([CAT](#)) for the use of chimeric antigen receptor-T (CAR-T) cell-based therapies in EU during shortages of tocilizumab. As a result of this recommendation, MAHs of CAR-T cell-based therapies authorised in EU will be requested to submit type II variations to amend their product information and the conditions of their marketing authorisation(s) in order to ensure that CAR-T cell-based therapies can be used in the EU/EEA also during confirmed tocilizumab shortages by treating physicians who consider that alternative suitable treatments for cytokine release syndrome (CRS) can be used and such treatments are made available to manage this adverse reaction associated with CAR-T cell-based therapies use. PRAC supported the recommendation.

## 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.

PRAC also agreed on timetable steps for upcoming summary safety reports (SSR) procedures.

## 12.5. Cooperation with International Regulators

None

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

None

## **12.7. PRAC work plan**

### **12.7.1. PRAC work plan 2022 - preparation**

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PRAC lead: Sabine Straus, Martin Huber

At the organisational, regulatory and methodological matters (ORGAM) meeting on 11 November 2021, the EMA secretariat provided an overview of planned topics to be included in the PRAC work plan 2022 based on the experience in 2021. Further discussion is planned in January 2022.

## **12.8. Planning and reporting**

### **12.8.1. EU Pharmacovigilance system - quarterly workload measures and performance indicators – Q3 2021 and predictions**

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At the organisational, regulatory and methodological matters (ORGAM) meeting on 11 November 2021, 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 September 2021](#).

### **12.8.2. PRAC workload statistics – Q3 2021**

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At the organisational, regulatory and methodological matters (ORGAM) meeting on 11 November 2021, the EMA secretariat presented to PRAC the quarterly and cumulative figures to estimate the evolution of the workload of PRAC for Q3 2021, by reflecting on the number of procedures and agenda items covered at each PRAC plenary meeting. [PRAC minutes July 2021](#).

## **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 November 2021, reflecting the PRAC's comments impacting on the data lock point (DLP) and PSUR submission frequencies of the substances/combinations. PRAC endorsed the newly allocated Rapporteurs for upcoming PSUSAs in accordance with the principles previously endorsed by PRAC (see [PRAC minutes April 2013](#)).

Post-meeting note: following the PRAC meeting of November 2021, the updated EURD list was adopted by CHMP and CMDh at their November 2021 meetings and published on the EMA website on 17/11/2021, 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 \(PSURs\)](#)

### **12.10.5. PSUR single assessment (PSUSA) recommendation for nationally approved products (NAP) - outcome of EMA survey on recommendation implementation**

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At the organisational, regulatory and methodological matters (ORGAM) meeting on 11 November 2021, the EMA secretariat presented for information to PRAC the results of a survey performed to understand the timeframe of the full implementation of PSUR single assessment (PSUSA) procedure recommendations for substances of nationally approved products (NAP) since 2012. PRAC noted the results.

## **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 on 27/10/2021, 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

## **12.15. 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

## **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**

### **12.21.1. EU pharmaceutical legislation – revision of Directive 2001/83/EC and Regulation (EC) No 726/2004**

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PRAC lead: Sabine Straus, Martin Huber, Amelia Cupelli, Menno van der Elst, Liana Gross-Martirosyan, Maria del Pilar Rayon, Eva Segovia, Ulla Wändel Liminga

As a follow-up to the discussion held at the October 2021 PRAC meeting (for background, see [PRAC minutes October 2021](#)<sup>69</sup>), the EMA Secretariat provided PRAC with a status update on the preparation of the concept papers to support the upcoming revision of Directive 2001/83/EC and Regulation (EC) No 726/2004. Status updates will be given on a regular basis.

### **12.21.2. Lifecycle regulatory submissions metadata project (LRSM) - presentation**

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The topic was postponed to December 2021.

## **13. Any other business**

None

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<sup>69</sup> Held 27-30 September 2021

## 14. Annex I – Signals assessment and prioritisation<sup>70</sup>

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

As per 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>71</sup>.

#### 14.1.1. Alemtuzumab - LEMTRADA (CAP)

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Applicant: Sanofi Belgium

PRAC Rapporteur: Anette Kirstine Stark

Scope: Signal of vitiligo

EPITT 19737 – New signal

Lead Member State(s): DK

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

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Applicant(s): Novartis Europharm Limited

PRAC Rapporteur: Anette Kirstine Stark

Scope: Signal of vasoplegia syndrome

EPITT 19739 – New signal

Lead Member State(s): DK

#### 14.1.3. Tocilizumab – ROACTEMRA (CAP)

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Applicant: Roche Registration GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Signal of encephalopathy including posterior reversible encephalopathy syndrome (PRES)

EPITT 19731 – New signal

Lead Member State(s): DE

### 14.2. New signals detected from other sources

None

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<sup>70</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>71</sup> Submission of cumulative review(s) within 60 days followed by a 60-day-timetable assessment or within an ongoing or upcoming PSUR/PSUSA procedure (if the data lock point (DLP) is within 90 days), and no disagreement was raised before the meeting

### 14.3. Signals follow-up and prioritisation

None

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

#### 14.4.1. Coronavirus (COVID-19) mRNA<sup>72</sup> vaccine (nucleoside-modified) - SPIKEVAX (CAP) - EMEA/H/C/005791/II/0028

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Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Hans Christian Siersted

Scope: Submission of an updated RMP (version 2.1) to include myocarditis and pericarditis in the list of the safety concerns as an important identified risk, as requested in the outcome of the signal procedure on myocarditis and pericarditis (EPITT 19713) adopted in July 2021 (SDA 033)

## 15. Annex I – Risk management plans

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

As per 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. Casirivimab, imdevimab - EMEA/H/C/005814

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Scope: Prevention and treatment of coronavirus disease-2019 (COVID-19)

#### 15.1.2. Formoterol fumarate dihydrate, glycopyrronium, budesonide - EMEA/H/C/005311

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Scope: Maintenance treatment of chronic obstructive pulmonary disease (COPD)

#### 15.1.3. Pegfilgrastim - EMEA/H/C/004780

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Scope: Treatment of neutropenia

#### 15.1.4. Sotrovimab - EMEA/H/C/005676

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Scope: Treatment of coronavirus disease 2019 (COVID-19)

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

As per 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).

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<sup>72</sup> Messenger ribonucleic acid

### 15.2.1. Brinzolamide, timolol - AZARGA (CAP) - EMEA/H/C/000960/II/0045

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Applicant: Novartis Europharm Limited

PRAC Rapporteur: Anette Kirstine Stark

Scope: Submission of an updated RMP (version 3.0) to remove important identified risks (respiratory disorders, cardiovascular disorders, corneal decompensation and metabolic acidosis), important potential risk (long term use of preserved eye drops) and missing information (use in paediatric patients)

### 15.2.2. Coronavirus (COVID-19) vaccine (ChAdOx1-S [recombinant]) - VAXZEVRIA (CAP) - EMEA/H/C/005675/II/0040

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Applicant: AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

Scope: Submission of an updated RMP (version 4.1) in order to add 'thrombosis in combination with thrombocytopenia' as an important potential risk as requested in the outcome of the signal procedure on immune thrombocytopenia (ITP) (EPITT 19678) adopted in July 2021 (SDA/034.1), to add acute macular neuroretinopathy, acute macular outer retinopathy, paracentral acute middle maculopathy, paresthesia and dysaesthesia in the list of adverse events of special interest (AESI) as requested in the outcome of the signal procedure on acute macular outer retinopathy (EPITT 19703) adopted in July 2021 (SDA/065). In addition, the updated RMP include the removal of the enhanced active surveillance (EAS) studies D8111R00003 [EU], D8110R00001 [US], D8111C00004 [UK], the update of the important potential risk of 'nervous system disorders, including immune-mediated neurological conditions' to reflect the recent product information on Guillain-Barré syndrome (IB/0034) as requested in the outcome of fourth monthly summary safety update (MSSR) (MEA 027.3) adopted in July 2021. Finally, the updated RMP includes the addition of the UK effectiveness study D8111R00007 as per the CHMP conclusion (MEA 010.1) dated June 2021 and the addition of study D8111R00010 to assess the relationship between the exposure to COVID-19 vaccines and the risk of thrombotic thrombocytopenia syndrome

### 15.2.3. Coronavirus (COVID-19) mRNA<sup>73</sup> vaccine (nucleoside-modified) - SPIKEVAX (CAP) - EMEA/H/C/005791/II/0022

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Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Hans Christian Siersted

Scope: Submission of an updated RMP (version 2.0) to include clinical safety data from study mRNA-1273 P203 (NCT04649151): a phase 2/3, randomised, observer-blind, placebo-controlled study evaluating the safety, reactogenicity and effectiveness of the mRNA-1273 vaccine in healthy adolescents aged  $\geq 12$  to  $< 18$  years

### 15.2.4. Fentanyl - PECFENT (CAP) - EMEA/H/C/001164/II/0054

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Applicant: Kyowa Kirin Holdings B.V.

