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SCIENCE MEDICINES HEALTH

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Human Medicines Division

## Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC minutes on 08-11 February 2021

Chair: Sabine Straus – Vice-Chair: Martin Huber

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

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## **1. Introduction**

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

The Chairperson opened the meeting by welcoming all participants. Due to the current coronavirus (COVID-19 outbreak), and the associated EMA Business Continuity Plan (BCP), the meeting was held remotely.

Based on the declarations of interest submitted by the Committee members, alternates and experts and based on the topics in the agenda of the current meeting, the Committee Secretariat announced the restricted involvement of some Committee members in upcoming discussions; in accordance with the Agency's policy on the handling of conflicts of interests, participants in this meeting were asked to declare any changes, omissions or errors to their declared interests concerning the matters for discussion (see Annex II – List of participants). No new or additional conflicts were declared.

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 revision 2 of the Rules of Procedure ([EMA/PRAC/567515/2012 Rev.2](#)). All decisions taken at this meeting held under the conditions of an emergency situation, the Agency's BCP and in compliance with internal guidelines were made in the presence of a quorum of members (i.e. 18 or more members were present in the room). All decisions, recommendations and advice were agreed unanimously, unless otherwise specified.

The PRAC Chair announced that Gudrun Kirstin Steingrimsdottir stepped down on as the alternate for Iceland leaving the position vacant for the time being.

### **1.2. Agenda of the meeting on 08-11 February 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 11-14 January 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 11-14 January 2021 were published on the EMA website on 23 September 2021 ([EMA/PRAC/532676/2021](#)).

## **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

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

Applicant(s): Artegoda GmbH, Temmler Pharma GmbH

PRAC Rapporteur: Anette Kristine 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

Amfepramone is a sympathomimetic agent with indirect action, belonging to the group of anorexigens, indicated as an adjunctive therapy to diet, in patients with obesity and a body mass index (BMI) of 30 kg/m<sup>2</sup> or higher, who have not responded to an appropriate weight-reducing regimen alone.

The Romanian Medicines Agency ([ANMDMR](#))<sup>1</sup> sent a letter of [notification](#) dated 25 January 2021 of a referral under Article 31 of Directive 2001/83/EC for the review of amfepramone-containing product(s) following the completion of the PSUSA on amfepramone (PSUSA/00000138/202006) in January 2021. In light of the known serious safety concerns related to the therapeutic class of anorexigens, reported cases of cardiac-related adverse drug reactions, cases of pulmonary hypertension, and the off-label use, serious concerns were raised as to the effectiveness of the risk minimisation measures in place for amfepramone-containing product(s). Therefore, the PRAC considered that such serious concerns had to be further investigated taking into account all available data on the safety and efficacy of amfepramone. For further background, see [PRAC minutes January 2021](#).

In the context of uncertainties as to clinical relevance of the modest efficacy of short-term treatment with amfepramone-containing product(s) in treatment of obesity, this led the ANMDMR to raise concerns about the benefit-risk balance of these medicinal products. Therefore, in the interest of the Union, the ANMDMR referred the matter to PRAC for further evaluation and requested that it gives its recommendation as to whether the marketing authorisation(s) for amfepramone-containing product(s) should be maintained, varied, suspended or revoked.

#### Discussion

The PRAC noted the notification letter from the ANMDMR.

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<sup>1</sup> National Agency for Medicines and Medical Devices of Romania

The Committee appointed Anette Kristine Stark as Rapporteur and Eva Jirsová as Co-Rapporteur for the procedure.

The PRAC discussed a list of questions (LoQ) to be addressed during the procedure together with a timetable for conducting the review. The PRAC also discussed the need for a public hearing.

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

- The Committee adopted a LoQ to the MAHs for amfepramone-containing solution(s) ([EMA/PRAC/51715/2021](#)) and a timetable for the procedure (EMA/PRAC/51714/2021).
- The PRAC also discussed the option to conduct a public hearing in the context of the current procedure according to the pre-defined criteria set out in the rules of procedure<sup>2</sup> ([EMA/363479/2015](#)). It was agreed by the Committee that at this stage of the procedure, in light of the currently available data and the need to determine the appropriate approach to stakeholder engagement, a public hearing would not be appropriate. The PRAC can reconsider this at a later stage of the procedure, as needed.

See EMA press release ([EMA/53585/2021](#)) entitled 'Review of amfepramone medicines started'.

## **3.2. Ongoing procedures**

None

## **3.3. Procedures for finalisation**

None

## **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. Remdesivir – VEKLURY (CAP)**

Applicant(s): Gilead Sciences Ireland UC

<sup>2</sup> Rules of procedure on the organisation and conduct of public hearings at the PRAC

<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

PRAC Rapporteur: Eva Jirsová

Scope: Signal of sinus bradycardia

EPITT 19659 – New signal

Lead Member State(s): CZ

### **Background**

Remdesivir is an adenosine nucleotide antiviral prodrug indicated, as Veklury a centrally authorised product, for the treatment of coronavirus disease 2019 (COVID-19) in adults and adolescents aged 12 years and older with body weight at least 40 kg with pneumonia requiring supplemental oxygen.

Veklury (remdesivir) is estimated to have been used by 214,805–393,810 patients worldwide depending on the 5-day or 10-day regimen, in the period from first authorisation in May 2020 to October 2020.

During routine signal detection activities, a signal of sinus bradycardia was identified by Italy based on 11 cases retrieved from the Italian pharmacovigilance network and a total of 27 cases in EudraVigilance. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

### **Discussion**

Having considered the available evidence from case reports in EudraVigilance and in the literature, the PRAC agreed that further assessment is required. Therefore, the Committee agreed to request a cumulative review of cases of sinus bradycardia and related terms from the MAH of Veklury (remdesivir) in the framework of the ongoing PSUR single assessment (PSUSA).

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

- The MAH for Veklury (remdesivir) should provide to EMA, within 90 days, a cumulative review of cases of sinus bradycardia as part of the comment phase of the ongoing PSUSA procedure<sup>5</sup>.

## **4.2. New signals detected from other sources**

None

## **4.3. Signals follow-up and prioritisation**

### **4.3.1. Ceftriaxone (NAP)**

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Applicant(s): various

PRAC Rapporteur: Zane Neikena

Scope: Signal of hepatitis

EPITT 19603 – Follow-up to September 2020

### **Background**

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<sup>5</sup> Due for an outcome in June 2021



For background information, see [PRAC minutes September 2020](#)<sup>6</sup>.

The MAH for the originator ceftriaxone-containing product(s) replied to the request for information on the signal of hepatitis and the responses were assessed by the Rapporteur.

### Discussion

Having considered the available evidence provided by the MAH for the originator ceftriaxone-containing products and supported by a further EMA analysis, the PRAC agreed that further evidence is necessary before concluding the signal, and hence further assessment is warranted. Therefore, the PRAC agreed to request additional information from the MAH for the originator ceftriaxone-containing product(s).

### Summary of recommendation(s)

- The MAH for the originator ceftriaxone-containing product(s) should submit to EMA, within 60 days, a detailed analysis of cases reporting hepatotoxicity from post-marketing setting and clinical trials with a causality assessment as well as a detailed causality assessment of cases with positive dechallenge and discuss the observed temporal pattern. In addition, the MAH should provide a causality assessment of cases of drug-induced liver injury (DILI) where hepatic disorders related to cholelithiasis/cholestasis are reported. Furthermore, the MAH should include a thorough analysis of literature publications by *Peker E et al.*<sup>7</sup>, *Kaur I et al.*<sup>8</sup> and *Miranda M et al.*<sup>9</sup> together with a review of literature publications on clinical and non-clinical data regarding hepatotoxicity in the context of ceftriaxone treatment. Based on these reviews, the MAH should discuss the need for risk minimisation measures, including an update of the product information as warranted.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

#### 4.3.2. [Filgrastim – ACCOFIL \(CAP\), FILGRASTIM HEXAL \(CAP\), GRASTOFIL \(CAP\), NIVESTIM \(CAP\), RATIOGRASTIM \(CAP\), TEVAGRASTIM \(CAP\), ZARZIO \(CAP\); NAP](#)

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Applicant(s): Accord Healthcare S.L.U. (Accofil, Grastofil), AbZ Pharma GmbH (Biograstim), Pfizer Europe MA EEIG (Nivestim), Ratiopharm GmbH (Ratiograstim), Sandoz GmbH (Zarzio), Teva GmbH (Tevagrastim), various

PRAC Rapporteur: Kirsti Villikka

Scope: Signal of immune reconstitution inflammatory syndrome (IRIS)

EPITT 19587 – Follow-up to September 2020

### Background

For background information, see [PRAC minutes September 2020](#)<sup>10</sup>.

The MAH Amgen for the originator filgrastim-containing product and the MAHs Accord Healthcare, Hexal AG, Pfizer, Ratiopharm GmbH, Sandoz GmbH and Teva GmbH for biosimilar filgrastim-containing products replied to the request for information on the signal

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<sup>6</sup> Held 31 August – 03 September 2020

<sup>7</sup> Ceftriaxone induced toxic hepatitis. World Journal of Gastroenterology 2009;15(21):2669-2671

<sup>8</sup> Cholestatic hepatitis with intravenous ceftriaxone. Indian journal of pharmacology 2011;43 (4); p. 474-5

<sup>9</sup> Biliary pseudolithiasis secondary to ceftriaxone-an entity not to forget. Revista de Pediatria SOPERJ. 2016; 16(3) 93

<sup>10</sup> Held 31 August – 03 September 2020

of immune reconstitution inflammatory syndrome (IRIS) and the responses were assessed by the Rapporteur.

### **Discussion**

Based on the available data and assessment, the PRAC agreed that the number of possible cases of IRIS with a temporal relationship to filgrastim-containing products is limited and that there is insufficient evidence at this stage to confirm a causal relationship between IRIS and filgrastim. Therefore, the PRAC concluded that no further action is warranted at present.

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

- The MAHs for filgrastim-containing products should continue to monitor cases of IRIS as part of routine safety surveillance.

#### **4.3.3. 3-hydroxy 3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins): atorvastatin (NAP); fluvastatin (NAP); lovastatin (NAP); pitavastatin (NAP); pravastatin (NAP); rosuvastatin (NAP); simvastatin (NAP)**

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Applicant(s): various

PRAC Rapporteur: Adrien Inoubli

Scope: Signal of bullous pemphigoid

EPITT 19586 – Follow-up to September 2020

### **Background**

For background information, see [PRAC minutes September 2020](#)<sup>11</sup>.

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

### **Discussion**

Having considered the available evidence from preclinical studies, clinical trials, literature, EudraVigilance and the cumulative reviews provided by the MAHs for the originator atorvastatin-, fluvastatin-, lovastatin-, pitavastatin-, pravastatin-, rosuvastatin- and simvastatin-mono-component containing products, the PRAC agreed that there is insufficient evidence at this stage to confirm a causal association between bullous pemphigoid and statins administration.

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

- The MAHs of statin-containing products should continue to monitor cases of bullous pemphigoid, particularly cases with a positive de-challenge and positive re-challenge as part of routine safety surveillance.
- In the next PSUR, the MAH for the originator atorvastatin-containing product(s) should provide a cumulative review of cases of bullous pemphigoid associated with any atorvastatin-containing products from all data sources including EudraVigilance.

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<sup>11</sup> Held 31 August – 03 September 2020

#### 4.3.4. Prednisolone (NAP); prednisone (NAP)

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Applicant(s): various

PRAC Rapporteur: Anette Kirstine Stark

Scope: Signal of bradycardia

EPITT 19613 – Follow-up to October 2020

##### **Background**

For background information, see [PRAC minutes October 2020](#)<sup>12</sup>.

The MAHs Takeda and Mundipharma as brandleaders for prednisolone- and prednisone-containing products respectively replied to the request for information on the signal of bradycardia and the responses were assessed by the Rapporteur.

##### **Discussion**

Having considered the available evidence, including the MAHs' cumulative reviews of cases from clinical trials and post-marketing setting, data from EudraVigilance and clinical trials, and taking into account the biological plausibility for a possible association of prednisolone/prednisone and bradycardia, the PRAC agreed that there is sufficient evidence for a causal association between treatment with high doses of prednisolone- and prednisone-containing products and bradycardia. Therefore, the PRAC agreed that the product information for prednisone- and prednisolone-containing products for systemic use should be updated accordingly.