PRAC Rapporteur: Martin Huber

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<sup>73</sup> Messenger ribonucleic acid

Scope: Submission of an updated RMP (version 7.1) in line with the outcome of the last PSUR single assessment (PSUSA) procedure (PSUSA 00001369/202004) finalised in January 2021 in order to update the key messages of the educational materials in line with another centrally authorised product containing fentanyl. As a result, Annex II-D on 'Conditions or restrictions with regard to the safe and effective use of the medicinal product' is updated accordingly. Finally, the MAH took the opportunity to bring the RMP in line with revision 2 of GVP module V on 'Risk management systems' and the product information in line with the latest quality review of documents (QRD) template (version 10.2)

#### **15.2.5. Fesoterodine - TOVIAZ (CAP) - EMEA/H/C/000723/II/0062**

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Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Submission of an updated RMP (version 10.0) in order to bring the important identified risks, important potential risks and missing information in line with revision 2 of GVP module V on 'Risk management systems' and in line with the PRAC outcome of the last PSUR single assessment (PSUSA) procedure (PSUSA/00001387/202004) adopted in December 2020 by removing safety in paediatric patients as missing information

#### **15.2.6. Influenza virus surface antigens (inactivated) of strain A/Vietnam/1194/2004 (H5N1) - 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 (influenza virus surface antigens (inactivated) of strain A/Vietnam/1194/2004 (H5N1)) 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

#### **15.2.7. Mecasermin - INCRELEX (CAP) - EMEA/H/C/000704/II/0067**

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Applicant: Ipsen Pharma

PRAC Rapporteur: Kirsti Villikka

Scope: Update of the conditions of the non-interventional PASS (listed as a specific obligation in Annex II) by using different criteria of patient exposure and long term follow up to assess the relevant safety data, with consequential amendment of the study completion date. The RMP (version 13) is updated accordingly and submitted together with an amended global registry protocol (amendment 8). The package leaflet is updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet and to bring the product information in line with the latest quality review of documents (QRD) template (version 10.2)

#### 15.2.8. [Varicella vaccine \(live\) - ZOSTAVAX \(CAP\) - EMEA/H/C/000674/II/0138](#)

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Applicant: MSD Vaccins

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Submission of an updated RMP (version 9.1) in order to reflect the completion of study V211-024: a post-licensure observational study of the long-term effectiveness of Zostavax (varicella vaccine (live)) and to bring it in line with revision 2.0.1 of the guidance on the format of RMP in the EU (template)

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

As per 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. [Alpelisib - PIQRAY \(CAP\) - EMEA/H/C/004804/II/0008/G](#)

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Applicant: Novartis Europharm Limited

PRAC Rapporteur: Menno van der Elst

Scope: Update of section 5.1 of the SmPC based on final results from study CBYL719C2301 (SOLAR-1) (listed as a post-authorisation efficacy study (PAES) in Annex II): a phase 3, randomized, double-blind, placebo-controlled study of alpelisib in combination with fulvestrant for men and postmenopausal women with hormone receptor positive, epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer which progressed on or after aromatase inhibitor treatment. Annex II is updated accordingly. In addition, the MAH is updating the anatomical therapeutic chemical (ATC) code in the SmPC. The RMP (version 5.0) is also updated in accordance

#### 15.3.2. [Avapritinib - AYVAKYT \(CAP\) - EMEA/H/C/005208/X/0004/G, Orphan](#)

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Applicant: Blueprint Medicines (Netherlands) B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Grouped applications consisting of: 1) line extension to add two new strengths of film-coated tablets (25 mg and 50 mg); 2) introduction of a new therapeutic indication to include treatment of adult patients with advanced systemic mastocytosis (AdvSM), including aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated haematological neoplasm (SM-AHN) and mast cell leukaemia (MCL), after at least one systemic therapy for Ayvakyt (avapritinib) based on the results of study BLU-285-2101: a phase 1 study of avapritinib in patients with AdvSM and relapsed or refractory myeloid malignancies and study BLU-285-2202: an open-label, single arm, phase 2 study to evaluate efficacy and safety of avapritinib in patients with AdvSM. The new indication is applicable to the new and existing presentations (25 mg, 50 mg, 100 mg and 200 mg film-coated tablets). As a consequence, sections 1, 2, 3, 4.1, 4.2, 4.4, 4.5, 4.6, 4.8, 5.1, 5.2, 5.3, 6.1 and 8 of the SmPC are updated. The labelling, package leaflet and the RMP (version 1.1) are updated in accordance



### **15.3.3. Axicabtagene ciloleucel - YESCARTA (CAP) - EMEA/H/C/004480/II/0042, Orphan**

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Applicant: Kite Pharma EU B.V., ATMP<sup>74</sup>

PRAC Rapporteur: Anette Kirstine Stark

Scope: Extension of indication to include the treatment of adult patients with relapsed or refractory follicular lymphoma (FL) after three or more lines of systemic therapy. As a consequence, sections 4.1, 4.8, 5.1 and 5.2 of the SmPC, Annex II-D on 'Conditions or restrictions with regard to the safe and effective use of the medicinal product' and the package leaflet are updated. The RMP (version 5.1) is updated in accordance. In addition, the applicant took the opportunity to make minor editorial corrections throughout the SmPC and package leaflet to align with the latest quality review of documents (QRD) template (version 10.2)

### **15.3.4. Brolucizumab - BEOVU (CAP) - EMEA/H/C/004913/II/0010**

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Applicant: Novartis Europharm Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include treatment of visual impairment due to diabetic macular oedema (DME). As a consequence, sections 4.1, 4.4, 4.8, and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 4.0) are updated in accordance

### **15.3.5. Cabozantinib - CABOMETYX (CAP) - EMEA/H/C/004163/II/0023**

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Applicant: Ipsen Pharma

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication to include monotherapy treatment of adults and adolescent patients aged 12 years and older, with locally advanced or metastatic differentiated thyroid carcinoma (DTC), refractory or not eligible to radioactive iodine (RAI) who have progressed during or after prior systemic therapy. 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 6.0) are updated in accordance

### **15.3.6. 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

### **15.3.7. Cariprazine - REAGILA (CAP) - EMEA/H/C/002770/II/0023**

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Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Ana Sofia Diniz Martins

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<sup>74</sup> Advanced therapy medicinal product

Scope: Update of sections 4.4, 4.5, 4.6 and 5.2 of the SmPC in order to update pharmacokinetic information based on final results from RGH-188-302 (CAROLA) study (listed as a category 3 study in the RMP): an open-label, single-arm, fixed-sequence, phase 1 trial in female schizophrenia patients to investigate the effect of multiple-dose administration of cariprazine on the pharmacokinetics of a combined oral contraceptive containing ethinylestradiol and levonorgestrel. The package leaflet and the RMP (version 2.0) are updated accordingly. In addition, the MAH took the opportunity to implement minor editorial changes in the SmPC and the package leaflet

#### 15.3.8. [Cobicistat, elvitegravir, emtricitabine, tenofovir alafenamide - GENVOYA \(CAP\) - EMEA/H/C/004042/X/0079/G](#)

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Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ilaria Baldelli

Scope: Grouped applications consisting of: 1) extension application to introduce a new strength (90 mg/90 mg/120 mg/6 mg film-coated tablets); 2) to include treatment of human immunodeficiency virus 1 (HIV 1) infection without any known mutations associated with resistance to the integrase inhibitor class, emtricitabine or tenofovir in paediatric patients aged from 2 years and with body weight at least 14 kg. Sections 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC and the package leaflet are updated to support the extended indication. The RMP (version 5.1) is updated in accordance

#### 15.3.9. [Corifollitropin alfa - ELONVA \(CAP\) - EMEA/H/C/001106/II/0061](#)

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Applicant: Organon N.V.

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication to include treatment of adolescent males (14 to less than 18 years) with hypogonadotropic hypogonadism in combination with human chorionic gonadotropin (hCG) based on final results of paediatric study P043: an open-label, non-comparative, multicentre safety and efficacy study of corifollitropin in association with hCG in male adolescents with hypogonadotropic hypogonadism, part of the paediatric investigation plan (PIP). As a consequence, sections 4.1, 4.2, 4.4, 4.6, 4.8, 4.9, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 9.2) are updated in accordance. In addition, the MAH took the opportunity to implement some minor editorial and formatting changes throughout the product information

#### 15.3.10. [Daunorubicin, cytarabine - VYXEOS LIPOSOMAL \(CAP\) - EMEA/H/C/004282/II/0018/G, Orphan](#)

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Applicant: Jazz Pharmaceuticals Ireland Limited

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Grouped variations consisting of: 1) extension of indication to add treatment of relapsed/refractory acute myeloid leukaemia (AML) in paediatric patients. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated based on the new safety and efficacy data from the paediatric clinical study AAML1421: a phase 1/2 study of liposomal daunorubicin/cytarabine alone followed by fludarabine, cytarabine, and granulocyte colony-stimulating factor (G-CSF) (FLAG) for children with relapsed AML. The

package leaflet and the RMP (version 1.1) are updated accordingly. In addition, the product information is updated in line with the latest quality review of documents (QRD) template (version 10.2); 2) submission of the final data from paediatric clinical study CPX-MA-1201: a phase 1/pilot study of liposomal daunorubicin/cytarabine for children, adolescents and young adults with recurrent or refractory hematologic malignancies, in support of the extension of indication

#### 15.3.11. Deferiprone - FERRIPROX (CAP) - EMEA/H/C/000236/X/0145

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Tiphaine Vaillant

Scope: Extension application to introduce a new pharmaceutical form (gastro-resistant tablets). The RMP (version 14.0) is updated in accordance

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

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) 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

#### 15.3.13. Dimethyl fumarate - TECFIDERA (CAP) - EMEA/H/C/002601/II/0069/G

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Martin Huber

Scope: Grouped variations consisting of: 1) update of section 4.8 of the SmPC in order to add rhinorrhoea to the list of adverse drug reactions (ADRs) with frequency not known based on a systematic review of information from clinical and non-clinical studies, post-marketing data and scientific literature. The package leaflet is updated accordingly; 2) update of sections 4.4, 4.8 and 5.1 of the SmPC in order to update efficacy and safety information based on final results from study 109MS303 (ENDORSE) (listed as a category 3 study in the RMP): a dose-blind, multicentre, extension study to determine the long-term safety and efficacy of two doses of BG00012 (dimethyl fumarate) monotherapy in subjects with relapsing-remitting multiple sclerosis. The RMP (version 11.1) is updated accordingly

#### 15.3.14. Doravirine - PIFELTRO (CAP) - EMEA/H/C/004747/WS2065/0019; doravirine, lamivudine, tenofovir disoproxil - DELSTRIGO (CAP) - EMEA/H/C/004746/WS2065/0026

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Extension of indication to include the new indication to the paediatric population weighing at least 35 kg. 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 2.1) are updated in accordance. In addition, the MAH took the opportunity to make minor editorial corrections and to update the list of local representatives in the package leaflet

#### **15.3.15. Dupilumab - DUPIXENT (CAP) - EMEA/H/C/004390/X/0045/G**

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Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Kimmo Jaakkola

Scope: Grouped applications consisting of: 1) extension of application to add a new strength (100 mg solution for injection) consisting of: one presentation containing 2 pre-filled syringes and one presentation containing 6 pre-filled syringes (multipack of 3 packs of 2); 2) extension of indication to include treatment of paediatric patients with severe asthma with type 2 inflammation aged 6 to 11 years old. The RMP (version 6.0) are updated accordingly

#### **15.3.16. Exenatide - BYDUREON (CAP) - EMEA/H/C/002020/II/0073**

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Applicant: AstraZeneca AB

PRAC Rapporteur: Annika Folin

Scope: Extension of indication to include the treatment of adolescents and children aged 10 years and above based on the results from study BCB114 (D5551C00002): a phase 3, double-blind, placebo-controlled, randomised, multicentre study to assess the safety and efficacy of exenatide once weekly in adolescents with type 2 diabetes (T2DM), which was initially submitted and assessed by CHMP as part of post-authorisation measure (PAM) P46 028. 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 35s1) are updated in accordance

#### **15.3.17. Febuxostat - ADENURIC (CAP) - EMEA/H/C/000777/II/0062**

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Applicant: Menarini International Operations Luxembourg S.A.

PRAC Rapporteur: Jan Neuhauser

Scope: Update of sections 4.4 and 4.5 of the SmPC in order to amend an existing warning on the drug-drug interaction information with mercaptopurine/azathioprine based on final results from study FAI-01 (listed as a category 3 study in the RMP): a phase 1, drug-drug interaction study investigating the pharmacokinetic (PK) profile of 6-mercaptopurine following coadministration of two doses febuxostat and azathioprine in healthy subjects. The RMP (version 9.0) is updated accordingly

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

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Applicant: Alnylam Netherlands B.V.

PRAC Rapporteur: Martin Huber

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

#### [15.3.19. Guselkumab - TREMFYA \(CAP\) - EMEA/H/C/004271/II/0031](#)

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Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of sections 4.8 and 5.1 of the SmPC based on 2-year data from study CNTO1959PSA3002: a phase 3, multicentre, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of guselkumab administered subcutaneously in subjects with active psoriatic arthritis. The RMP (version 8.2) is updated accordingly

#### [15.3.20. Ibalizumab - TROGARZO \(CAP\) - EMEA/H/C/004961/II/0015](#)

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Applicant: Theratechnologies Europe Limited

PRAC Rapporteur: David Olsen

Scope: Updated timelines for a post-authorisation efficacy study (PAES) to further characterise the efficacy of ibalizumab in combination with other anti-retroviral medicinal products, for the treatment of adults infected with multidrug resistant human immunodeficiency virus-1 (HIV-1) infection for whom it is otherwise not possible to construct a suppressive antiviral regimen (PROMISE study) to provide the final study report from October 2025 to October 2026. Annex II of the product information is updated accordingly. The RMP (version 2.0) is updated accordingly and in line with the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00010797/202009) adopted in April 2021

#### [15.3.21. Ipilimumab - YERVOY \(CAP\) - EMEA/H/C/002213/WS2113/0090; nivolumab - OPDIVO \(CAP\) - EMEA/H/C/003985/WS2113/0108](#)

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Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include first-line treatment of adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma (OSCC) for Opdivo (nivolumab) in combination with Yervoy (ipilimumab). As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 24.0 for Opdivo and version 33.0 for Yervoy) are updated in accordance

#### [15.3.22. Ipilimumab - YERVOY \(CAP\) - EMEA/H/C/002213/WS2134/0091; nivolumab - OPDIVO \(CAP\) - EMEA/H/C/003985/WS2134/0109](#)

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Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of sections 4.2, 4.8 and 5.1 of the SmPC based on final results from study CA209908: a phase 1b/2 clinical trial of nivolumab monotherapy and nivolumab in

combination with ipilimumab in paediatric subjects with high grade primary central nervous system (CNS) malignancies. The RMP (version 22.3 for Opdivo) is updated in accordance

#### **15.3.23. Ipilimumab - YERVOY (CAP) - EMEA/H/C/002213/WS2153/0093; nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/WS2153/0111**

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Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of sections 4.2 and 6.6 of the SmPC to change the infusion time for ipilimumab when used as monotherapy or in combination with nivolumab in the melanoma indications. The package leaflet for Yervoy (ipilimumab) is updated in accordance. The RMP (version 26.0 for Opdivo and version 34.0 for Yervoy) are updated accordingly. In addition, the MAH took the opportunity to introduce an administrative update in Annex II of Yervoy (ipilimumab)

#### **15.3.24. Ixazomib - NINLARO (CAP) - EMEA/H/C/003844/II/0033, Orphan**

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Applicant: Takeda Pharma A/S

PRAC Rapporteur: Annika Folin

Scope: Submission of the final report for the final analysis of overall survival (OS) for study C16010 (listed as an obligation in Annex II): a phase 3, randomised, double-blind multicentre study comparing ixazomib in combination with lenalidomide and dexamethasone (LenDex) versus placebo plus LenDex in adult patients with relapsed and/or refractory multiple myeloma. Annex II-D on 'Conditions or restrictions with regard to the safe and effective use of the medicinal product' and the RMP (version 7.0) are updated accordingly

#### **15.3.25. Mercaptamine - PROCYSBI (CAP) - EMEA/H/C/002465/X/0035, Orphan**

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Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension application to introduce a new pharmaceutical form associated with two new strengths (75 and 300 mg gastro-resistant granules). The RMP (version 7.2) is updated in accordance

#### **15.3.26. Nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/II/0107**

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Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include in combination with fluoropyrimidine- and platinum-based combination chemotherapy the first-line treatment of adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma (OSCC) for OPDIVO based on study CA209648: a randomized phase 3 study of nivolumab plus ipilimumab or nivolumab combined with fluorouracil plus cisplatin versus fluorouracil plus cisplatin in subjects with unresectable advanced, recurrent or metastatic previously untreated oesophageal squamous cell carcinoma. As a consequence, sections 4.1, 4.2, 4.4,

4.8, 5.1 and 6.6 of the SmPC are updated. The package leaflet and the RMP (version 25.0) are updated in accordance

#### **15.3.27. Parathyroid hormone - NATPAR (CAP) - EMEA/H/C/003861/II/0029, Orphan**

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Applicant: Shire Pharmaceuticals Ireland Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Submission of the final results of study SHP634-101: an open-label, randomised, crossover study to assess the pharmacokinetic and pharmacodynamic profiles of once-daily and twice-daily dose regimens of recombinant human parathyroid hormone (rhPTH[1-84]) administered subcutaneously to subjects with hypoparathyroidism. Further clinical evaluation of an alternative dosing regimen is no longer warranted, as outlined in the current specific obligation (study SHP634-403). The conditional marketing authorisation can therefore be converted into a standard marketing authorisation (no longer subject to a specific obligation) valid for 5 years. The RMP (version 3.2) is updated accordingly

#### **15.3.28. Pembrolizumab - KEYTRUDA (CAP) - EMEA/H/C/003820/II/0110**

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Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication in combination with chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment after surgery of adults with locally advanced, inflammatory, or early-stage triple-negative breast cancer at high-risk of recurrence; as a consequence, sections 4.1, 4.2, and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 37.1) are updated in accordance

#### **15.3.29. Pembrolizumab - KEYTRUDA (CAP) - EMEA/H/C/003820/II/0111**

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Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication to include the adjuvant treatment of adults and adolescents aged 12 years and older with stage IIB, stage IIC or stage III melanoma and to include the treatment of adolescents aged 12 years and older with advanced melanoma. As a consequence, sections 4.1, 4.2, and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 36.1) are updated in accordance

#### **15.3.30. Posaconazole - NOXAFIL (CAP) - EMEA/H/C/000610/X/0063/G**

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Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Nathalie Gault

Scope: Grouped applications consisting of: 1) extension application to introduce a new pharmaceutical form (gastro-resistant powder and solvent for oral suspension); 2) extension of indication to the paediatric population. As a consequence, sections 4.1, 4.2, 4.8, 5.1, 5.2 of the SmPC are updated. The package leaflet and the RMP (version 17.1) are updated in accordance



### 15.3.31. Rucaparib - RUBRACA (CAP) - EMEA/H/C/004272/II/0029

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Applicant: Clovis Oncology Ireland Limited

PRAC Rapporteur: Annika Folin

Scope: Update of sections 4.4, 4.8 and 5.1 of the SmPC based on final results from study CO-338-043 (ARIEL4) (listed as a specific obligation in Annex II): a phase 3, multicentre, open-label, randomised study evaluating the efficacy and safety of rucaparib versus chemotherapy for treatment of relapsed ovarian cancer. The package leaflet and the RMP (version 6.1) are updated accordingly. In addition, the MAH took the opportunity to make minor editorial changes and bring the product information in line with the latest quality review of documents (QRD) template (version 10.2 Rev.1)

### 15.3.32. Sofosbuvir, velpatasvir - EPCLUSA (CAP) - EMEA/H/C/004210/X/0056/G

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Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Grouped applications consisting of: 1) extension application to introduce a new pharmaceutical form (coated granules in sachet) associated with strengths 200mg/50mg and 150mg/37.5mg. The new presentations are indicated for the treatment of chronic hepatitis C virus (HCV) infection in patients 3 years of age and older; 2) inclusion of paediatric use in patients 3 years of age and older to the existing presentations of the film-coated tablets. 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 7.1) are updated accordingly. In addition, the MAH took the opportunity to implement minor updates and corrections throughout the product information

### 15.3.33. Teduglutide - REVESTIVE (CAP) - EMEA/H/C/002345/II/0054/G, Orphan

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Applicant: Shire Pharmaceuticals Ireland Limited

PRAC Rapporteur: Anette Kirstine Stark

Scope: Grouped variations consisting of: 1) extension of indication to include patients from 4 months corrected gestational aged 1 year and above. Consequently sections 4.1, 4.2, 4.8, 5.1 and 5.2 are updated. The package leaflet and the RMP (version 9.1) are updated accordingly; 2) update of Annex II-D on 'Conditions or restrictions with regards to the safe and effective use of the medicinal product' to amend the date of completion of the imposed post authorisation study: an international short bowel syndrome registry, from Q3 2031 to Q2 2032. In addition, the MAH took the opportunity to amend the list of local representatives