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

- The MAH for prednisone- and prednisolone-containing products for systemic use should submit to the National Competent Authorities (NCAs) of the Member States, within 60 days, a variation to amend<sup>13</sup> the product information.

For the full PRAC recommendation, see [EMA/PRAC/82059/2021](#) published on 08 March 2021 on the EMA website.

#### 4.3.5. Remdesivir - VEKLURY (CAP)

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Applicant(s): Gilead Sciences Ireland UC

PRAC Rapporteur: Eva Jirsová

Scope: Signal of acute kidney injury

EPITT 19605 – Follow-up to October 2020

##### **Background**

For background information, see [PRAC minutes October 2020](#)<sup>14</sup>.

The MAH for Veklury (remdesivir) replied to the request for information on the signal of acute kidney injury and the responses were assessed by the Rapporteur.

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<sup>12</sup> Held 28 September – 01 October 2020

<sup>13</sup> Update of SmPC section 4.8. The package leaflet is to be updated accordingly

<sup>14</sup> Held 28 September – 01 October 2020

## Discussion

Having considered the available evidence provided by the MAH for Veklury (remdesivir), including data from clinical trials and published literature, the PRAC concurred that there is insufficient evidence to demonstrate a causal association between remdesivir and acute kidney injury/renal events. Therefore, the PRAC concluded that an update of the product information is not warranted at present.

## Summary of recommendation(s)

- The MAH should continue to closely monitor renal events as part routine safety surveillance. In the next PSUR, the MAH should provide stratified cases reporting renal toxicity split per formulations of Veklury (remdesivir) and include a detailed discussion accordingly.

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

None

## 5. Risk management plans (RMPs)

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

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

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

#### 5.1.1. Azacitidine - EMEA/H/C/004761

Scope: Treatment for acute myeloid leukaemia

#### 5.1.2. Coronavirus (COVID-19) vaccine (Ad26.COV2-S, recombinant) - EMEA/H/C/005737

Scope: Active immunisation for prevention of coronavirus disease-2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in adults ≥18 years old

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

#### 5.1.3. Istradefylline - EMEA/H/C/005308

Scope: Adjunctive treatment to levodopa-based regimens in patients with Parkinson's disease

#### 5.1.4. Lenadogene nolparvovec - EMEA/H/C/005047, Orphan

Applicant: GenSight Biologics S.A., ATMP<sup>15</sup>

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<sup>15</sup> Advanced therapy medicinal product

Scope: Treatment of vision loss due to Leber hereditary optic neuropathy (LHON)

#### **5.1.5. Odevixibat - EMEA/H/C/004691, Orphan**

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Applicant: Albireo

Scope (accelerated assessment): Treatment of progressive familial intrahepatic cholestasis (PFIC)

#### **5.1.6. Roxadustat - EMEA/H/C/004871**

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Scope: Treatment of anaemia

#### **5.1.7. Selumetinib - EMEA/H/C/005244, Orphan**

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Applicant: AstraZeneca AB

Scope: Treatment of neurofibromatosis type 1 (NF1)

#### **5.1.8. Tirbanibulin mesilate - EMEA/H/C/005183**

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Scope: Topical field treatment of non-hyperkeratotic, non-hypertrophic actinic keratosis

#### **5.1.9. Tralokinumab - EMEA/H/C/005255**

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Scope: Treatment of moderate-to-severe atopic dermatitis in adult patients who are candidates for systemic therapy

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

#### **5.2.1. Emtricitabine, tenofovir disoproxil - TRUVADA (CAP) - EMEA/H/C/000594/II/0169**

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Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Submission of an updated RMP (version 16.1) to remove registry study GS-EU-276-4487 (as a category 3 study in the RMP): a prospective, longitudinal, observational registry of emtricitabine/tenofovir disoproxil fumarate for human immunodeficiency virus 1 (HIV-1) pre-exposure prophylaxis (PrEP) in the European Union

##### **Background**

Emtricitabine is a nucleoside analogue of cytidine and tenofovir disoproxil converted in vivo to tenofovir, a nucleoside monophosphate (nucleotide) analogue of adenosine monophosphate. In combination, emtricitabine/tenofovir disoproxil is indicated, as Truvada, for the treatment of human immunodeficiency virus 1 (HIV-1) infection and for pre-exposure prophylaxis (PrEP) under specific conditions.

The PRAC is evaluating a type II variation procedure for Truvada, a centrally authorised medicine containing emtricitabine/tenofovir disoproxil, proposing to update the RMP by removing a study GS-EU-276-4487, an observational registry on HIV-1 PrEP in the European Union. The PRAC is responsible for adopting an outcome based on the assessment report

from the PRAC Rapporteur, to be further considered at the level of the CHMP, responsible for adopting an opinion on this variation.

### Summary of advice

- The RMP for Truvada (emtricitabine/tenofovir disoproxil) in the context of the variation procedure under evaluation could be considered acceptable provided that an update to RMP version 16.1 and satisfactory responses to the request for supplementary information (RSI) are submitted.
- The MAH should submit to EMA a detailed review of PrEP failure and risk of HIV acquisition with resistance in all target population, including pregnancy. In addition, the MAH should further categorise seroconversion cases as occurring during PrEP and after the end or before PrEP mode of administration. Moreover, the MAH should collect further data from ongoing projects/clinical trials during the period April 2020-April 2021 to identify any changes since January 2020 in terms of seroconversion incidence, monitoring and follow-up in order to guide communication to health care providers/subjects. Finally, a discussion on the need for further risk minimisations should be included.

#### 5.2.2. Tacrolimus - ADVAGRAF (CAP) - EMEA/H/C/000712/WS1805/0057; MODIGRAF (CAP) - EMEA/H/C/000954/WS1805/0035; NAP

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Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Ronan Grimes

Scope: Submission of an updated RMP (version 3) in order to add a non-interventional study related to the safety concerns of use during pregnancy and use during lactation. The MAH took the opportunity to combine the two important potential risks of 'exchangeability between the granule and capsule formulations of tacrolimus' for Modigraf (tacrolimus) and 'if administered accidentally either arterially or perivascularly, the reconstituted solution may cause irritation at the injection site' for Prograf (tacrolimus) concentrate for solution for infusion into the important identified risk of 'medication errors'. Finally, the RMP is updated in line with revision 2.0.1 of the guidance on the format of RMP in the EU (template)

### Background

Tacrolimus is a calcineurin inhibitor and immunosuppressant indicated for the treatment of allograft rejection resistant to treatment with other immunosuppressive medicinal products in adult and paediatric patients. It is also indicated in the prophylaxis of transplant rejection in adult and paediatric kidney, liver or heart allograft recipients, under certain conditions.

The PRAC is evaluating a worksharing type II variation procedure for Avagraf and Modigraf, centrally authorised medicines containing tacrolimus as well as Prograf, a nationally approved medicine containing tacrolimus, proposing to update the RMP to include certain elements, in particular, a non-interventional study concerning use during pregnancy and during lactation. The PRAC is responsible for adopting an outcome based on the assessment report from the PRAC Rapporteur, to be further considered at the level of the CHMP, responsible for adopting an opinion on this variation. For further background, see [PRAC minutes February 2020](#) and [PRAC minutes November 2020](#)<sup>16</sup>.

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<sup>16</sup> Held 26-29 October 2020

### Summary of advice

- The RMP (version 3.2) for Advagraf, Modigraf and Prograf (tacrolimus) in the context of the variation under evaluation by the PRAC is considered acceptable.
- The PRAC agreed with the inclusion of the non-interventional study based on secondary data from the Transplant Pregnancy Registry International (TPRI). In addition, PRAC considered acceptable to remove long-term follow-up of children exposed in utero as an objective of this study given the assessed limitations. Finally, PRAC advised to request the MAH to submit to EMA a feasibility assessment to use alternative data sources in order to complement the study in TPRI.

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

### 5.3.1. Nitisinone - NITISINONE MDK (CAP) - EMEA/H/C/004281/X/0007

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Applicant: MendeliKABS Europe Limited

PRAC Rapporteur: Amelia Cupelli

Scope: Extension application to add a new strength of 20 mg (hard capsule). The RMP (version 2.0) is updated accordingly

#### Background

Nitisinone is a competitive inhibitor of 4-hydroxyphenylpyruvate dioxygenase indicated for the treatment of adult and paediatric (in any age range) patients with confirmed diagnosis of hereditary tyrosinemia type 1 (HT-1) in combination with dietary restriction of tyrosine and phenylalanine.

The CHMP is evaluating an extension application (line extension) for Nitisinone MDK, a centrally authorised product containing nitisinone, to add a new strength of 20 mg hard capsule. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this variation. For further background, see [PRAC minutes September 2020](#)<sup>17</sup>.

#### Summary of advice

- The RMP for Nitisinone MDK (nitisinone) in the context of the extension application under evaluation by the CHMP could be considered acceptable provided that an update to RMP version 2.1 is submitted.
- The PRAC supported a single follow-up questionnaire (FUQ) to collect information on developmental and cognitive disorders observed during treatment with nitisinone. In addition, the PRAC agreed with the removal of the pan-Canadian patient registry study (listed as a category 3 study in the RMP) as the recent completion of study Sobi.NTBC-005<sup>18</sup> for the originator product containing nitisinone confirmed the previously known safety profile of nitisinone after exposure for up to 15 years with the originator product. As a result, routine pharmacovigilance is considered sufficient to identify and characterise the risks of the product at the moment.

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<sup>17</sup> Held 31 August – 03 September 2020

<sup>18</sup> A non-interventional PASS to evaluate long-term safety of Orfadin treatment in HT-1 patients in standard care

## 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. Carfilzomib - KYPROLIS (CAP) - PSUSA/00010448/202007

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Evaluation of a PSUSA procedure

##### Background

Carfilzomib is a tetrapeptide epoxyketone proteasome inhibitor indicated, as Kyprolis, in combination with either lenalidomide and dexamethasone or dexamethasone alone for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Kyprolis, a centrally authorised medicine containing carfilzomib, 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 Kyprolis (carfilzomib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend an existing warning on electrocardiographic changes to reflect that cases of ventricular tachycardia and occurrence of QT prolongation in post-marketing setting were reported and to add ventricular tachycardia as an undesirable effect with a frequency 'uncommon'. In addition, the product information should be updated to add bradycardia to the existing warning on infusion reactions. Finally, acute pancreatitis should be added as an undesirable effect with a frequency 'uncommon'. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>19</sup>.
- In the next PSUR, the MAH should include a cumulative review of cases of haemolysis and haemolytic anaemia as well as a detailed review on syncope with a causality assessment. The MAH should also provide a discussion on cases of bradycardia and heart blocks as possible underlying causes for syncope and discuss the need for an update of the product information as warranted.

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

<sup>19</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 the CHMP for adoption of an opinion



### 6.1.2. Evolocumab - REPATHA (CAP) - PSUSA/00010405/202007

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Applicant: Amgen Europe B.V.

PRAC Rapporteur: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

#### **Background**

Evolocumab is an inhibitor of proprotein convertase subtilisin/kexin type 9 (PCSK9). It is indicated, as Repatha, for the treatment of adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet in combination with a statin or statin with other lipid-lowering therapies in patients unable to reach low-density lipoprotein-cholesterol (LDL-C) goals with the maximum tolerated dose of a statin and alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated. It is also indicated in adults and adolescents aged 12 years and over with homozygous familial hypercholesterolaemia in combination with other lipid-lowering therapies and in adults with established atherosclerotic cardiovascular disease to reduce cardiovascular risk by lowering low-density lipoprotein cholesterol (LDL-C) levels, subject to certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Repatha, a centrally authorised medicine containing evolocumab 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 Repatha (evolocumab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add headache as an undesirable effect with a frequency 'common'. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>20</sup>.

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

### 6.1.3. Inotersen - TEGSEDI (CAP) - PSUSA/00010697/202007

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Applicant: Akcea Therapeutics Ireland Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

#### **Background**

Inotersen is an antisense oligonucleotide (ASO) inhibitor of human transthyretin (TTR) production. It is indicated, as Tegsedi, for the treatment of stage 1 or stage 2 polyneuropathy in adult patients with hereditary transthyretin amyloidosis (hATTR).