### 15.3.34. Tenofovir disoproxil - VIREAD (CAP) - EMEA/H/C/000419/II/0204

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Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Nathalie Gault

Scope: Submission of final study report for study GS-US-174-0144 (listed as category 3 study in the RMP): a randomised, double-blind evaluation of the antiviral efficacy, safety and tolerability of tenofovir disoproxil fumarate. This application fulfils the Article 46



commitment to provide the final week 192 study results for clinical measure 'study 5' (study GS\_US\_174-0144) listed in the paediatric investigation plan (PIP). As a consequence, section 5.1 of the SmPC is updated accordingly. Additionally, the risk minimisation measures for paediatrics are removed from the RMP and Annex II of the product information. The package leaflet and the RMP (version 25.1) are updated accordingly. In addition, the MAH took the opportunity to implement minor linguistic amendments throughout the product information. Furthermore, the expression of lactose content in Annex I for the tablets was changed to refer to lactose base (not as monohydrate) in line with current practice

### 15.3.35. Tildrakizumab - ILUMETRI (CAP) - EMEA/H/C/004514/X/0023

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Applicant: Almirall S.A

PRAC Rapporteur: Adam Przybylkowski

Scope: Extension application to introduce a new strength (200 mg solution for injection). The RMP (version 1.0) is updated accordingly

## 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 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. 5-aminolevulinic acid<sup>75</sup> - GLIOLAN (CAP) - PSUSA/00000009/202103

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Applicant: medac Gesellschaft für klinische Spezialpräparate mbH

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Evaluation of a PSUSA procedure

#### 16.1.2. Alogliptin - VIPIDIA (CAP); alogliptin, metformin - VIPDOMET (CAP); alogliptin, pioglitazone - INCRESYNC (CAP) - PSUSA/00010061/202104

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Applicant(s): Takeda Pharma A/S

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

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<sup>75</sup> Indicated for the treatment of glioma only

#### 16.1.3. Brolucizumab - BEOVU (CAP) - PSUSA/00010829/202104

Applicant: Novartis Europharm Limited  
PRAC Rapporteur: Brigitte Keller-Stanislawski  
Scope: Evaluation of a PSUSA procedure

#### 16.1.4. Bupivacaine - EXPAREL LIPOSOMAL (CAP) - PSUSA/00010889/202104

Applicant: Pacira Ireland Limited  
PRAC Rapporteur: Rhea Fitzgerald  
Scope: Evaluation of a PSUSA procedure

#### 16.1.5. Bupivacaine, meloxicam - ZYNRELEF (CAP) - PSUSA/00010880/202103

Applicant: Heron Therapeutics, B.V.  
PRAC Rapporteur: Liana Gross-Martirosyan  
Scope: Evaluation of a PSUSA procedure

#### 16.1.6. Ciclosporin<sup>76</sup> - IKERVIS (CAP); VERKAZIA (CAP) - PSUSA/00010362/202103

Applicant(s): Santen Oy  
PRAC Rapporteur: Jan Neuhauser  
Scope: Evaluation of a PSUSA procedure

#### 16.1.7. Colesevelam - CHOLESTAGEL (CAP) - PSUSA/00000864/202103

Applicant: Cheplapharm Arzneimittel GmbH  
PRAC Rapporteur: Menno van der Elst  
Scope: Evaluation of a PSUSA procedure

#### 16.1.8. Dacomitinib - VIZIMPRO (CAP) - PSUSA/00010757/202103

Applicant: Pfizer Europe MA EEIG  
PRAC Rapporteur: Menno van der Elst  
Scope: Evaluation of a PSUSA procedure

#### 16.1.9. Dapagliflozin - EDISTRIDE (CAP); FORXIGA (CAP) - PSUSA/00010029/202104

Applicant(s): AstraZeneca AB  
PRAC Rapporteur: Annika Folin  
Scope: Evaluation of a PSUSA procedure

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<sup>76</sup> Topical use only

#### 16.1.10. Darvadstrocel - ALOFISEL (CAP) - PSUSA/00010676/202103

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Applicant: Takeda Pharma A/S, ATMP<sup>77</sup>  
PRAC Rapporteur: Brigitte Keller-Stanislawski  
Scope: Evaluation of a PSUSA procedure

#### 16.1.11. Dimethyl fumarate<sup>78</sup> - SKILARENCE (CAP) - PSUSA/00010647/202103

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Applicant: Almirall S.A  
PRAC Rapporteur: Annika Folin  
Scope: Evaluation of a PSUSA procedure

#### 16.1.12. Ebola vaccine (rDNA<sup>79</sup>, replication-incompetent) - MVABEA (CAP); ZABDENO (CAP) - PSUSA/00010857/202103

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Applicant(s): Janssen-Cilag International N.V.  
PRAC Rapporteur: Jean-Michel Dogné  
Scope: Evaluation of a PSUSA procedure

#### 16.1.13. Enfuvirtide - FUZEON (CAP) - PSUSA/00001217/202103

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Applicant: Roche Registration GmbH  
PRAC Rapporteur: Ulla Wändel Liminga  
Scope: Evaluation of a PSUSA procedure

#### 16.1.14. Exenatide - BYDUREON (CAP); BYETTA (CAP) - PSUSA/00009147/202103

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Applicant(s): AstraZeneca AB  
PRAC Rapporteur: Annika Folin  
Scope: Evaluation of a PSUSA procedure

#### 16.1.15. Filgotinib - JYSELECA (CAP) - PSUSA/00010879/202103

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Applicant: Gilead Sciences Ireland UC  
PRAC Rapporteur: Nikica Mirošević Skvrce  
Scope: Evaluation of a PSUSA procedure

#### 16.1.16. Galcanezumab - EMGALITY (CAP) - PSUSA/00010733/202103 (with RMP)

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Applicant: Eli Lilly Nederland B.V.  
PRAC Rapporteur: Kirsti Villikka

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<sup>77</sup> Advanced therapy medicinal product

<sup>78</sup> Indicated for the treatment of psoriasis only

<sup>79</sup> Recombinant deoxyribonucleic acid

Scope: Evaluation of a PSUSA procedure

**16.1.17. Gilteritinib - XOSPATA (CAP) - PSUSA/00010832/202103**

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Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

**16.1.18. Herpes zoster vaccine (recombinant, adjuvanted) - SHINGRIX (CAP) - PSUSA/00010678/202104**

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Applicant: GlaxoSmithkline Biologicals SA

PRAC Rapporteur: Sonja Hrabcik

Scope: Evaluation of a PSUSA procedure

**16.1.19. Ixekizumab - TALTZ (CAP) - PSUSA/00010493/202103**

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Applicant: Eli Lilly and Co (Ireland) Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

**16.1.20. Japanese encephalitis virus (inactivated) - IXIARO (CAP) - PSUSA/00001801/202103**

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Applicant: Valneva Austria GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

**16.1.21. Lorlatinib - LORVIQUA (CAP) - PSUSA/00010760/202103**

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Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Evaluation of a PSUSA procedure

**16.1.22. Lusutrombopag - MULPLEO (CAP) - PSUSA/00010755/202103**

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Applicant: Shionogi B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

**16.1.23. Mogamulizumab - POTELIGEO (CAP) - PSUSA/00010741/202103**

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Applicant: Kyowa Kirin Holdings B.V.

PRAC Rapporteur: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

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**16.1.24. Naldemedine - RIZMOIC (CAP) - PSUSA/00010753/202103**

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Applicant: Shionogi B.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

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**16.1.25. Nintedanib<sup>80</sup> - OFEV (CAP) - PSUSA/00010319/202104**

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Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Evaluation of a PSUSA procedure

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**16.1.26. Niraparib - ZEJULA (CAP) - PSUSA/00010655/202103**

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Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

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**16.1.27. Risankizumab - SKYRIZI (CAP) - PSUSA/00010765/202103**

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Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

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**16.1.28. Siponimod - MAYZENT (CAP) - PSUSA/00010818/202103**

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Applicant: Novartis Europharm Limited

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

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**16.1.29. Sodium zirconium cyclosilicate - LOKELMA (CAP) - PSUSA/00010675/202103**

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Applicant: AstraZeneca AB

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

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**16.1.30. Solriamfetol - SUNOSI (CAP) - PSUSA/00010831/202103**

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Applicant: Jazz Pharmaceuticals Ireland Limited

PRAC Rapporteur: Julia Pallos

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<sup>80</sup> Respiratory indication(s) only

Scope: Evaluation of a PSUSA procedure

#### **16.1.31. Tildrakizumab - ILUMETRI (CAP) - PSUSA/00010720/202103**

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Applicant: Almirall S.A

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

#### **16.1.32. Tolcapone - TASMAR (CAP) - PSUSA/00002985/202103**

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Applicant: Meda AB

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

#### **16.1.33. Tucatinib - TUKYSA (CAP) - PSUSA/00010918/202104**

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Applicant: Seagen B.V.

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

#### **16.1.34. Velmanase alfa - LAMZEDE (CAP) - PSUSA/00010677/202103**

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Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

#### **16.1.35. Vildagliptin - GALVUS (CAP), JALRA (CAP), XILIARX (CAP); vildagliptin, metformin - EUCREAS (CAP), ICANDRA (CAP), ZOMARIST (CAP) - PSUSA/00003113/202102**

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Applicant: Novartis Europharm Limited

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

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

None

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

#### **16.3.1. Ampicillin, sulbactam (NAP) - PSUSA/00000197/202102**

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Applicant(s): various

PRAC Lead: Ilaria Baldelli

Scope: Evaluation of a PSUSA procedure

#### **16.3.2. Bilastine (NAP) - PSUSA/00003163/202103**

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Applicant(s): various

PRAC Lead: Roxana Dondera

Scope: Evaluation of a PSUSA procedure

#### **16.3.3. Butoconazole (NAP) - PSUSA/00000471/202102**

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Applicant(s): various

PRAC Lead: Melinda Palfi

Scope: Evaluation of a PSUSA procedure

#### **16.3.4. Calcium chloride, glutamic acid, glutathione, histidine, lactobionic acid, magnesium chloride, mannitol, potassium chloride, sodium hydroxide (NAP) - PSUSA/00009162/202103**

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Applicant(s): various

PRAC Lead: Maria Popova-Kiradjieva

Scope: Evaluation of a PSUSA procedure

#### **16.3.5. Citrulline malate (NAP) - PSUSA/00010579/202103**

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Applicant(s): various

PRAC Lead: Eva Jirsová

Scope: Evaluation of a PSUSA procedure

#### **16.3.6. Ethinylestradiol, gestodene (NAP) - PSUSA/00001308/202103**

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Applicant(s): various

PRAC Lead: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

#### **16.3.7. Fluorodopa (<sup>18</sup>F) (NAP) - PSUSA/00010002/202103**

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Applicant(s): various

PRAC Lead: John Joseph Borg

Scope: Evaluation of a PSUSA procedure

#### **16.3.8. Gliclazide (NAP) - PSUSA/00001532/202102**

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Applicant(s): various

PRAC Lead: Gudrun Stefansdottir

Scope: Evaluation of a PSUSA procedure

#### **16.3.9. Nitrazepam (NAP) - PSUSA/00002170/202103**

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Applicant(s): various

PRAC Lead: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

#### **16.3.10. Nitrofurantoin, nifurtoinol (NAP) - PSUSA/00002174/202102**

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Applicant(s): various

PRAC Lead: Rugilė Pilvinienė

Scope: Evaluation of a PSUSA procedure

#### **16.3.11. Olodaterol (NAP) - PSUSA/00010245/202103**

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Applicant(s): various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

#### **16.3.12. Rabies vaccine (NAP) - PSUSA/00009277/202103**

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Applicant(s): various

PRAC Lead: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

#### **16.3.13. Tenoxicam (NAP) - PSUSA/00002893/202102**

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Applicant(s): various

PRAC Lead: Ilaria Baldelli

Scope: Evaluation of a PSUSA procedure

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

#### **16.4.1. Dexmedetomidine - DEXDOR (CAP) - EMEA/H/C/002268/LEG 016.4**

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Applicant: Orion Corporation

PRAC Rapporteur: Ulla Wändel Liminga

Scope: MAH's response to LEG 016.3 [analysis of available mortality data from controlled clinical trials in the dexmedetomidine development programme as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00000998/201903) adopted in November 2019] as per the request for supplementary information (RSI) adopted in July 2021



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

### 16.5.1. Coronavirus (COVID-19) mRNA<sup>81</sup> vaccine (nucleoside-modified) - SPIKEVAX (CAP) - EMEA/H/C/005791/II/0015/G

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Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Hans Christian Siersted

Scope: Grouped variations to address PRAC requests as per the conclusions of the second and third monthly safety summary report (MSSR) procedures (MEA 011.1 and MEA 011.2) respectively: 1) update of sections 4.4 of the SmPC to provide additional safety information regarding hypersensitivity and anaphylaxis, as requested by PRAC in the second MSSR. The package leaflet is updated accordingly; 2) update of section 4.8 of the SmPC to include 'delayed injection site reaction' as an adverse reaction with a frequency 'common', as requested by PRAC in the third MSSR. The package leaflet is updated accordingly. In addition, the MAH submitted a justification for not adding diarrhoea to the product information as an adverse reaction as requested by PRAC in the third MSSR and took the opportunity to introduce minor editorial changes in the product information

## 16.6. Expedited summary safety reviews<sup>82</sup>

### 16.6.1. Coronavirus (COVID-19) mRNA<sup>83</sup> vaccine (nucleoside-modified) - COMIRNATY (CAP) - EMEA/H/C/005735/MEA 002.9

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Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Tenth expedited monthly summary safety report (MSSR) for Comirnaty (COVID-19 mRNA vaccine (nucleoside-modified)) during the coronavirus disease (COVID-19) pandemic

### 16.6.2. Coronavirus (COVID-19) mRNA<sup>84</sup> vaccine (nucleoside-modified) - SPIKEVAX (CAP) - EMEA/H/C/005791/MEA 011.8

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Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Hans Christian Siersted

Scope: Ninth expedited monthly summary safety report (MSSR) for Spikevax (COVID-19 mRNA vaccine (nucleoside-modified)) 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.

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<sup>81</sup> Messenger ribonucleic acid

<sup>82</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>83</sup> Messenger ribonucleic acid

<sup>84</sup> Messenger ribonucleic acid

## **17.1. Protocols of PASS imposed in the marketing authorisation(s)<sup>85</sup>**

### **17.1.1. Elivaldogene autotemcel - SKYSONA (CAP) - EMEA/H/C/PSA/S/0079**

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Applicant: bluebird bio (Netherlands) B.V, ATMP<sup>86</sup>

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Substantial amendment to a protocol previously agreed in the initial marketing authorisation application (MAA)/marketing authorisation for study REG-502 (listed as an obligation in Annex II and RMP): a prospective, multicentre, international, observational, long-term safety and effectiveness registry study of patients with cerebral adrenoleukodystrophy (CALD) treated with elivaldogene autotemcel or allogeneic hematopoietic stem cell transplantation (Stargazer)

### **17.1.2. Tolvaptan - JINARC (CAP) - EMEA/H/C/PSA/S/0078**

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Applicant: Otsuka Pharmaceutical Netherlands B.V.

PRAC Rapporteur: Amelia Cupelli

Scope: Substantial amendment to a protocol previously agreed in March 2016 (PSP/0028.2) for a 7.5-year, multicentre, non-interventional PASS to characterise and quantify the identified risk of idiosyncratic liver injury in Jinarc (tolvaptan) treated patients with autosomal dominant polycystic kidney disease (ADPKD) in routine clinical practice

### **17.1.3. Valproate (NAP) - EMEA/H/N/PSP/J/0072.5**

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

PRAC Rapporteur: Liana Gross-Martirosyan

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

### **17.1.4. Valproate (NAP) - EMEA/H/N/PSP/J/0075.6**

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

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Second interim report for a joint drug utilisation study (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)

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<sup>85</sup> In accordance with Article 107n of Directive 2001/83/EC

<sup>86</sup> Advanced therapy medicinal product

### 17.1.5. Valproate (NAP) - EMEA/H/N/PSP/J/0094.1

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

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: MAH's response to PSP/J/0094 [protocol for a joint retrospective study of multiple European data sources characterising neurodevelopmental disorders in children exposed in utero to valproate and/or other antiepileptic drugs with long-term follow-up] as per the request for supplementary information (RSI) adopted in June 2021

## 17.2. Protocols of PASS non-imposed in the marketing authorisation(s)<sup>87</sup>

### 17.2.1. Alpelisib - PIQRAY (CAP) - EMEA/H/C/004804/MEA 002.1

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Applicant: Novartis Europharm Limited

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to MEA 002 [protocol for study CBYL719C2404: a non-interventional study of Piqray (alpelisib) in combination with fulvestrant in postmenopausal women and men with hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative, locally advanced or metastatic breast cancer with a PIK3CA mutation in the real-world setting in European countries, as per the outcome of variation II/001 finalised in March 2021. The safety concerns addressed are hyperglycaemia and osteonecrosis of the jaw] as per the request for supplementary information (RSI) adopted in June 2021

### 17.2.2. Coronavirus (COVID-19) mRNA<sup>88</sup> vaccine (nucleoside-modified) - COMIRNATY (CAP) - EMEA/H/C/005735/MEA 010.1

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Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Amendment to a protocol previously agreed in the initial marketing authorisation application (MAA)/marketing authorisation for study C4591012 assessing the occurrence of safety events of interest, including severe or atypical COVID-19 in real-world use of COVID-19 mRNA vaccine [final clinical study report (CSR) expected in December-2023]

### 17.2.3. Coronavirus (COVID-19) mRNA<sup>89</sup> vaccine (nucleoside-modified) - COMIRNATY (CAP) - EMEA/H/C/005735/MEA 011.2

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Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to MEA 011.1 [protocol for study C4591010: assessment of occurrence of safety events in real-world use of COVID-19 mRNA vaccine [final clinical study report (CSR) expected in September 2024] (from initial opinion/marketing authorisation)] as per the request for supplementary information (RSI) adopted in May

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<sup>87</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>88</sup> Messenger ribonucleic acid

<sup>89</sup> Messenger ribonucleic acid

2021

**17.2.4. Coronavirus (COVID-19) mRNA<sup>90</sup> vaccine (nucleoside-modified) - COMIRNATY (CAP) - EMEA/H/C/005735/MEA 037**

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Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Protocol for study C4591009: a non-interventional PASS in US to assess the occurrence of safety events of interest, including myocarditis and pericarditis (from variation II/0059 finalised in October 2021)

**17.2.5. Coronavirus (COVID-19) mRNA<sup>91</sup> vaccine (nucleoside-modified) - SPIKEVAX (CAP) - EMEA/H/C/005791/MEA 003.3**

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Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Hans Christian Siersted

Scope: MAH's response to MEA 003 [protocol for a study (listed as a category 3 study in the RMP): an enhanced pharmacovigilance study to provide additional evaluation of adverse events of special interest (AESI) and emerging validated safety signals - post authorisation safety of SARS-CoV-2 mRNA-1273 vaccine in the US [final clinical study report (CSR) expected in June 2023] (from initial opinion/marketing authorisation)] as adopted in March 2021

**17.2.6. Daratumumab - DARZALEX (CAP) - EMEA/H/C/004077/MEA 011**

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Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Protocol for study AMY2009: a Multicentre, prospective study of daratumumab-based therapy in newly diagnosed patients with AL amyloidosis (from variation II/0043)

**17.2.7. Drospirenone, estetrol - DROVELIS (CAP) - EMEA/H/C/005336/MEA 001**

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Applicant: Chemical Works of Gedeon Richter Plc. (Gedeon Richter Plc.)