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<sup>20</sup> Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Tegsedi, a centrally authorised medicine containing inotersen 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 Tegsedi (inotersen) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add hypersensitivity as an undesirable effect with a frequency 'uncommon'. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>21</sup>.
- In the next PSUR, the MAH should provide a cumulative review of cases of lymphocyte count decreased, including data from clinical trials and literature, as well as a discussion on the need to update the product information as warranted. The MAH should also provide a cumulative review of cases of urinary tract infection, including post-marketing data, data from clinical trials and literature. Finally, the MAH should provide a discussion on cases of drug-induced lupus together with a proposal 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.

#### **6.1.4. Nivolumab - OPDIVO (CAP) - PSUSA/00010379/202007**

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Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

#### **Background**

Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody (HuMAb) indicated, as Opdivo, as monotherapy or in combination with ipilimumab for the treatment of advanced (unresectable or metastatic) melanoma in adults. It is also indicated, as monotherapy, for the adjuvant treatment of adults with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection, for the treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy in adults and in combination with ipilimumab and 2 cycles of platinum-based chemotherapy for the first-line treatment of metastatic NSCLC in adults whose tumours have no sensitising epidermal growth factor receptor (EGFR) mutation or anaplastic lymphoma kinase (ALK) translocation. In addition, it is indicated for the treatment of advanced renal cell carcinoma after prior therapy in adults and in combination with ipilimumab for the first-line treatment of adult patients with intermediate/poor-risk advanced renal cell carcinoma, for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma after autologous stem cell transplant (ASCT) and treatment with brentuximab vedotin, recurrent or metastatic squamous cell cancer of the head and neck in adults progressing on or after platinum-based therapy, locally advanced unresectable or metastatic urothelial carcinoma in adults after

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<sup>21</sup> Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

failure of prior platinum-containing therapy and for the treatment of adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma after prior fluoropyrimidine- and platinum-based combination chemotherapy.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Opdivo, a centrally authorised medicine containing nivolumab 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 Opdivo (nivolumab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add lichen sclerosus and other lichen disorders as undesirable effects with a frequency 'not known' for both nivolumab monotherapy and nivolumab in combination with ipilimumab. In addition, the product information should be updated to amend the warning on immune-related adverse reactions by including information on simultaneous immune-mediated disorders. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>22</sup>.
- In the next PSUR, the MAH should provide a detailed review of cases of cardiac failure and late cardiac adverse reactions from post-marketing, clinical trials and from the literature. The MAH should also provide a comprehensive review of cases of seizures from clinical trials, post-marketing and literature data and discuss the physiological mechanism, as well as nonclinical data. The MAH should also provide a detailed review of cases of extremity necrosis, nail necrosis from clinical trials, post-marketing and literature data, as well as discuss the potential associated physiological mechanism. Finally, the MAH should review information on immune mediated myocarditis in light of recent management guidelines and update the product information as applicable.
- The MAH should update the RMP with information regarding lichen sclerosus and other lichen disorders, within the next upcoming regulatory procedure affecting the RMP.

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. Perampanel - FYCOMPA (CAP) - PSUSA/00009255/202007**

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Applicant: Eisai GmbH

PRAC Rapporteur: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

#### **Background**

Perampanel is an antagonist of the ionotropic  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptor and is indicated, as Fycompa, for the adjunctive treatment of partial-onset seizures with or without secondarily generalised

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<sup>22</sup> Update of SmPC section 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

seizures in patients from 4 years of age and older. It is also indicated for the adjunctive treatment of primary generalised tonic-clonic seizures in patients from 7 years of age and older with idiopathic generalised epilepsy.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Fycompa, a centrally authorised medicine containing perampanel 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 Fycompa (perampanel) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the information regarding overdose by including coma and depressed level of consciousness as reported adverse reactions. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>23</sup>.
- In the next PSUR, the MAH should provide an analysis of cases of depressed level of consciousness which occurred at recommended doses and propose an update of the product information as warranted. The MAH should also closely monitor cases of depressed level of consciousness and cases of absences (atypical or not) as well as information on pregnancies among women of childbearing age. In addition, the MAH should provide a cumulative review of cases of syndrome of inappropriate antidiuretic hormone secretion and hyponatremia from post-marketing, clinical trials and literature data and discuss the potential pharmacological mechanism of action of perampanel. Furthermore, the MAH should provide further analysis of cases of falls, together with a discussion on the risk factors and the underlying mechanism. Finally, the MAH should provide a detailed analysis of cases of homicidal ideation, suicidality and psychiatric reaction.

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

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

See Annex I 16.2.

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

See also Annex I 16.3.

### **6.3.1. Clonazepam (NAP) - PSUSA/00000812/202006**

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Applicant(s): various

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<sup>23</sup> Update of SmPC section 4.9. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

PRAC Lead: Maia Uusküla

Scope: Evaluation of a PSUSA procedure

### **Background**

Clonazepam is a benzodiazepine indicated for the treatment of all clinical forms of epileptic disease and seizures in children and adults, especially absence seizures (petit mal) including atypical absence, for primary or secondarily generalised tonic-clonic (grand mal), tonic or clonic seizures, for partial (focal) seizures with elementary or complex symptomatology and for various forms of myoclonic seizures, myoclonus and associated abnormal movements.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing clonazepam 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 clonazepam-containing product(s) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, all MAHs should provide a cumulative review of cases of dementia. MAHs should also continue to monitor cases of pneumonia through routine pharmacovigilance. Should any new relevant information emerge, MAHs should present a review of pneumonia in future PSURs.

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

## **6.3.2. Ethinylestradiol, etonogestrel (NAP) - PSUSA/00001307/202007**

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Applicant(s): various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

### **Background**

Ethinylestradiol is a synthetic oestrogen and etonogestrel is a synthetic biologically active metabolite of the synthetic progestin desogestrel. In combination, ethinylestradiol/etonogestrel is indicated as vaginal ring, for contraception for women of fertile age.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing ethinylestradiol/etonogestrel<sup>24</sup> and issued a recommendation on their marketing authorisation(s).

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

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<sup>24</sup> As vaginally administered combined hormonal contraceptive

- Based on the review of the data on safety and efficacy, the benefit-risk balance of ethinylestradiol/etonogestrel<sup>25</sup>-containing product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the frequency of urticaria as an undesirable effect from 'not known' to 'uncommon'. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>26</sup>.
- In the next PSUR, the MAH(s) should provide detailed reviews of cases of anaphylactic reaction and meningioma. A review of cases of cervical dysplasia should be added if new relevant epidemiological data become available.

The PRAC considered that the product information of ethinylestradiol/etonogestrel (vaginal rings)-containing and other ethinylestradiol-containing products should be updated to include the risk of pharmacodynamic drug-drug interaction between ethinylestradiol and glecaprevir/pibrentasvir. Further consideration is to be given at CMDh.

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

### 6.3.3. Iohexol (NAP) - PSUSA/00001768/202006

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Applicant(s): various

PRAC Lead: Karen Pernille Harg

Scope: Evaluation of a PSUSA procedure

#### **Background**

Iohexol is a non-ionic, water-soluble, tri-iodinated monomer indicated as a contrast agent for diagnostic use in adults and children during X-ray or computed tomography (CT) examinations.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing iohexol 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 iohexol-containing product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a warning on an increased risk of bronchospasm in asthmatic patients, as well as a reduced effect of adrenaline treatment when iohexol is used concomitantly with beta-adrenergic blocking agents. In addition, a warning on contrast-induced encephalopathy following iohexol administration is added. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>27</sup>.

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<sup>25</sup> As vaginally administered combined hormonal contraceptive

<sup>26</sup> Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

<sup>27</sup> Update of SmPC section 4.4. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

- In the next PSUR, the MAH(s) should closely monitor cases of exacerbation of myasthenia gravis and provide a discussion on whether an update of the product information is warranted. In addition, the MAH(s) should also closely monitor and discuss the role of iodinated contrast media in deoxyribonucleic acid (DNA) double-strand breaks.

The PRAC considered that detailed reviews of cases of extravasation, transient hepatic dysfunction and acute pancreatitis should be made, and the product information updated as warranted. Further consideration is to be given at CMDh.

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. Iopromide (NAP) - PSUSA/00001773/202006

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Applicant(s): various

PRAC Lead: Karen Pernille Harg

Scope: Evaluation of a PSUSA procedure

##### **Background**

Iopromide is a non-ionic, monomeric, water-soluble X-ray contrast medium indicated for X-ray and computerised tomography (CT) examinations, arteriography, venography, digital subtraction angiography (DSA), urography, endoscopic retrograde cholangiopancreatography (ERCP), arthrography, angiocardiology, checking the patency of dialysis shunt, and examination of other body cavities.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing iopromide 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 iopromide-containing product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add contrast encephalopathy as a warning and as an undesirable effect with a frequency 'not known'. Also, the product information should be updated to add acute generalised exanthematous pustulosis (AGEP) and drug reaction with eosinophilia and systemic symptoms (DRESS) as undesirable effects with a frequency 'not known' and to include a warning on severe cutaneous adverse reactions (SCARs). Therefore, the current terms of the marketing authorisation(s) should be varied<sup>28</sup>.
- In the next PSUR, the MAH Bayer should provide a detailed review on the occurrence of contrast-induced nephropathy in the context of chemotherapy.

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<sup>28</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 the CMDh for adoption of a position

The PRAC considered that a detailed review of cases of hypothyroidism in adult patients should be conducted, and the product information updated as warranted. Further consideration is to be given at CMDh.

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

#### 6.3.5. Lidocaine hydrochloride, phenylephrine hydrochloride, tropicamide (NAP) - PSUSA/00010390/202007

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Applicant(s): various

PRAC Lead: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

##### **Background**

Lidocaine is a local anaesthetic, phenylephrine a sympathomimetic agent and tropicamide an anticholinergic. In combination, lidocaine hydrochloride/phenylephrine hydrochloride/tropicamide is indicated, in adults for cataract surgery to obtain mydriasis and intraocular anaesthesia during surgical procedures.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing lidocaine hydrochloride/phenylephrine hydrochloride/tropicamide 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 lidocaine hydrochloride/phenylephrine hydrochloride/tropicamide-containing product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add a warning on the increased risk of iridocyclitis and floppy iris syndrome in patients with shallow anterior chamber, a history of acute narrow angle glaucoma and/or insufficient pupil dilation. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>29</sup>.
- In the next PSUR, the MAH(s) should provide a cumulative review of cases of convulsions from clinical trial and literature data, including a literature review for other tropicamide-containing products and discuss whether an update of the product information is warranted. In addition, floppy iris syndrome, iridocyclitis and intentional product misuse should be added as important potential risks in the PSUR summary of safety concerns.

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

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<sup>29</sup> Update of SmPC section 4.4. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position



### 6.3.6. Octreotide (NAP) - PSUSA/00002201/202006

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Applicant(s): various

PRAC Lead: Ronan Grimes

Scope: Evaluation of a PSUSA procedure

#### **Background**

Octreotide is a synthetic octapeptide derivative of somatostatin indicated for the treatment of symptomatic control and reduction of growth hormone (GH) and insulin-like growth factor (IGF-1) plasma levels in patients with acromegaly who are inadequately controlled by surgery or radiotherapy and for acromegalic patients unfit or unwilling to undergo surgery, or in the interim period until radiotherapy becomes fully effective. It is also indicated for the relief of symptoms associated with functional gastro-entero-pancreatic endocrine tumours, for the treatment of patients with advanced neuroendocrine tumours (NET) of the midgut or unknown primary tumour location, for prevention of complications following pancreatic surgery and in association with specific treatment, for emergency management to stop bleeding and to protect from re-bleeding owing to gastro-oesophageal varices in patients with cirrhosis, as well for the treatment of thyroid-stimulating hormone (TSH)-secreting pituitary adenomas, subject to certain conditions.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing octreotide 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 octreotide-containing product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add a warning on atrioventricular block to octreotide solution for injection/infusion in case of administration of high doses of the product and need for appropriate cardiac monitoring as well as to add information on the risk of overdose. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>30</sup>.
- In the next PSUR, the MAHs should provide a detailed analysis of cases of necrotising enterocolitis. In addition, MAHs should provide a cumulative review of cases of embolia cutis medicamentosa.