PRAC Rapporteur: Martin Huber

Scope: Protocol for an international active surveillance study (INAS-NEES): a prospective non-interventional comparative cohort observational study to characterize and compare the risks of estetrol/drospirenone with combined oral contraceptive-containing levonorgestrel (COC-LNG) in a study population that is representative of the actual users of these preparations. The main clinical outcome of interest is venous thromboembolism (VTE), specifically deep venous thrombosis (DVT) and pulmonary embolism (PE) [final study report expected in December 2029] (from initial opinion/marketing authorisation (MA))

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<sup>90</sup> Messenger ribonucleic acid

<sup>91</sup> Messenger ribonucleic acid

#### 17.2.8. Drospirenone, estetrol - LYDISILKA (CAP) - EMEA/H/C/005382/MEA 001

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Applicant: Estetra SRL

PRAC Rapporteur: Martin Huber

Scope: Protocol for an international active surveillance study (INAS-NEES): a prospective non-interventional comparative cohort observational study to characterize and compare the risks of estetrol/drospirenone with combined oral contraceptive-containing levonorgestrel (COC-LNG) in a study population that is representative of the actual users of these preparations. The main clinical outcome of interest is venous thromboembolism (VTE), specifically deep venous thrombosis (DVT) and pulmonary embolism (PE) [final study report expected in December 2029] (from initial opinion/marketing authorisation (MA))

#### 17.2.9. Empagliflozin - JARDIANCE (CAP) - EMEA/H/C/002677/MEA 002.11

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Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Eva Segovia

Scope: Amendment to a protocol previously agreed in September 2019 for study 1245.96 (version 8.0): a non-interventional PASS in patients with type 2 diabetes mellitus (T2DM) to assess the risk of acute liver injury, acute kidney injury and chronic kidney disease, severe complications of urinary tract infection, genital infections, and diabetic ketoacidosis among patients treated with empagliflozin compared to patients treated with dipeptidyl peptidase 4 (DPP-4) inhibitors

#### 17.2.10. Empagliflozin, metformin - SYNJARDY (CAP) - EMEA/H/C/003770/MEA 003.8

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Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Eva Segovia

Scope: Amendment to a protocol previously agreed in September 2019 for study 1245.96 (version 8.0): a non-interventional PASS in patients with type 2 diabetes mellitus (T2DM) to assess the risk of acute liver injury, acute kidney injury and chronic kidney disease, severe complications of urinary tract infection, genital infections, and diabetic ketoacidosis among patients treated with empagliflozin compared to patients treated with dipeptidyl peptidase 4 (DPP-4) inhibitors

#### 17.2.11. Migalastat - GALAFOLD (CAP) - EMEA/H/C/004059/MEA 001.1

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Applicant: Amicus Therapeutics Europe Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: MAH's response to MEA 001 [protocol for study AT1001-030: a prospective, multicentre, multinational, observational disease registry in Fabry disease patients treated with migalastat and untreated patients to evaluate the long-term safety and effectiveness of migalastat in Fabry disease patients in real-world setting] as per the request for supplementary information (RSI) adopted in December 2016

#### 17.2.12. Ozanimod - ZEPOSIA (CAP) - EMEA/H/C/004835/MEA 001.2

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Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Maria del Pilar Rayon

Scope: MAH's response to MEA 001.1 [protocol for study RPC-1063-MS-004 (listed as a category 3 study in the RMP): a post authorisation multinational long-term non-interventional study (ORION) study on ozanimod real world safety [final clinical study report (CSR) expected in December 2031]] as per the request for supplementary information (RSI) adopted in September 2021

### 17.3. Results of PASS imposed in the marketing authorisation(s)<sup>92</sup>

#### 17.3.1. Dexketoprofen, tramadol (NAP) - EMEA/H/N/PSR/S/0035

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Applicant: Menarini International Operations Luxembourg S.A. (Dextradol, Enanplus, Skudexa, Takudex)

PRAC Rapporteur: Eva Segovia

Scope: Results of a drug utilisation study (DUS) and PASS on dexketoprofen-tramadol (DKP-TRAM) fixed combination to evaluate the pattern of prescriptions of DKP-TRAM and assess the risk of adverse events (AE) (e.g. nausea, vomiting, diarrhoea, vertigo) in DKP-TRAM vs. tramadol monotherapy (including tramadol-paracetamol combinations) users, with a special focus on patients 75 years old and over

### 17.4. Results of PASS non-imposed in the marketing authorisation(s)<sup>93</sup>

#### 17.4.1. Coronavirus (COVID-19) vaccine (ChAdOx1-S [recombinant]) - VAXZEVRIA (CAP) - EMEA/H/C/005675/II/0038

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Applicant: AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

Scope: Submission of the final report from study MS1222-0003 (listed as a category 3 study in the RMP) as assessment of anti-platelet factor 4 (PF4) antibodies prior to, and following, vaccination with AZD1222: a study where sera of vaccinated individuals in study D8110C00001 are tested to elucidate whether vaccination with Vaxzevria (COVID-19 vaccine) leads to increased levels of circulating anti-PF4 antibodies, a key component of the hypothesised mechanism underlying thrombosis with thrombocytopenia syndrome (TTS)

#### 17.4.2. Denosumab - XGEVA (CAP) - EMEA/H/C/002173/II/0078

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Applicant: Amgen Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of the final report from study 20101102 (listed as a category 3 study in the RMP) as 'osteonecrosis of the jaw (ONJ) case registry': an observational PASS with the primary objective to estimate the rate and describe the time course of resolution of ONJ, in

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<sup>92</sup> In accordance with Article 107p-q of Directive 2001/83/EC

<sup>93</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 04 August 2013

subjects 18 years of age with cancer who had newly diagnosed, positively adjudicated ONJ

#### **17.4.3. Lomitapide - LOJUXTA (CAP) - EMEA/H/C/002578/II/0047**

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Applicant: Amryt Pharmaceuticals DAC

PRAC Rapporteur: Menno van der Elst

Scope: Introduction of an enhanced pharmacovigilance system to evaluate the occurrence and outcomes of pregnancy in females of reproductive potential treated with lomitapide who decide to continue the pregnancy following advice from a teratologist/clinician, replacing the currently agreed pregnancy exposure register (PER) (listed as part of Annex II-E on 'specific obligation to complete post-authorisation measures for the marketing authorisation under exceptional circumstances'). The RMP (version 6.5) is updated accordingly. In addition, the MAH took the opportunity to introduce minor administrative changes

#### **17.4.4. Naloxegol - MOVENTIG (CAP) - EMEA/H/C/002810/II/0034**

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Applicant: Kyowa Kirin Holdings B.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: Submission of the final report from study D3820R00006 (listed as a category 3 study in the RMP): an observational drug utilisation in selected European populations. The RMP (version 7.0) is updated accordingly

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

#### **17.5.1. Arsenic trioxide - TRISENOX (CAP) - EMEA/H/C/000388/MEA 050.3**

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Applicant: Teva B.V.

PRAC Rapporteur: Tiphaine Vaillant

Scope: MAH's response to MEA 050.2 [first interim report for study C18477-ONC-50025: a post-authorisation long term safety cohort study in acute promyelocytic leukaemia (APL) patients treated with Trisenox (arsenic trioxide) to assess the long-term safety of all-trans retinoic acid (ATRA) + arsenic trioxide (ATO) in newly diagnosed low to intermediate risk APL patients in a real-world clinical practice setting [final report expected in 2Q 2023]] as per the request for supplementary information (RSI) adopted in June 2021

#### **17.5.2. Belimumab - BENLYSTA (CAP) - EMEA/H/C/002015/MEA 003.5**

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Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Interim report for study BEL115467/HGS1006-C1113: a randomized, double-blind placebo-controlled large safety study, based on a protocol agreed with CHMP, evaluating over a minimum of one year the incidence of all-cause mortality and adverse events of special interest (AESI) in patients with systemic lupus erythematosus receiving belimumab [three years' malignancy and mortality follow-up.] [final report with 5-year follow-up data expected in December 2023]

### 17.5.3. Coronavirus (COVID-19) mRNA<sup>94</sup> vaccine (nucleoside-modified) - COMIRNATY (CAP) - EMEA/H/C/005735/MEA 011.3

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Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Interim report for study C4591010: assessment of occurrence of safety events in real-world use of COVID-19 mRNA vaccine [final clinical study report (CSR) expected in September 2024] (from initial opinion/marketing authorisation)

### 17.5.4. Defibrotide - DEFITELIO (CAP) - EMEA/H/C/002393/LEG 011.2

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Applicant: Gentium S.r.l.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: MAH's response to LEG 011.1 [second interim report for a national, post-registration observational study of the long-term safety and health outcome of patients treated with Defitelio (defibrotide), including patients with severe hepatic veno-occlusive disease (VOD) after hematopoietic stem-cell transplantation (HSCT) (DEFIFRANCE registry)] as per the request for supplementary information (RSI) adopted in July 2021

### 17.5.5. Imiglucerase - CERZYME (CAP) - EMEA/H/C/000157/MEA 040.11

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Applicant: Genzyme Europe BV

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Ninth interim report from the Gaucher pregnancy and lactation sub-registry to assess the pregnancy outcomes including adverse events in women with Gaucher disease, untreated and treated with Cerezyme (imiglucerase) during pregnancy. This report covers the period from 01 June 2018 to 31 May 2021

### 17.5.6. Infliximab - FLIXABI (CAP) - EMEA/H/C/004020/MEA 009

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Applicant: Samsung Bioepis NL B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Biennial interim report for the Chronisch Entzündliche Darmerkrankungen, ein Unabhängiges Register (CEDUR) to describe the long-term effectiveness of treatment with inflammatory bowel disease (IBD) therapies such as drug survival, effectiveness, side effects of treatment combination, and disease activity achieved

### 17.5.7. Infliximab - FLIXABI (CAP) - EMEA/H/C/004020/MEA 010

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Applicant: Samsung Bioepis NL B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Biennial interim report for the Czech Register of inflammatory bowel disease (IBD) Patients on Biological Therapy (CREDIT) to monitor effectiveness of total population of IBD patients on biological medication in the Czech Republic and regular analytical evaluation of

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<sup>94</sup> Messenger ribonucleic acid



the effectiveness

#### **17.5.8. Naloxegol - MOVENTIG (CAP) - EMEA/H/C/002810/MEA 006.11**

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Applicant: Kyowa Kirin Holdings B.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: Interim progress report for study D3820R00009 (EUPAS12669): an observational PASS of Moventig (naloxegol) among patients aged 18 years and older treated with opioids chronically

#### **17.5.9. Nonacog beta pegol - REFIXIA (CAP) - EMEA/H/C/004178/LEG 006.2**

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Applicant: Novo Nordisk A/S

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Third yearly progress report for PASS NN7999-4031 (Paradigm 8): a non-interventional study in male haemophilia B patients receiving nonacog beta pegol (N9-GP) prophylaxis treatment to investigate the potential effects of polyethylene glycol (PEG) accumulation in the choroid plexus of the brain and other tissues/organs

#### **17.5.10. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/MEA 044.12**

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Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Rhea Fitzgerald

Scope: MAH's response to MEA 0044.11 [third interval safety registry for study CNTO1275PSO4056: an observational PASS of ustekinumab in the treatment of paediatric patients aged 12 years and older with moderate to severe plaque psoriasis (adolescent registry)] as per the request for supplementary information (RSI) adopted in June 2021

#### **17.5.11. Velaglucerase alfa - VPRIV (CAP) - EMEA/H/C/001249/LEG 013.3**

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Applicant: Shire Pharmaceuticals Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: Annual report 2021 from the post-marketing Gaucher disease outcome survey (GOS) to assess the long-term safety and effectiveness of velaglucerase alfa in patients with Gaucher disease

### **17.6. Others**

#### **17.6.1. Givosiran - GIVLAARI (CAP) - EMEA/H/C/004775/MEA 004**

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Applicant: Alnylam Netherlands B.V.