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.

### 6.3.7. Primidone (NAP) - PSUSA/00002525/202006

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Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

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<sup>30</sup> Update of SmPC sections 4.4 and 4.9. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

## Background

Primidone is an anticonvulsant indicated for the management of grand mal and psychomotor (temporal lobe) epilepsy. It is also indicated for the management of focal or Jacksonian seizures, myoclonic jerks, akinetic attacks and essential tremor.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing primidone 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 primidone-containing 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 an 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>31</sup>.
- In the next PSUR, the MAHs should provide detailed information on adverse pregnancy outcomes, including a discussion on the risk of major congenital malformation or neurodevelopmental disorder following in utero exposure to primidone (or phenobarbital to which primidone is metabolised).

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

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

### 6.4.1. Baricitinib - OLUMIANT (CAP) - EMEA/H/C/004085/LEG 011.1

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Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: MAH's response to LEG 011 [detailed review of cases with potential increase of immunosuppression-related serious infections, opportunistic infections and varicella-zoster infections when baricitinib is used in combination with other rheumatoid arthritis (RA) drugs as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00010578/201908) adopted in March 2020] as per the request for supplementary information (RSI) adopted in September 2020

## Background

Baricitinib is a selective inhibitor of Janus kinase (JAK) enzymes (JAK1/JAK2) indicated, as Olumiant a centrally authorised product, in monotherapy or in combination with methotrexate for the treatment of moderate to severe active rheumatoid arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drugs (DMARDs). It is also indicated for the treatment of moderate to severe atopic dermatitis in adult patients who are candidates for systemic therapy.

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<sup>31</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 the CMDh for adoption of a position

Following the evaluation of the most recently submitted PSUR(s) for the above-mentioned medicine, the PRAC requested the MAH to provide a detailed analysis of cases of serious infections, opportunistic infections and varicella-zoster infections risk related when baricitinib is used in combination with other rheumatoid arthritis (RA) medicines. For background information, see [PRAC minutes March 2020](#) and [PRAC minutes September 2020](#)<sup>32</sup>. The initial responses together with the responses to the 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, the PRAC agreed that the MAH should continue to monitor cases with potential increase of immunosuppression-related-serious infections, opportunistic infections and varicella-zoster infections when baricitinib is used in combination with other rheumatoid arthritis medicines (especially systemic glucocorticoids and leflunomide) and provide an analysis of these cases within the next PSUR.

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

### **6.5.1. Evolocumab - REPATHA (CAP) - EMEA/H/C/003766/II/0047**

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Applicant: Amgen Europe B.V.

PRAC Rapporteur: Kimmo Jaakkola

Scope: Update of section 4.8 of the SmPC in order to add myalgia to the list of adverse drug reactions (ADRs) with a frequency common following the review of nonclinical, clinical, post-marketing safety, and external spontaneous reporting databases as requested in the as requested in the conclusions of the latest periodic safety update report single assessment (PSUSA) procedure (PSUSA/00010405/201907) adopted in February 2020. The package leaflet is updated accordingly. In addition, the MAH took the opportunity to add a traceability statement in line with a statement previously added to the SmPC and to propose minor updates to instructions for use of evolocumab SureClick pre-filled pen for enhanced usability

#### **Background**

Evolocumab is an inhibitor of proprotein convertase subtilisin/kexin type 9 (PCSK9). It is indicated, as Repatha a centrally authorised product, for the treatment of adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet in combination with a statin or statin with other lipid-lowering therapies in patients unable to reach low-density lipoprotein cholesterol (LDL-C) goals with the maximum tolerated dose of a statin and alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated. It is also indicated in adults and adolescents aged 12 years and over with homozygous familial hypercholesterolaemia in combination with other lipid-lowering therapies and in adults with established atherosclerotic cardiovascular disease to reduce cardiovascular risk by lowering LDL-C levels, subject to certain conditions.

Following the evaluation of the most recently submitted PSUR(s) for the above-mentioned medicine(s), the PRAC requested the MAH to submit a variation to update the product

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<sup>32</sup> Held 31 August – 03 September 2020

information in line with the conclusions of the PSUR single assessment (PSUSA) procedure. For background information, see [PRAC minutes February 2020](#). The PRAC is responsible for adopting an outcome based on the assessment report from the PRAC Rapporteur, to be further considered at the level of the CHMP, responsible for adopting an opinion on this variation.

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

- Based on the available data and the Rapporteur's assessment, PRAC agreed to amend<sup>33</sup> the product information to add myalgia as an undesirable effect with a frequency 'common'. In addition, PRAC agreed with the minor updates to the instructions for use of evolocumab SureClick pre-filled pen for enhanced usability.

## **6.6. Expedited summary safety reviews<sup>34</sup>**

### **6.6.1. Coronavirus (COVID-19) mRNA<sup>35</sup> vaccine (nucleoside-modified) BNT162b1 - COMIRNATY (CAP) - EMEA/H/C/005735/MEA 002.1**

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Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

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

#### **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 16 years and older.

The PRAC assessed the second monthly summary safety report (MSSR) for Comirnaty ((COVID-19) mRNA vaccine (nucleoside-modified)) as part of the safety monitoring of the vaccine. At the organisational, regulatory and methodological matters (ORGAM)<sup>36</sup> meeting on 25 February 2021, the PRAC adopted its conclusions.

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

- The PRAC agreed that the MAH should submit to EMA a variation to include vomiting and diarrhoea as adverse drug reactions (ADRs).
- In the next MSSR, the MAH should include cumulative reviews of cases of immune thrombocytopenic purpura (ITP), of serious ear and labyrinth disorders, of dizziness and of Guillain-Barré syndrome (GBS). In addition, the MAH should further detail on the risk on worsened outcome of diarrhoea and/or vomiting in frail or elderly with underlying morbidities. Moreover, the summary safety report should include information on duration of insomnia and on follow-up of cases of facial paralysis. Observed/expected analyses are expected for facial paralysis and for arrhythmia and arterial hypertension.

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<sup>33</sup> Update of SmPC section 4.8. The package leaflet is to be updated accordingly

<sup>34</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>35</sup> Messenger ribonucleic acid

<sup>36</sup> Extended to specific COVID-19-related procedure(s) during EMA business continuity plan (BCP)

#### 6.6.2. Coronavirus (COVID-19) mRNA<sup>37</sup> vaccine (nucleoside-modified) BNT162b1 - COMIRNATY (CAP) - EMEA/H/C/005735/LEG 022

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Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Cumulative analysis of all cases reporting anaphylaxis after vaccination with Comirnaty ((COVID-19) mRNA vaccine (nucleoside-modified)) as requested in the conclusions of the first monthly summary safety report (MSSR) for Comirnaty (COVID-19 mRNA vaccine (nucleoside-modified)) adopted in January 2021

##### **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 16 years and older.

The PRAC assessed a cumulative analysis of all cases reporting anaphylaxis after vaccination with Comirnaty ((COVID-19) mRNA vaccine (nucleoside-modified)) requested in the conclusions of the first monthly summary safety report (MSSR). For further background, see [PRAC minutes January 2021](#). At the organisational, regulatory and methodological matters (ORGAM)<sup>38</sup> meeting on 25 February 2021, the PRAC adopted its conclusions.

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

- In the next MSSR, the MAH should include further reviews of fatal cases meeting Brighton collaboration (BC) level 1-2 for anaphylaxis, anaphylaxis BC level 1-2 cases and anaphylaxis BC level 3-4 cases. With regard to hypersensitivity reactions that are not meeting BC level 1-4 for anaphylaxis, the MAH should also include further clarifications together with a proposal to update the product information as warranted.

#### 6.6.3. Coronavirus (COVID-19) mRNA<sup>39</sup> vaccine (nucleoside-modified) - COVID-19 VACCINE MODERNA (CAP) - EMEA/H/C/005791/MEA 011

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Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Hans Christian Siersted

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

##### **Background**

Nucleoside-modified messenger ribonucleic acid (mRNA) vaccine is indicated, as COVID-19 Vaccine Moderna, for active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in adults.

The PRAC assessed the first monthly summary safety report (MSSR) for COVID-19 Vaccine Moderna ((COVID-19) mRNA vaccine (nucleoside-modified)) as part of the safety monitoring of the vaccine. At the organisational, regulatory and methodological matters

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<sup>37</sup> Messenger ribonucleic acid

<sup>38</sup> Extended to specific COVID-19-related procedure(s) during EMA business continuity plan (BCP)

<sup>39</sup> Messenger ribonucleic acid

(ORGAM)<sup>40</sup> meeting on 25 February 2021, the PRAC adopted its conclusions.

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

- In the next MSSR, the MAH should examine the disproportionality for cases of diarrhoea and, if relevant provide an analysis. In addition, the MAH should provide a discussion whether subjects who experienced a hypersensitivity (non-anaphylactic) reaction following receipt of their first dose, should still receive a second dose. Moreover, the MAH should examine the disproportionality for paraesthesia and hypoesthesia events and if these reactions occur in relation to a hypersensitivity or anxiety reaction.

#### **6.6.4. Remdesivir - VEKLURY (CAP) - EMEA/H/C/005622/MEA 017.6**

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Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Eva Jirsová

Scope: Eighth expedited summary safety report (MSSR) for Veklury (remdesivir) during the coronavirus disease (COVID-19) pandemic

#### **Background**

Remdesivir is an adenosine nucleotide prodrug indicated, as Veklury a centrally authorised product, for the treatment of coronavirus disease 2019 (COVID-19) in adults and adolescents from 12 years of age and weighing at least 40 kg with pneumonia requiring supplemental oxygen under certain conditions.

The PRAC assessed the eighth monthly summary safety report (MSSR) for Veklury (remdesivir) as part of the safety monitoring of the vaccine. The PRAC adopted its conclusions.

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

- In the next MSSR, the MAH should provide a cumulative review of cases of urticaria. For ongoing signals, see under 4.1.1. and 4.3.5.

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

### **7.1. Protocols of PASS imposed in the marketing authorisation(s)<sup>41</sup>**

See also Annex I 17.1.

#### **7.1.1. Avapritinib - AYVAKYT (CAP) - EMEA/H/C/PSP/S/0089**

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Applicant: Blueprint Medicines (Netherlands) B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Protocol for study BLU-285-1406: an observational study evaluating safety and efficacy of avapritinib in the first line treatment of patients with platelet derived growth factor alpha D842V mutated gastrointestinal stromal tumour (GIST)

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<sup>40</sup> Extended to specific COVID-19-related procedure(s) during EMA business continuity plan (BCP)

<sup>41</sup> In accordance with Article 107n of Directive 2001/83/EC

## Background

Avapritinib is a type 1 kinase inhibitor indicated, as Ayyakyt, as monotherapy for the treatment of adult patients with unresectable or metastatic gastrointestinal stromal tumours (GIST) harbouring the platelet-derived growth factor receptor alpha (PDGFRA) D842V mutation.

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 Blueprint Medicines Corporation submitted to EMA a protocol version 1.0 dated 9 November 2020 for study BLU-285-1406 entitled: 'observational study evaluating the long-term safety and efficacy of avapritinib in the first-line treatment of patients with platelet-derived growth factor receptor alfa (PDGFRA) D842Vmutated gastrointestinal stromal tumour (GIST)' for review by the PRAC.

## Endorsement/Refusal of the protocol

- The PRAC, having considered the protocol version 1.0 in accordance with Article 107n of Directive 2001/83/EC, objected to the draft protocol for the above listed medicinal product(s). The PRAC agreed that the PASS is non-interventional but the study design does not fulfil the study objectives at this stage.
- The PRAC considered that the primary objective should be amended to include the description of types, severity and rates of adverse events leading to a decreased dose of avapritinib. Moreover, with regards to the study design when considering the patients enrolled retrospectively it should be ensured that they are fully eligible for inclusion according to selection criteria, and that their corresponding data provide sufficient information on the variables. Furthermore, patients should be followed for efficacy and safety data for at least 24 months. In addition, the MAH should ensure that information on dates of dose modifications of avapritinib is collected. Finally, the statistical analysis plan (SAP) should be amended to include the number and proportions of patients with dose reductions or interruptions, or discontinuing avapritinib treatment due to an adverse event (AE) during the study period stratified for comorbidity, and the MAH should amend the adverse event of special interest (AESI) 'cardiac toxicity, including QT prolongation' into 'cardiac toxicity, including QT prolongation and related symptoms' as well as ensure the pre-plan handling of missing data.
- The MAH should submit a revised PASS protocol within 60 days to EMA. A 60 day-assessment timetable will be followed.