PRAC Rapporteur: Martin Huber

Scope: Interim report for study ALN-AS1-003 (ENVISION): a phase 3 randomised, double-blind, placebo-controlled, multicentre study with an open-label extension to evaluate the efficacy and safety of givosiran in patients with acute hepatic porphyrias (from initial

opinion/marketing authorisation)

### **17.6.2. Somatropin - OMNITROPE (CAP) - EMEA/H/C/000607/MEA 010.3**

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Applicant: Sandoz GmbH

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Fourth interim report for study EP00-401: a phase 4 multicentre study on the safety and efficacy of Omnitrope (somatropin) in short children born small for gestational age (SGA) and MAH's proposal to terminate interventional study EP00-401 and provide the final study report in 2022

### **17.7. New Scientific Advice**

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

### **17.8. Ongoing Scientific Advice**

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

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

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

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

Based on the review of the available pharmacovigilance data for the 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 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. Galsulfase - NAGLAZYME (CAP) - EMEA/H/C/000640/S/0087 (without RMP)**

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Applicant: BioMarin International Limited

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Annual reassessment of the marketing authorisation

#### **18.1.2. Nelarabine - ATRIANCE (CAP) - EMEA/H/C/000752/S/0055 (without RMP)**

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Applicant: Novartis Europharm Limited

PRAC Rapporteur: Anette Kirstine Stark

Scope: Annual reassessment of the marketing authorisation

**18.1.3. Smallpox vaccine (live modified vaccinia virus Ankara) - IMVANEX (CAP) - EMEA/H/C/002596/S/0069 (without RMP)**

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Applicant: Bavarian Nordic A/S

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Annual reassessment of the marketing authorisation

**18.1.4. Vestronidase alfa - MEPSEVII (CAP) - EMEA/H/C/004438/S/0025 (without RMP)**

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Applicant: Ultragenyx Germany GmbH

PRAC Rapporteur: Eva Segovia

Scope: Annual reassessment of the marketing authorisation

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

**18.2.1. Bedaquiline - SIRTURO (CAP) - EMEA/H/C/002614/R/0045 (without RMP)**

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Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Conditional renewal of the marketing authorisation

**18.2.2. Obeticholic acid - OCALIVA (CAP) - EMEA/H/C/004093/R/0027 (without RMP)**

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Applicant: Intercept Pharma International Limited

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Conditional renewal of the marketing authorisation

**18.2.3. Vandetanib - CAPRELSA (CAP) - EMEA/H/C/002315/R/0050 (without RMP)**

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Applicant: Genzyme Europe BV

PRAC Rapporteur: Tiphaine Vaillant

Scope: Conditional renewal of the marketing authorisation

**18.3. Renewals of the marketing authorisation**

**18.3.1. Cerliponase alfa - BRINEURA (CAP) - EMEA/H/C/004065/R/0034 (without RMP)**

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Applicant: BioMarin International Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: 5-year renewal of the marketing authorisation

### 18.3.2. Chlormethine - LEDAGA (CAP) - EMEA/H/C/002826/R/0030 (with RMP)

Applicant: Helsinn Birex Pharmaceuticals Limited

PRAC Rapporteur: Tiphaine Vaillant

Scope: 5-year renewal of the marketing authorisation

### 18.3.3. Daratumumab - DARZALEX (CAP) - EMEA/H/C/004077/R/0054 (without RMP)

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: 5-year renewal of the marketing authorisation

### 18.3.4. Dimethyl fumarate - SKILARENCE (CAP) - EMEA/H/C/002157/R/0030 (with RMP)

Applicant: Almirall S.A

PRAC Rapporteur: Annika Folin

Scope: 5-year renewal of the marketing authorisation

### 18.3.5. Dinutuximab beta - QARZIBA (CAP) - EMEA/H/C/003918/R/0029 (without RMP)

Applicant: EUSA Pharma (Netherlands) B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: 5-year renewal of the marketing authorisation

### 18.3.6. Emtricitabine, tenofovir disoproxil - EMTRICITABINE/TENOFOVIR DISOPROXIL KRKA D.D. (CAP) - EMEA/H/C/004686/R/0017 (without RMP)

Applicant: KRKA, d.d., Novo mesto

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: 5-year renewal of the marketing authorisation

### 18.3.7. Etanercept - ERELZI (CAP) - EMEA/H/C/004192/R/0037 (with RMP)

Applicant: Sandoz GmbH

PRAC Rapporteur: Eva Segovia

Scope: 5-year renewal of the marketing authorisation

### 18.3.8. Miglustat - YARGESA (CAP) - EMEA/H/C/004016/R/0011 (with RMP)

Applicant: Piramal Critical Care B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: 5-year renewal of the marketing authorisation

#### 18.3.9. Nonacog beta pegol - REFIXIA (CAP) - EMEA/H/C/004178/R/0025 (with RMP)

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: 5-year renewal of the marketing authorisation

#### 18.3.10. Nusinersen - SPINRAZA (CAP) - EMEA/H/C/004312/R/0025 (without RMP)

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: 5-year renewal of the marketing authorisation

#### 18.3.11. Osimertinib - TAGRISSO (CAP) - EMEA/H/C/004124/R/0044 (with RMP)

Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: 5-year renewal of the marketing authorisation

#### 18.3.12. Pentosan polysulfate sodium - ELMIRON (CAP) - EMEA/H/C/004246/R/0024 (without RMP)

Applicant: bene-Arzneimittel GmbH

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: 5-year renewal of the marketing authorisation

#### 18.3.13. Umeclidinium - ROLUFTA ELLIPTA (CAP) - EMEA/H/C/004654/R/0019 (without RMP)

Applicant: GlaxoSmithKline Trading Services Limited

PRAC Rapporteur: Ilaria Baldelli

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 25-28 October 2021 meeting (marked as "a"), for the 04 November 2021 extraordinary PRAC meeting on MSSR (marked as "b"), for the 11 November 2021 ORGAM teleconference (marked as "c") and for the 23 November 2021 extraordinary PRAC meeting (marked as "d").