## 7.2. Protocols of PASS non-imposed in the marketing authorisation(s)<sup>42</sup>

See also Annex I 17.2.

### 7.2.1. Coronavirus (COVID-19) vaccine (ChAdOx1-S [recombinant]) - COVID-19 VACCINE ASTRAZENECA (CAP) - EMEA/H/C/005675/MEA 005

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Applicant: AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

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<sup>42</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



Scope: Protocol for study D8111R00003(EU) (D8110R00001 (US)): a phase 4 enhanced active surveillance study of people vaccinated with AZD1222 (COVID-19 Vaccine AstraZeneca (COVID-19 vaccine)) (from initial opinion/marketing authorisation(s) (MA))

### Background

ChAdOx1-S [recombinant] is a monovalent vaccine composed of a single recombinant, replication-deficient chimpanzee adenovirus (ChAdOx1) vector encoding the S glycoprotein of SARS-CoV-2. ChAdOx1-S [recombinant] is indicated, as COVID-19 Vaccine AstraZeneca, a centrally authorised vaccine, for active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in people aged 18 years and older.

As part of the [RMP](#) of COVID-19 Vaccine AstraZeneca ((COVID-19) vaccine (ChAdOx1-S [recombinant])), the MAH is requested to conduct a phase 4 non-interventional enhanced active surveillance study to assess the safety and tolerability of COVID-19 Vaccine AstraZeneca ((COVID-19) vaccine (ChAdOx1-S [recombinant])) in adults vaccinated in real world settings. The MAH AstraZeneca AB submitted to EMA a draft protocol version 1.0 dated February 2021 for study D8111R00003 entitled: 'a phase 4 non-interventional enhanced active surveillance study of adults vaccinated with AZD1222' which was assessed by the Rapporteur. The PRAC was requested to provide advice to CHMP on the protocol submitted by the MAH.

### Summary of advice

- Based on the review of the draft protocol version 1.0 dated February 2021 and the assessment from the Rapporteur, the PRAC considered that the protocol for COVID-19 Vaccine AstraZeneca ((COVID-19) vaccine (ChAdOx1-S [recombinant])) can be endorsed provided that several points are addressed in the final protocol before the study starts. In particular, the MAH should provide 3-monthly interim study reports until the end of data collection. The main objectives of the study should be reformulated to align them on the main outcomes of interest. Based on the current sample size and recruitment challenges, the MAH should reconsider if there are secondary or exploratory objectives. Strategies should be proposed to stimulate recruitment and retention. Additionally, the content of the planned interim reports should be clarified.

## 7.2.2. Coronavirus (COVID-19) vaccine (ChAdOx1-S [recombinant]) - COVID-19 VACCINE ASTRAZENECA (CAP) - EMEA/H/C/005675/MEA 006

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Applicant: AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

Scope: Protocol for study AZD1222 pregnancy registry: a pregnancy registry of women exposed to AZD1222 (COVID-19 Vaccine AstraZeneca (COVID-19 vaccine)) immediately before or during pregnancy (C-VIPER) (from initial opinion/marketing authorisation(s) (MA))

### Background

ChAdOx1-S [recombinant] is a monovalent vaccine composed of a single recombinant, replication-deficient chimpanzee adenovirus (ChAdOx1) vector encoding the S glycoprotein of SARS-CoV-2. ChAdOx1-S [recombinant] is indicated, as COVID-19 Vaccine AstraZeneca, for active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in people aged 18 years and older.



As part of the [RMP](#) of COVID-19 Vaccine AstraZeneca ((COVID-19) vaccine (ChAdOx1-S [recombinant])), the MAH is requested to estimate the risk of the most common obstetric outcomes, neonatal outcomes, and infant outcomes among pregnant women exposed to ((COVID-19) vaccine (ChAdOx1-S [recombinant])) in order to address the limited information on long term safety and health status in specific populations such as pregnant women at the time of the initial marketing authorisation. This study will utilise data from a prospective registry, C-VIPER, an international, prospective, observational cohort study of pregnant women vaccinated immediately before or during their pregnancy. The MAH AstraZeneca AB submitted on 28 January 2021 a PASS protocol version 1 dated 4 January 2021 for study D8110C00003 entitled: 'COVID-19 Vaccines International Pregnancy Exposure Registry (C-VIPER)' which was assessed by the Rapporteur. The protocol submitted is generic for all COVID-19 vaccines and does not specifically mention COVID-19 Vaccine AstraZeneca ((COVID-19) vaccine (ChAdOx1-S [recombinant])). The PRAC was requested to provide advice to CHMP on the protocol submitted by the MAH.

### **Summary of advice**

- Based on the review of protocol version 1 and the assessment from the Rapporteur, the PRAC considered the protocol could be acceptable provided that an updated protocol is submitted to EMA. Given C-VIPER is a common protocol for different vaccines, it is understood that the possibility for significant changes is limited. Nevertheless, the MAH should clarify those points specific to its vaccine such as milestones, including a plan for submitting interim reports or other aspects of the study for which the company could intervene. Moreover, the MAH should discuss the size of study population per vaccine brand with the consequence on its power to estimate relative risks for infrequent outcomes as well as the confounding factors control.

### **7.2.3. Osilodrostat - ISTURISA (CAP) - EMEA/H/C/004821/MEA 003.1**

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Applicant: Recordati Rare Diseases

PRAC Rapporteur: Eva Segovia

Scope: MAH's response to MEA 003 [protocol for registry LCI699-RECAG-CL 0565: a multi-country, observational study to collect clinical information on patients with endogenous Cushing's syndrome treated with osilodrostat and to document the long-term safety [final study results expected in December 2027]] as per the request for supplementary information (RSI) adopted in September 2020

### **Background**

Osilodrostat is a cortisol synthesis inhibitor indicated, as Isturisa a centrally authorised product, for the treatment of endogenous Cushing's syndrome (CS) in adults.

As part of the [RMP](#) of Isturisa (osilodrostat), the MAH is requested to conduct a PASS listed as a category 3 study using a registry to further document the long-term safety of osilodrostat administered in routine clinical practice in patients with CS treated with osilodrostat. The MAH Recordati Rare Diseases submitted a protocol on 6 May 2020 for study LCI699-RECAG-CL 0565: a multi-country, observational study to collect clinical information on patients with endogenous CS treated with osilodrostat and to document the long-term safety which was assessed by the Rapporteur. For further background, see [PRAC minutes](#)

[September 2020](#)<sup>43</sup>. Further to the request for supplementary information (RSI) adopted in September 2020, the MAH submitted an updated protocol on 16 November 2020 as part of the responses to the RSI, which was assessed by the Rapporteur. The PRAC was requested to provide advice to CHMP on the protocol submitted by the MAH.

### Summary of advice

- Based on the review of the protocol for study LCI699-RECAG-CL 0565 and the assessment from the Rapporteur, the PRAC agreed that in absence of discussion of the feasibility for a registry within ERCUSYN<sup>44</sup>, the single cohort observational study to collect long-term safety data on the use of osilodrostat in a real-world setting as proposed by the MAH is not adequate to evaluate missing information around long-term safety and use of osilodrostat in non-Cushing disease CS patients in routine clinical practice. In addition, the design of the proposed PASS with primary data sources a lack of comparator and small sample size does not address the research questions and objectives agreed at the time of the initial marketing authorisation. Therefore, PRAC agreed with the removal of the study from the pharmacovigilance plan.
- The MAH should update the RMP at the next regulatory opportunity to remove the PASS. In addition, the MAH should explore other options to further characterise, in timely manner, missing information around long-term safety and use of osilodrostat in non-Cushing disease CS patients. The MAH should also provide interim results of the ongoing study CLCI699C2X01B<sup>45</sup> in each future PSUR. Finally, the MAH should detail cases in non-Cushing disease CS patients and if available, analyse safety data by type of CS in each PSUR.

## 7.3. Results of PASS imposed in the marketing authorisation(s)<sup>46</sup>

None

## 7.4. Results of PASS non-imposed in the marketing authorisation(s)<sup>47</sup>

See also Annex I 17.4.

### 7.4.1. [Dulaglutide - TRULICITY \(CAP\) - EMEA/H/C/002825/II/0051](#)

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Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Ilaria Baldelli

Scope: Submission of the final study report for study B009 (listed as a category 3 study in the RMP): a multi-database collaborative research programme of observational studies to monitor the drug utilisation and safety of dulaglutide in the EU (in fulfilment of MEA 002). The RMP (version 6.1) is updated accordingly

### Background

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<sup>43</sup> Held 31 August – 03 September 2020

<sup>44</sup> European Register on Cushing's Syndrome

<sup>45</sup> A roll over study (listed as a category 3 study in the RMP) to evaluate long-term safety of osilodrostat in patients who have already received osilodrostat treatment in a previous global Novartis sponsored trial and who, based on investigators' judgement, will continue benefiting from its administration

<sup>46</sup> In accordance with Article 107p-q of Directive 2001/83/EC

<sup>47</sup> In accordance with Article 61a (6) of Regulation (EC) No 726/2004, in line with the revised variations regulation for any submission as of 4 August 2013

Dulaglutide is a long-acting glucagon-like peptide 1 (GLP-1) receptor agonist indicated, as Trulicity a centrally authorised product, for the treatment of adults with insufficiently controlled type 2 diabetes mellitus (T2DM) as an adjunct to diet and exercise, under certain conditions.

As stated in the [RMP](#) of Trulicity (dulaglutide), the MAH conducted a non-imposed non-interventional category 3 dulaglutide drug utilisation study (study H9X-MC-B009) entitled 'dulaglutide modified-prescription-event monitoring and network database study in the EU'. The Rapporteur assessed the MAH's final study report together with the MAH's responses to requests for supplementary information (RSI). For further background, see [PRAC minutes July 2020](#) and [PRAC minutes December 2020](#)<sup>48</sup>.

### Summary of advice

- Based on the available data, the MAH's responses to the RSIs and the Rapporteur's review, the PRAC agreed that all safety concerns of the RMP can be removed with the exception of 'thyroid C cell-tumours' and 'pancreatic malignancy' which should remain included as important potential risks in the RMP. Regarding gastro-intestinal events, further to the assessment of study PASS H9X-MC-B009, and taking into account the data from the pooled clinical trials, the REWIND<sup>49</sup> trial, post-marketing surveillance and EudraVigilance, PRAC agreed with the addition of 'delayed gastric emptying' to the product information<sup>50</sup> as a new undesirable effect with a frequency 'rare'. In conclusion, PRAC advised that the variation procedure can be recommended for approval.

## 7.4.2. Insulin detemir - LEVEMIR (CAP) - EMEA/H/C/000528/II/0101

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Applicant: Novo Nordisk A/S

PRAC Rapporteur: Anette Kirstine Stark

Scope: Update of sections 4.6 and 5.1 of the SmPC in order to update information on pregnancy, based on final results from non-interventional study NN304-4016 (listed as a category 3 study in the RMP): a diabetes pregnancy registry study conducted to assess the long-term safety of insulin use in pregnant women. The RMP (version 21.0) is updated accordingly

### Background

Insulin detemir is a soluble, long-acting insulin analogue used as a basal insulin indicated, as Levemir a centrally authorised product, for treatment of diabetes mellitus in adults, adolescents and children aged 1 year and above.

As stated in the RMP of Levemir (insulin detemir), the MAH conducted a non-interventional study (listed as a category 3 study in the RMP) to assess the long-term safety of Levemir (insulin detemir) in pregnant women (study NN304-4016). The Rapporteur assessed the MAH's final study report.

### Summary of advice

- Based on the available data and the Rapporteur's review, the PRAC considered that further information was necessary before the ongoing variation assessing the final study

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<sup>48</sup> Held 23-26 November 2020

<sup>49</sup> Effect of dulaglutide on major cardiovascular events in patients with type 2 diabetes: researching cardiovascular events with a weekly incretin in diabetes (REWIND)

<sup>50</sup> SmPC section 4.8. The package leaflet is updated accordingly

report can be recommended for approval. In particular, the MAH should provide clarifications on the reported adverse pregnancy outcome in women receiving Levemir (insulin detemir) during pregnancy as well as information on the average birth weight of children at birth in the PASS. The MAH should further review the proposed amendments to the product information in line with PRAC's comments.

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

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Applicant: Shire Pharmaceuticals Ireland Limited

PRAC Rapporteur: Martin Huber

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

##### **Background**

Velaglucerase alfa is an enzyme glycoprotein produced by gene activation technology indicated, as Vpriv a centrally authorised product, for long-term enzyme replacement therapy (ERT) in patients with type 1 Gaucher disease.

As stated in the RMP of Vpriv (velaglucerase alfa), the MAH conducted a PASS (listed as a category 3 study in the RMP) to evaluate the effectiveness of risk minimisation measures to assess the knowledge of healthcare professionals (HCPs) and patient/caregivers on prescribing and home administration conditions of velaglucerase alfa in Europe. The Rapporteur assessed the MAH's final study report together with the MAH's responses to the request for supplementary information (RSI). For further background, see [PRAC minutes December 2020](#)<sup>51</sup>.

##### **Summary of advice**

- Based on the available data, the MAH's responses to the RSI and the Rapporteur's review, the PRAC considered that further information was necessary before the ongoing variation assessing the final study report can be recommended for approval. The MAH should submit to EMA an updated RMP to revise the current key elements, in order to better convey the most important issues of the educational material and improve its effectiveness. In addition, the MAH should submit a protocol for an additional survey to investigate patients' and home infusion teams' knowledge of risks and recommendations to minimise the risks at the home setting, which should be added as a category 3 PASS to the pharmacovigilance plan. Also, the MAH should describe the best redistribution for the updated educational material and discuss actions to increase awareness of the educational material update among physicians and others involved who have previously received educational material for Vpriv (velaglucerase alfa).

#### 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.

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<sup>51</sup> Held 23-26 November 2020

## **7.6. Others**

See Annex I 17.6.

## **7.7. New Scientific Advice**

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

## **7.8. Ongoing Scientific Advice**

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

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

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

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

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

See Annex I 18.1.

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

See Annex I 18.2.

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

See also Annex I 18.3.

### **8.3.1. Autologous CD34+ enriched cell fraction that contains CD34+ cells transduced with retroviral vector that encodes for the human ADA cDNA sequence - STRIMVELIS (CAP) - EMEA/H/C/003854/R/0029 (without RMP)**

Applicant: Orchard Therapeutics (Netherlands) BV, ATMP<sup>52</sup>

PRAC Rapporteur: Menno van der Elst

Scope: 5-year renewal of the marketing authorisation

#### **Background**

Autologous CD34+ enriched cell fraction that contains CD34+ cells transduced with retroviral vector that encodes for the human adenosine deaminase (ADA) complementary deoxyribonucleic acid (cDNA) sequence are immunostimulants indicated for the treatment of patients with severe combined immunodeficiency due to adenosine deaminase deficiency

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<sup>52</sup> Advanced therapy medicinal product

(ADA-SCID), for whom no suitable human leukocyte antigen (HLA)-matched related stem cell donor is available.

Strimvelis, a centrally authorised medicine containing autologous CD34+ enriched cell fraction that contains CD34+ cells transduced with retroviral vector that encodes for the human adenosine deaminase (ADA) complementary deoxyribonucleic acid (cDNA) sequence, was authorised in 2016.

The MAH submitted an application for renewal of the marketing authorisation(s) for opinion by the CHMP. The PRAC is responsible for providing advice to the CHMP on this renewal with regard to safety and risk management aspects. For further background, see [PRAC minutes December 2020](#)<sup>53</sup>.

### Summary of advice

- Based on the review of the available pharmacovigilance data for Strimvelis (autologous CD34+ enriched cell fraction that contains CD34+ cells transduced with retroviral vector that encodes for the human ADA cDNA sequence) and the CHMP Rapporteur's assessment report, the PRAC supported the distribution of a direct healthcare professional communication ([DHPC](#)) in line with an agreed communication plan. The Committee considered that a DHPC is necessary to inform healthcare professionals (HCPs) on a reported case of lymphoid T cell leukaemia due to insertional oncogenesis, and ensure that patients are monitored long term. In addition, 'malignancy due to insertional oncogenesis' should be changed in the RMP from an important potential risk to an important identified risk. In addition, this issue should remain under close scrutiny in the context of the currently ongoing imposed study STRIM-003<sup>54</sup> patient registry. In view of the further information provided on the case of lymphoid T cells leukaemia and the measures taken, PRAC advised that a second five-year renewal of the marketing authorisation(s) is not warranted any longer based on pharmacovigilance grounds.

## 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

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<sup>53</sup> Held 23-26 November 2020

<sup>54</sup> Adenosine deaminase severe combined immunodeficiency (ADA-SCID) registry for patients treated with Strimvelis (previously GSK2696273) gene therapy: long-term prospective, non-interventional follow-up of safety and effectiveness

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

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

#### 10.1.1. Onasemnogene abeparvovec – ZOLGENSMA (CAP) - EMEA/H/C/004750/II/0008

Applicant: Novartis Gene Therapies EU Limited, ATMP<sup>55</sup>

PRAC Rapporteur: Ulla Wändel Liminga

Scope: PRAC consultation on a variation to update sections 4.4 and 4.8 of the SmPC to add thrombotic microangiopathy. The package leaflet is updated accordingly

##### Background

Onasemnogene abeparvovec is a gene therapy designed to introduce a functional copy of the survival motor neuron gene (SMN1) in the transduced cells, indicated as Zolgensma a centrally authorised product, for the treatment of patients with 5q spinal muscular atrophy (SMA) with a bi-allelic mutation in the SMN1 gene and a clinical diagnosis of SMA type 1, or patients with 5q SMA with a bi-allelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene.

A type II variation proposing to update the product information of Zolgensma (onasemnogene abeparvovec) with information on thrombotic microangiopathy (TMA) is under evaluation at CAT and CHMP. The PRAC was requested to provide advice on this variation.

##### Summary of advice

- Based on the review of the available information and assessment, the PRAC supported the distribution of a direct healthcare professional communication ([DHPC](#)) in line with an agreed communication plan. The Committee considered that a DHPC is necessary to inform healthcare professionals (HCPs) about TMA as it is a serious condition that has been reported after Zolgensma (onasemnogene abeparvovec) administration. In addition, the PRAC advised that educational material for caregivers should be developed to inform on the newly identified risk of TMA.

#### 10.1.2. Venetoclax - VENCLYXTO (CAP) - EMEA/H/C/004106/II/0031

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Eva Jirsová

Scope: PRAC consultation on a variation to update sections 4.2 and 4.4 of the SmPC on tumour lysis syndrome (TLS) prophylaxis and management following an update to the company core data sheet (CCDS) as result of a medical safety assessment conducted on TLS post-marketing reports

##### Background

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<sup>55</sup> Advanced therapy medicinal product

Venetoclax is an inhibitor of B-cell lymphoma (BCL)-2 indicated, as Venclyxto a centrally authorised product, for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL) and for the treatment of adult patients with CLL who have received at least one prior therapy under certain conditions. It is also indicated for the treatment of CLL in the presence of 17p deletion or TP53 mutation in adult patients who are unsuitable for or have failed a B-cell receptor pathway inhibitor, or in the absence of 17p deletion or TP53 mutation in adult patients who have failed both chemoimmunotherapy and a B-cell receptor pathway inhibitor.

A type II variation proposing to update the product information of Venclyxto (venetoclax) with information on tumour lysis syndrome (TLS) prophylaxis is under evaluation at the CHMP. The PRAC was requested to provide advice on this variation.

#### **Summary of advice**

- Based on the review of the available information and assessment, the PRAC supported the distribution of a direct healthcare professional communication ([DHPC](#)) in line with an agreed communication plan. The Committee considered that a DHPC is necessary to communicate on the risk of TLS and to indicate the need to strictly adhere to dose titration and TLS risk minimisation measures by healthcare professionals (HCPs). In addition, the PRAC agreed on the need for a patient card and proposed some key elements for further review. In the next PSUR, the MAH should be requested to discuss the impact of the newly implemented risk minimisation measures on the adherence to the existing and new recommendations.

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

None

### **10.3. Other requests**

None

### **10.4. Scientific Advice**

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

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

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

#### **11.1.1. Iopamidol (NAP) - IE/H/xxxx/WS/137**

Applicant(s): Bracco Imaging SPA (Niopam)

PRAC Lead: Ronan Grimes

Scope: PRAC consultation on a worksharing variation procedure evaluating several safety



topics, namely: contrast induced encephalopathy, neonatal hypothyroidism, drug reaction with eosinophilia and systemic symptoms (DRESS) and persistence in the foetus/neonate secondary to transplacental passage, as discussed at PRAC and agreed by CMDh following the conclusion of the PSUSA procedure (PSUSA/00001771/201912) concluded in September 2020, on request of Ireland

### **Background**

Iopamidol is a non-ionic monomeric low-osmolar X-ray contrast agent indicated as solution for injection for contrast enhancement in diagnostic procedures such as excretory urography, angiography, computed tomography and myelography and can be administered intravascularly and intrathecally.

Based on the assessment of the recent PSUR single assessment (PSUSA) procedure for iopamidol (PSUSA/00001771/201912) concluded in September 2020, the PRAC considered that the risks of contrast-induced encephalopathy, drug reaction with eosinophilia and systemic symptoms (DRESS), and persistence of iopamidol in the foetus/neonate secondary to transplacental passage of non-ionic, iodinated contrast media need to be further assessed. For further background, see to [PRAC minutes September 2020](#)<sup>56</sup>.

On request of the CMDh, MAH Bracco for nationally approved iopamidol-containing product(s) submitted a worksharing variation evaluating the safety reviews. Ireland, as lead Member State (LMS), requested PRAC advice on its assessment.

### **Summary of advice**

- Based on the review of the available information and submitted data, the PRAC supported the LMS assessment. The PRAC agreed there is sufficient evidence to update the product information<sup>57</sup> to include contrast encephalopathy as a warning and as an undesirable effect with a frequency 'not known', and to also include neonatal hypothyroidism as a warning. In addition, the PRAC agreed that no further action is warranted at the moment regarding DRESS and persistence in the foetus/neonate secondary to transplacental passage in light of the current knowledge.

## **11.2. Other requests**

None

## **12. Organisational, regulatory and methodological matters**

### **12.1. Mandate and organisation of the PRAC**

#### **12.1.1. PRAC working group - Best practice guide on using PRAC plenary time efficiently and effectively – update on the implementation of quantitative goals – Q4 2020**

In line with the adopted PRAC best practice guidance (BPG) on Committee efficiency (see [PRAC minutes May 2016](#) and [PRAC minutes June 2018](#)) and the adopted implementation plan for the BPG including goals to measure compliance with the recommendations (see [PRAC minutes June 2016](#) and [PRAC minutes June 2018](#)), the EMA secretariat informed the

<sup>56</sup> 31 August – 03 September 2020

<sup>57</sup> SmPC sections 4.4, 4.6 and 4.8. The package leaflet is to be updated accordingly

PRAC about the quantitative measures collected for the Q4 2020 of PRAC meetings. For previous update, see [PRAC minutes October 2020](#)<sup>58</sup>.

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

None

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

### **12.3.1. CHMP Scientific Advice Working Party (SAWP) PRAC working group – SAWP members - new appointments**

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In view of the current SAWP workload and current vacant positions for a PRAC representative as SAWP alternate and second PRAC-SAWP member/alternate, the EMA Secretariat requested the temporary possibility to have these positions assigned to additional SAWP member/alternate(s). The EMA Secretariat clarified that the appointment(s) is/are conditional, and the position(s) can be made immediately available to the PRAC should PRAC decide on further appointment(s) to SAWP. PRAC agreed with the proposal.