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Sabine Straus <sup>a, b, c, d</sup>	Chair	Netherlands	No interests declared	Full involvement
Jan Neuhauser <sup>a, b, c, d</sup>	Member	Austria	No interests declared	Full involvement
Sonja Hrabčik <sup>a, b</sup>	Alternate	Austria	No interests declared	Full involvement
Jean-Michel Dogné <sup>a, b, c, d</sup>	Member	Belgium	No interests declared	Full involvement
Laurence de Fays <sup>a, b, d</sup>	Alternate	Belgium	No interests declared	Full involvement
Maria Popova-Kiradjieva <sup>a, b, c, d</sup>	Member	Bulgaria	No interests declared	Full involvement
Nikica Mirošević Skvrce <sup>a, c, d</sup>	Member	Croatia	No interests declared	Full involvement
Željana Margan Koletić <sup>d</sup>	Alternate	Croatia	No interests declared	Full involvement
Panagiotis Psaras <sup>a, b, c</sup>	Member (alternate as of 10/11/2021)	Cyprus	No interests declared	Full involvement
Eva Jirsová <sup>a, b, d</sup>	Member	Czechia	No interests declared	Full involvement
Jana Lukacisinova <sup>a, b, d</sup>	Alternate	Czechia	No interests declared	Full involvement
Anette Kirstine Stark <sup>a, b, c, d</sup>	Member	Denmark	No interests declared	Full involvement
Hans Christian Siersted <sup>a, b</sup>	Alternate	Denmark	No restrictions applicable to this meeting	Full involvement
Maia Uusküla <sup>a, d</sup>	Member	Estonia	No interests declared	Full involvement
Krõõt Aab <sup>a, b, d</sup>	Alternate	Estonia	No interests declared	Full involvement
Kirsti Villikka <sup>a, b, c, d</sup>	Member	Finland	No interests declared	Full involvement
Kimmo Jaakkola <sup>a, b, c, d</sup>	Alternate	Finland	No interests declared	Full involvement
Tiphaine Vaillant <sup>a, c, d</sup>	Member	France	No interests declared	Full involvement
Nathalie Gault <sup>a, b, c, d</sup>	Alternate	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
Martin Huber <sup>a, b, c, d</sup>	Member (Vice-Chair)	Germany	No interests declared	Full involvement
Brigitte Keller-Stanislawski <sup>a, b</sup>	Alternate	Germany	No interests declared	Full involvement
Sofia Trantza <sup>a, b, c, d</sup>	Alternate	Greece	No interest declared	Full involvement
Melinda Palfi <sup>a, b, c, d</sup>	Member	Hungary	No interests declared	Full involvement
Julia Pallos <sup>a, b, d</sup>	Alternate	Hungary	No participation in final deliberations and voting on:	4.2.1. Olmesartan (NAP)
Guðrún Stefánsdóttir <sup>a, b, d</sup>	Member	Iceland	No participation in discussion, final deliberations and voting on:	4.3.1. Adalimumab - AMGEVITA (CAP); AMSPARITY (CAP); HEFIYA (CAP); HULIO (CAP); HUMIRA (CAP) - EMEA/H/C/00048 1/SDA/124; HYRIMOZ (CAP); IDACIO (CAP); IMRALDI (CAP); YUFLYMA (CAP)  17.4.2. Denosumab - XGEVA (CAP) - EMEA/H/C/00217 3/II/0078
Ronan Grimes <sup>a, b, c, d</sup>	Alternate	Ireland	No interests declared	Full involvement
Amelia Cupelli <sup>a, b, c, d</sup>	Member	Italy	No interests declared	Full involvement
Ilaria Baldelli <sup>a, b, c, d</sup>	Alternate	Italy	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
Zane Neikena <sup>a, b, c, d</sup>	Member	Latvia	No interests declared	Full involvement
Rugile Pilviniene <sup>a, b, c, d</sup>	Member	Lithuania	No interests declared	Full involvement
Nadine Petitpain <sup>b, d</sup>	Member	Luxembourg	No restrictions applicable to this meeting	Full involvement
Anne-Cécile Vuillemin <sup>a, c, d</sup>	Alternate	Luxembourg	No interests declared	Full involvement
John Joseph Borg <sup>a, d</sup>	Member	Malta	No interests declared	Full involvement
Menno van der Elst <sup>a, b, c, d</sup>	Member	Netherlands	No interests declared	Full involvement
Liana Gross-Martirosyan <sup>a, b, c, d</sup>	Alternate	Netherlands	No interests declared	Full involvement
David Olsen <sup>a, b, c, d</sup>	Member	Norway	No participation in final deliberations and voting on:	5.2.1. Aflibercept - EYLEA (CAP) - EMEA/H/C/002392/II/0075  16.3.7. Ethinylestradiol, gestodene (NAP) - PSUSA/00001308/202103
Karen Pernille Harg <sup>a, b, c, d</sup>	Alternate	Norway	No interests declared	Full involvement
Adam Przybylkowski <sup>a</sup>	Member	Poland	No interests declared	Full involvement
Katarzyna Ziolkowska <sup>a, b, c, d</sup>	Alternate	Poland	No interests declared	Full involvement
Ana Diniz Martins <sup>a, b, c, d</sup>	Member	Portugal	No interests declared	Full involvement
Marcia Sofia Sanches de Castro Lopes Silva <sup>a, b, d</sup>	Alternate	Portugal	No interests declared	Full involvement
Roxana Dondera <sup>a, b, d</sup>	Member	Romania	No interests declared	Full involvement
Alexandra - Maria Spurni <sup>a, b, c, d</sup>	Alternate	Romania	No interests declared	Full involvement
Anna Mareková <sup>d</sup>	Member	Slovakia	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
	(as of 29/10/2021)			
Marek Juracka <sup>a, b, c, d</sup>	Alternate (as of 29/10/2021)	Slovakia	No interests declared	Full involvement
Polona Golmajer <sup>a, b, c, d</sup>	Alternate (as of 02/11/2021)	Slovenia	No interests declared	Full involvement
Eva Segovia <sup>a, b, c, d</sup>	Member	Spain	No interests declared	Full involvement
Maria del Pilar Rayon <sup>a, b, c, d</sup>	Alternate	Spain	No interests declared	Full involvement
Ulla Wändel Liminga <sup>a, b, c, d</sup>	Member	Sweden	No interests declared	Full involvement
Annika Folin <sup>a, c, d</sup>	Alternate	Sweden	No interests declared	Full involvement
Annalisa Capuano <sup>a, d</sup>	Member	Independent scientific expert	No interests declared	Full involvement
Milou Daniel Drici <sup>a, b, c, d</sup>	Member	Independent scientific expert	No restrictions applicable to this meeting	Full involvement
Maria Teresa Herdeiro <sup>a, b, d</sup>	Member	Independent scientific expert	No interests declared	Full involvement
Patricia McGettigan <sup>a, c</sup>	Member	Independent scientific expert	No interests declared	Full involvement
Daniel Morales <sup>a, d</sup>	Member	Independent scientific expert	No interests declared	Full involvement
Hedvig Nordeng <sup>a</sup>	Member	Independent scientific expert	No interests declared	Full involvement
Roberto Frontini <sup>a, b, c, d</sup>	Alternate	Healthcare Professionals Representative	No restrictions applicable to this meeting	Full involvement
Virginie Hivert <sup>a, d</sup>	Alternate	Patients' Organisation Representative	No restrictions applicable to this meeting	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Ulrike Heissenberger <sup>d</sup>	Expert – via Webex*	Austria	No interests declared	Full involvement
Christelle Bizimungu <sup>b, d</sup>	Expert - via Webex*	Belgium	No restrictions applicable to this meeting	Full involvement
Evelien De Clercq <sup>a</sup>	Expert - via Webex*	Belgium	No interests declared	Full involvement
Sophie Goethals <sup>a</sup>	Expert – via Webex*	Belgium	No restrictions applicable to this meeting	Full involvement
Jamila Hamdani <sup>a, b, d</sup>	Expert - via Webex*	Belgium	No interests declared	Full involvement
Piush Jain <sup>a, b</sup>	Expert - via Webex*	Belgium	No restrictions applicable to this meeting	Full involvement
Tom Lams <sup>a, b</sup>	Expert - via Webex*	Belgium	No interests declared	Full involvement
Jo Robays <sup>a, b</sup>	Expert - via Webex*	Belgium	No restrictions applicable to this meeting	Full involvement
Martine Sabbe <sup>a</sup>	Expert - via Webex*	Belgium	No interests declared	Full involvement
Françoise Wuillaume <sup>b, d</sup>	Expert - via Webex*	Belgium	No interests declared	Full involvement
Ivana Ljubičić <sup>a, b</sup>	Expert - via Webex*	Croatia	No restrictions applicable to this meeting	Full involvement
Magdalena Fabiánová <sup>c</sup>	Expert - via Webex*	Czechia	No interests declared	Full involvement
Petra Kaftanová <sup>a, b, d</sup>	Expert - via Webex*	Czechia	No interests declared	Full involvement
Jan Vosátka <sup>a</sup>	Expert - via Webex*	Czechia	No interests declared	Full involvement
Alexander Braathen <sup>a</sup>	Expert - via Webex*	Denmark	No interests declared	Full involvement
Karin Erneholm <sup>a, b, d</sup>	Expert - via Webex*	Denmark	No restrictions	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			applicable to this meeting	
Helle Esbjørn Kristensen <sup>a</sup>	Expert - via Webex*	Denmark	No interests declared	Full involvement
Helle Gerda Olsen <sup>a</sup>	Expert - via Webex*	Denmark	No interests declared	Full involvement
Marian Hjortlund Allon <sup>a</sup>	Expert - via Webex*	Denmark	No interests declared	Full involvement
Peter Horskjær Rose <sup>a</sup>	Expert - via Webex*	Denmark	No interests declared	Full involvement
Emma Louise Nautrup Ravn Stadsbjerg <sup>a</sup>	Expert - via Webex*	Denmark	No interests declared	Full involvement
Moritz Sander <sup>a</sup>	Expert - via Webex*	Denmark	No interests declared	Full involvement
Ditte Søgaard <sup>a</sup>	Expert - via Webex*	Denmark	No restrictions applicable to this meeting	Full involvement
Aynur Sert <sup>d</sup>	Expert - via Webex*	Denmark	No interests declared	Full involvement
Helene Stenbæk Hansen <sup>a</sup>	Expert - via Webex*	Denmark	No restrictions applicable to this meeting	Full involvement
Helve Vestman <sup>b</sup>	Expert - via Webex*	Estonia	No interests declared	Full involvement
Samuel Crommelynck <sup>a, d</sup>	Expert - via Webex*	France	No restrictions applicable to this meeting	Full involvement
Emmanuel Doyen <sup>a</sup>	Expert - via Webex*	France	No interests declared	Full involvement
Vincent Gazin <sup>a</sup>	Expert - via Webex*	France	No interests declared	Full involvement
Marie-Caroline Pesquidous <sup>a</sup>	Expert - via Webex*	France	No restrictions applicable to this meeting	Full involvement
Youssef Shaim <sup>b</sup>	Expert - via Webex*	France	No restrictions applicable to this meeting	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Laure Tiquet <sup>a</sup>	Expert - via Webex*	France	No interests declared	Full involvement
Jelena Katic <sup>a</sup>	Expert – via Webex*	Germany	No interests declared	Full involvement
Dennis Lex <sup>a</sup>	Expert – via Webex*	Germany	No restrictions applicable to this meeting	Full involvement
Karin Seifert <sup>a</sup>	Expert – via Webex*	Germany	No restrictions applicable to this meeting	Full involvement
Eamon O'Murchu <sup>a</sup>	Expert – via Webex*	Ireland	No interests declared	Full involvement
Marcel Kwa <sup>a</sup>	Expert – via Webex*	Netherlands	No interests declared	Full involvement
Lotte Minnema <sup>a</sup>	Expert – via Webex*	Netherlands	No interests declared	Full involvement
Peter Mol <sup>a</sup>	Expert – via Webex*	Netherlands	No restrictions applicable to this meeting	Full involvement
Bianca Mulder <sup>a</sup>	Expert – via Webex*	Netherlands	No interests declared	Full involvement
Maria Vanenburg <sup>a</sup>	Expert – via Webex*	Netherlands	No interests declared	Full involvement
Inge Zomerdijk <sup>a</sup>	Expert – via Webex*	Netherlands	No interests declared	Full involvement
Ferran Torres <sup>a</sup>	Expert – via Webex*	Spain	No restrictions applicable to this meeting	Full involvement
Charlotte Backman <sup>a, d</sup>	Expert – via Webex*	Sweden	No interests declared	Full involvement
Rickard Ljung <sup>a</sup>	Expert – via Webex*	Sweden	No restrictions applicable to this meeting	Full involvement
Karin Bolin <sup>a</sup>	Expert – via Webex*	Sweden	No restrictions applicable to this meeting	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Elina Rönnemaa <sup>a</sup>	Expert – via Webex*	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:

<http://www.ema.europa.eu/ema/>