## **12.4. Cooperation within the EU regulatory network**

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

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

### **12.4.2. Incident Review Network (IRN) – call for interest for a PRAC representative: renewal of composition of the EU regulatory network incident management plan for medicines for human use**

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In the context of the composition renewal of the EU regulatory network incident management plan for medicines for human use – Incident Review Network (IRN) for the new 3-year mandate to run until December 2023, the EMA Secretariat presented to PRAC a call for expression of interest to join the IRN. PRAC members were invited to send nominations by 12 February 2021.

### **12.4.3. PRAC strategic review and learning meeting (SRLM) under the Portuguese presidency of the European Union (EU) Council – Remote meeting, 19 March 2021 - agenda**

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PRAC lead: Ana Sofia Diniz Martins, Marcia Sofia Sanches de Castro Lopes Silva

The PRAC was presented with a draft agenda for the 'PRAC strategic review and learning meeting (SRLM)' to be held remotely on 19 March 2021, under the Portuguese presidency

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<sup>58</sup> 28 September – 01 October 2020

of the Council of the European Union (EU).

## **12.5. Cooperation with International Regulators**

None

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

### **12.6.1. Coronavirus (COVID-19)-vaccines monitoring: ACCESS<sup>59</sup> consortium project - update**

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As a follow-up to the December 2020 discussion (for background, see [PRAC minutes December 2020](#)<sup>60</sup>), the EMA secretariat further updated the PRAC on the ACCESS project deliverables including template protocols, background rates of adverse events of special interest (AESIs) as well as on other sources of background rates (including EMA). Finally, EMA Secretariat provided PRAC with an update on ongoing and planned observational vaccine safety studies, including EMA-funded early safety monitoring study and future European Commission (EC)-funded studies. This includes the Joint ECDC<sup>61</sup>/EMA COVID-19 vaccine monitoring platform, and in particular an EC-funded COVID-19 two year-prospective vaccine safety study. A call for PRAC interest to review proposals from contractors and deliverables of the study was shared with PRAC members. Further updates will be planned in due course.

### **12.6.2. Coronavirus (COVID-19)-medicines monitoring: CONSIGN<sup>62</sup> consortium project – COVID-19 infection and medicines in pregnancy – update**

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PRAC lead: Sabine Straus, Ulla Wändel Liminga

As a follow-up to the December 2020 discussion (for background, see [PRAC minutes December 2020](#)<sup>63</sup>), the EMA secretariat further updated the PRAC on the progress of the CONSIGN project set up to guide evidence based decision-making about COVID-19 vaccine indications, vaccination policies, and treatment options for pregnant women. EMA Secretariat shared some details on the CONSIGN work packages 2 and 3 (COVI-PREG<sup>64</sup> and INOSS<sup>65</sup> studies) and on ongoing international collaboration activities. Further updates will be planned in due course.

## **12.7. PRAC work plan**

None

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<sup>59</sup> vACcine Covid-19 monitoring readinESS

<sup>60</sup> Held 23-26 November 2020

<sup>61</sup> European Centre for Disease Prevention and Control

<sup>62</sup> Covid-19 infectiOn aNd medicineS In pregnancy

<sup>63</sup> Held 23-26 November 2020

<sup>64</sup> International COVID-19 and Pregnancy Registry

<sup>65</sup> International Network of Obstetric Survey Systems

## **12.8. Planning and reporting**

### **12.8.1. EU Pharmacovigilance system – quarterly workload measures and performance indicators – Q4 2020 and predictions**

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The EMA Secretariat presented to PRAC an overview of the quarterly figures on the EMA pharmacovigilance system-related workload and performance indicators. For previous update, see [PRAC minutes November 2020](#)<sup>66</sup>.

### **12.8.2. PRAC workload statistics – Q4 2020**

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The EMA secretariat presented to PRAC the quarterly and cumulative figures to estimate the evolution of the workload of the PRAC for Q4 2020, by reflecting on the number of procedures and agenda items covered at each PRAC plenary meeting. For previous update, see [PRAC minutes October 2020](#)<sup>67</sup>.

## **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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The PRAC endorsed the draft revised EURD list, version February 2021, reflecting the

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<sup>66</sup> Held 26-29 October 2020

<sup>67</sup> Held 28 September – 01 October 2020

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

Post-meeting note: following the PRAC meeting of February 2021, the updated EURD list was adopted by the CHMP and CMDh at their February 2021 meetings and published on the EMA website on 03/03/2021, 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 \(PSURs\)](#)

## **12.11. Signal management**

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

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PRAC lead: Menno van der Elst

The PRAC was updated on the progress from the signal management review technical (SMART) working group meeting held remotely on 22 January 2021. The SMART working group (WG) discussed the impact of Brexit on UK signals, vaccine targeted medical events and on dissemination of information on coronavirus-19 (COVID-19) vaccines cases. The SMART WG also received a status update on EudraVigilance (EV) signal detection methodologies for COVID-19 vaccines, including an update on the EMA dashboard which will be placed in EV data analysis system (EVDAS). Further update will be planned in due course.

## **12.12. Adverse drug reactions reporting and additional monitoring**

### **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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The 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 24/02/2021, see: [Home>Human Regulatory>Post-authorisation>Pharmacovigilance>Medicines under additional monitoring>List of medicines under additional monitoring](#)

### **12.12.4. Adverse events of special interest (AESI) for coronavirus (COVID-19) vaccines – follow-up questionnaires**

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Following initial plenary discussion in January 2021, the EMA Secretariat presented to PRAC

a proposed letter to send to MAHs for centrally authorised COVID-19 vaccines to remind that follow-up questionnaires (FUQ) require Member States' approval on format, language used and distribution path, and that FUQ should be used solely to facilitate collection of supplemental information that is not available in initial adverse drug reaction (ADR) reports. MAHs are to be invited to contact respective National Competent Authorities (NCA) in Member States where their respective COVID-19 vaccines are marketed to discuss practical arrangements of using the FUQ. PRAC supported the proposal.

## **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. Advanced therapy medicinal products (ATMPs) - EU data sources for long-term safety and efficacy follow-up**

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Following plenary discussion in January 2021, the EMA Secretariat prepared a briefing note including a list of potential options for future approach with regards to the imposition of long-term safety and efficacy studies for advanced therapy medicinal products (ATMP). Following CAT and PRAC reviews of the draft briefing note, the EMA Secretariat presented to PRAC a consolidated version of the briefing note including CAT/PRAC members' national experience that might be relevant to the decision, and favoured option(s) for existing authorised ATMPs and for ongoing and future applications. Further discussion will take place at CAT. Follow-up discussion and endorsement is planned in March 2021.

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

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None

### **12.15.3. 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. Others**

### **12.20.1. EMA pregnancy strategy - draft**

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The EMA Secretariat presented to PRAC the draft EMA pregnancy strategy in order to address the EMA regulatory science strategy 2025 (EMA RSS 2025) and the European medicines regulatory network (EMRN) commitment to improve information on benefit-risk for special populations, including pregnant and breastfeeding women. The EMA Secretariat provided PRAC with an outline of the issues, the implementation activities foreseen and of the ongoing activities in this area to build on. PRAC members were invited to send comments. Follow-up discussion will be scheduled in due course.

### **12.20.2. Strategy on measuring the impact of pharmacovigilance – PRAC interest group (IG) Impact: draft technical specifications for an impact study for methotrexate-containing products**

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PRAC lead: Antoine Pariente

The EMA Secretariat presented to PRAC on behalf of PRAC interest group (IG) Impact a proposal to prioritise for impact research the regulatory actions taken in the context of the referral procedure for methotrexate under Article 31 of Directive 2001/83/EC (EMEA/H/A-31/1463) finalised in 2019 to avoid inadvertent methotrexate overdose due to daily instead of weekly use in indications requiring once weekly methotrexate dosing. EMA Secretariat also presented draft technical specifications for a tender for an EMA funded impact research

on EU label changes for medicinal products containing methotrexate for weekly administration on risk awareness and adherence. PRAC members supported the proposed topic for EMA commissioned impact research. PRAC members were also invited to provide written comments by 24 February 2021. At the organisational, regulatory and methodological matters (ORGAM) meeting on 25 February 2021, PRAC endorsed the revised technical specifications.

## 13. Any other business

None

## 14. Annex I – Signals assessment and prioritisation<sup>68</sup>

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

As per agreed criteria for new signal(s), the PRAC adopted without further plenary discussion the recommendation of the Rapporteur to request MAH(s) to submit a cumulative review following standard timetables<sup>69</sup>.

#### 14.1.1. Olanzapine – OLANZAPINE APOTEX (CAP); OLANZAPINE GLENMARK (CAP); OLANZAPINE GLENMARK EUROPE (CAP); OLANZAPINE MYLAN (CAP); OLANZAPINE TEVA (CAP); OLAXAX (CAP); OLAXAX DISPERZI (CAP); ZALASTA (CAP); ZYPADHERA (CAP); ZYPREXA (CAP); ZYPREXA VELOTAB (CAP); NAP

Applicant(s): Apotex Europe BV (Olanzapine Apotex), Eli Lilly Nederland B.V. (Zypadhera, Zyprexa, Zyprexa Veotab), Glenmark Arzneimittel GmbH (Olanzapine Glenmark, Olanzapine Glenmark Europe), Glenmark Pharmaceuticals (Olaxax, Olaxax Disperzi), Krka, d.d., Novo mesto (Zalasta), Mylan S.A.S (Olanzapine Mylan); Teva B.V.

PRAC Rapporteur: Kimmo Jaakkola

Scope: Signal of cardiomyopathy

EPITT 19663 – New signal

Lead Member State(s): FI

#### 14.1.2. Olaparib – LYNPARZA (CAP)

Applicant(s): AstraZeneca AB

PRAC Rapporteur: Amelia Cupelli

Scope: Signal of Pneumocystis jirovecii pneumonia

EPITT 19651 – New signal

<sup>68</sup> <sup>68</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>69</sup> Either MA(s)'s submission within 60 days followed by a 60 day-timetable assessment or MAH's submission cumulative review within an ongoing or upcoming PSUR/PSUSA procedure (if the DLP is within 90 days), and no disagreement has been raised before the meeting



Lead Member State(s): IT

#### **14.1.3. Romosozumab – EVENITY (CAP)**

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Applicant(s): UCB Pharma S.A.

PRAC Rapporteur: Adrien Inoubli

Scope: Signal of renal impairment

EPITT 19648 – New signal

Lead Member State(s): FR

#### **14.2. New signals detected from other sources**

None

### **15. Annex I – Risk management plans**

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

As per agreed criteria, the 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. Abiraterone acetate - EMEA/H/C/005649**

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Scope: Treatment of prostate cancer in adult men

##### **15.1.2. Abiraterone acetate - EMEA/H/C/005368**

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Scope: Treatment of metastatic castration resistant prostate cancer

##### **15.1.3. Lonafarnib - EMEA/H/C/005271, Orphan**

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Applicant: EigerBio Europe Limited

Scope (accelerated assessment): Treatment of Hutchinson-Gilford progeria syndrome and progeroid laminopathies

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

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

##### **15.2.1. Guselkumab - TREMFYA (CAP) - EMEA/H/C/004271/II/0025**

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Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Submission of an updated RMP (version 7.1) in order to amend the study population for study C0168Z03 (PSOLAR): a multicentre open registry of patients with psoriasis who are candidates for systemic therapy including biologics. As a consequence, the MAH submitted an amendment to the protocol previously agreed in June 2018 for the registry study

#### 15.2.2. Melatonin - CIRCADIN (CAP) - EMEA/H/C/000695/II/0061

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Applicant: RAD Neurim Pharmaceuticals EEC SARL

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Submission of an updated RMP (version 7.0) to remove the following risks from the list of potential risks: drug interaction with levothyroxine, panic attacks, potential interaction with warfarin, sperm motility decreased/spermatozoa morphology abnormal and withdrawal. Furthermore, the MAH took the opportunity to introduce minor corrections throughout the RMP

#### 15.2.3. Neratinib - NERLYNX (CAP) - EMEA/H/C/004030/II/0020

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Applicant: Pierre Fabre Medicament

PRAC Rapporteur: Menno van der Elst

Scope: Submission of an updated RMP (version 1.1) in order to amend the list of important identified risks, to update data concerning PASS studies and to change the submission due date of the final results of study PUMA-NER-6201 (MEA 001): an open-label study to characterize the incidence and severity of diarrhoea in patients with early stage human epidermal growth factor receptor 2 positive (HER2+) breast cancer treated with neratinib and intensive loperamide prophylaxis, with/without anti-inflammatory treatment (budesonide) and with/without a bile acid sequestrant (colestipol), from Q1 2021 to Q4 2021

#### 15.2.4. Rotavirus vaccine (live, oral) - ROTATEQ (CAP) - EMEA/H/C/000669/II/0085

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Applicant: MSD Vaccins

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of an updated RMP (version 7.2) in order to bring it in line with revision 2 of GVP module V on 'Risk management systems'. As a consequence, the list of safety concerns is updated and a reclassification of important risks is proposed. In addition, the updated RMP includes the removal of hypersensitivity and severe combined immunodeficiency (SCID) from the list of safety concerns as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00002666/201911) adopted in June 2020

#### 15.2.5. Rotigotine - LEGANTO (CAP) - EMEA/H/C/002380/WS2000/0035; NEUPRO (CAP) - EMEA/H/C/000626/WS2000/0089

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Applicant: UCB Pharma S.A.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Submission of an updated RMP (version 5.0) in order to bring it in line with revision 2.0.1 of the guidance on the format of RMP in the EU (template)

#### **15.2.6. Trabectedin - YONDELIS (CAP) - EMEA/H/C/000773/II/0061**

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Applicant: Pharma Mar, S.A.

PRAC Rapporteur: Anette Kirstine Stark

Scope: Submission of an updated RMP (version 9.0) in order to reflect new available data from completed studies, removal of safety concerns and removal of a target follow-up questionnaire. The RMP is also brought in line with revision 2.0.1 of the guidance on the format of RMP in the EU (template)

#### **15.2.7. Zoledronic acid - ACLASTA (CAP) - EMEA/H/C/000595/II/0076**

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Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of an updated RMP (version 13.0) in order to bring it in line with revision 2 of GVP module V on 'Risk management systems' including consequential removal/reclassification of a number of important potential risks; to remove the education material on renal dysfunction and use in patients with severe renal impairment; to remove 'post-dose symptoms' from the list of important identified risks as per the conclusions of LEG 037 adopted in September 2019 and variation II/74/G adopted in March 2020; to update of the targeted questionnaire related to osteonecrosis of the jaw (ONJ) as per the conclusions of LEG 035 adopted in January 2017; to include the completed 5-year registry for study ZOL446H2422 (listed as a category 3 study in the RMP): a non-interventional post-authorisation safety study using health registries to compare safety of Aclasta (zoledronic acid) against oral bisphosphonates and untreated population controls as per the conclusions of variation II/69 adopted in January 2018. The additional risk minimisation measures in Annex II-D on 'Conditions or restrictions with regard to the safe and effective use of the medicinal product' are updated accordingly

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

As per agreed criteria, the 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. Abemaciclib - VERZENIOS (CAP) - EMEA/H/C/004302/II/0013**

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Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Extension of indication to include Verzenios (abemaciclib) in combination with endocrine therapy for adjuvant treatment of patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, node-positive early breast cancer at high risk of recurrence. As a consequence, sections 4.1, 4.2, 4.4, 4.6, 4.8, 5.1

and 5.3 of the SmPC are updated. The package leaflet and the RMP (version 1.1) are updated in accordance

#### **15.3.2. Aflibercept - EYLEA (CAP) - EMEA/H/C/002392/II/0069**

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Applicant: Bayer AG

PRAC Rapporteur: Tiphaine Vaillant

Scope: Update of sections 4.2 and 5.1 of the SmPC for the indication of the treatment of visual impairment due to diabetic macular oedema (DME) based on results from the post-authorisation efficacy study (PAES) study 17613 (VIOLET): an open-label, randomized, active-controlled, parallel-group, phase-3b study of the efficacy, safety, and tolerability of three different treatment regimens of 2 mg aflibercept administered by intravitreal injections to subjects with DME. The submission also includes data from study AQUA: an open-label phase-4 study to examine the change of vision-related quality of life in subjects with DME during treatment with intravitreal injections of 2 mg aflibercept according to EU label for the first year of treatment, which served as run-in study for VIOLET. The RMP (version 28.1) is updated accordingly

#### **15.3.3. Atezolizumab - TECENTRIQ (CAP) - EMEA/H/C/004143/II/0052**

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Applicant: Roche Registration GmbH

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Extension of indication to include Tecentriq (atezolizumab) in combination with nab-paclitaxel and anthracycline-based chemotherapy for the neoadjuvant treatment of adult patients with locally advanced or early triple negative breast cancer (TNBC) based on the results of the pivotal study WO39392 (IMpassion031): a phase 3 randomized study to investigate the efficacy and safety of atezolizumab in combination with neoadjuvant anthracycline/nab-paclitaxel-based chemotherapy compared with placebo and chemotherapy in patients with primary invasive triple-negative breast cancer. As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the Tecentriq (atezolizumab) 840 mg concentrate for solution for infusion SmPC and section 4.8 of the Tecentriq (atezolizumab) 1,200 mg concentrate for solution for infusion SmPC are updated. The package leaflet and the RMP (version 18.0) are updated in accordance

#### **15.3.4. Atezolizumab - TECENTRIQ (CAP) - EMEA/H/C/004143/II/0053**

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Applicant: Roche Registration GmbH

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Submission of the final report from study GO29322 (listed as a category 3 study in the RMP): a phase 1b study investigating the safety and pharmacology of atezolizumab administered with ipilimumab, interferon-alpha, or other immune modulating therapies in patients with locally advanced or metastatic solid tumours. The RMP (version 19.0) is updated accordingly

#### 15.3.5. Axicabtagene ciloleucel - YESCARTA (CAP) - EMEA/H/C/004480/II/0028, Orphan

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Applicant: Kite Pharma EU B.V., ATMP<sup>70</sup>

PRAC Rapporteur: Anette Kirstine Stark

Scope: Update of sections 4.4, 4.8 and 5.1 of the SmPC to update the safety information based on updates from study KTE-C19-101: a phase 1/2 multicentre study evaluating the safety and efficacy of Yescarta (axicabtagene ciloleucel (KTE-C19)) in subjects with refractory aggressive non-Hodgkin lymphoma (ZUMA-1). The updates include data from: 1) phase 2 safety management ZUMA-1 cohort 4 intended to assess the impact of earlier interventions on the rate and severity of cytokine release syndrome (CRS) and neurologic events; 2) a 36-month analysis from ZUMA-1 cohorts 1 and 2. The RMP (version 3.1) is updated accordingly

#### 15.3.6. Bortezomib - BORTEZOMIB ACCORD (CAP) - EMEA/H/C/003984/X/0023

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Applicant: Accord Healthcare S.L.U.

PRAC Rapporteur: Amelia Cupelli

Scope: Extension application to introduce a new pharmaceutical form associated with new strength (2.5 mg/mL, solution for injection). The RMP (version 11.0) is updated accordingly

#### 15.3.7. Buprenorphine - BUVIDAL (CAP) - EMEA/H/C/004651/X/0008/G

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Applicant: Camurus AB

PRAC Rapporteur: Tiphaine Vaillant

Scope: Grouped applications consisting of: 1) line extension to add a new strength of 160 mg for prolonged-release solution for injection pharmaceutical form. The RMP (version 1.1) is updated accordingly. The MAH took the opportunity to align the product information with the latest quality review of documents (QRD) template (version 10.1) and to implement new text regarding the content of ethanol in accordance with the EMA document on 'information for the package leaflet regarding ethanol used as an excipient in medicinal products for human use' in the package leaflet; 2) quality/manufacturing aspect related variation

#### 15.3.8. Burosumab - CRYSVITA (CAP) - EMEA/H/C/004275/II/0021, Orphan

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Applicant: Kyowa Kirin Holdings B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of section 4.2 of the SmPC in order to modify administration instructions to include the option of self/carer-administration based on results from two interventional clinical safety and efficacy studies, namely: 1) study KRN23-003: a phase 3 open-label trial to assess the efficacy and safety of burosumab (KRN23) in paediatric patients with X-linked hypophosphatemic rickets/osteomalacia (final study report); 2) study KRN23-004: a phase 3 long-term extension study of burosumab in adult patients with X-linked hypophosphatemic Rickets/osteomalacia and a post-marketing study of burosumab

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<sup>70</sup> Advanced therapy medicinal product

switched from the phase 3 long-term extension study (interim report). The package leaflet is updated accordingly and includes a new section with instructions for use. In addition, the MAH took the opportunity to implement editorial changes throughout the product information. The RMP (version 3.0) is also updated in accordance

#### **15.3.9. Cabozantinib - CABOMETYX (CAP) - EMEA/H/C/004163/II/0017**

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Applicant: Ipsen Pharma

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication to include in combination with nivolumab first line treatment of advanced renal cell carcinoma. 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 5.0) are updated in accordance

#### **15.3.10. Dapagliflozin - EDISTRIDE (CAP) - EMEA/H/C/004161/WS1941/0043; FORXIGA (CAP) - EMEA/H/C/002322/WS1941/0062**

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Applicant: AstraZeneca AB

PRAC Rapporteur: Annika Folin

Scope: Extension of indication to include treatment of chronic kidney disease. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC for Forxiga and Edistride (dapagliflozin) are updated based on the results from the renal outcomes study D169AC00001 (DAPA-CKD) (listed as a category 3 study in the RMP): a multicentre, event-driven, randomized, double-blind, parallel group, placebo-controlled study evaluating the effect of dapagliflozin versus placebo given once daily in addition to standard of care to evaluate the potential risk of lower limb amputation to prevent the progression of chronic kidney disease (CKD) or cardiovascular (CV)/renal death. Annex II-B on 'Conditions or restrictions regarding supply and use' and the package leaflet are updated accordingly. The RMP (version 22.1) is also updated in accordance

#### **15.3.11. Daratumumab - DARZALEX (CAP) - EMEA/H/C/004077/II/0043, Orphan**

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Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Extension of indication to include treatment of adult patients with systemic light chain (AL) amyloidosis. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 8.2) are updated in accordance

#### **15.3.12. Daratumumab - DARZALEX (CAP) - EMEA/H/C/004077/II/0044, Orphan**

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Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Extension of indication for Darzalex (daratumumab) subcutaneous formulation to include combination with pomalidomide and dexamethasone for the treatment of adult patients with relapsed and refractory multiple myeloma (RRMM), whose prior therapy

included a proteasome inhibitor and an immunomodulatory agent and who have demonstrated disease progression on the last therapy. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. In addition, section 4.8 of the SmPC for the intravenous formulation is updated based on pooled safety analysis data. The package leaflet and the RMP (version 8.2) are updated in accordance

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

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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

#### **15.3.14. Delafloxacin - QUOFENIX (CAP) - EMEA/H/C/004860/II/0003**

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Applicant: A. Menarini Industrie Farmaceutiche Riunite s.r.l.

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Extension of indication to include treatment of community acquired pneumonia (CAP) for Quofenix (delafloxacin) 450 mg tablets and 300 mg powder for concentrate for solution for infusion. 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 2.0) are updated in accordance

#### **15.3.15. Dengue tetravalent vaccine (live, attenuated) - DENGVAXIA (CAP) - EMEA/H/C/004171/II/0016/G**

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Applicant: Sanofi Pasteur

PRAC Rapporteur: Sonja Hrabcik

Scope: Grouped variations consisting of an update of section 4.5 of the SmPC to include co-administration data on Gardasil/Cervarix (human papillomavirus vaccine) and Adacel (tetanus toxoid/reduced diphtheria toxoid and acellular/pertussis vaccine (adsorbed)) based on the final results of studies (listed as category 3 studies in the RMP) dedicated to immunogenicity and safety of the concomitant administration, namely: 1) study CYD66: a phase 3b, randomized, multicentre, open-label study in 688 subjects aged from 9 to 60 years in the Philippines; 2) CYD67: a phase 3b, randomized, open-label, multicentre study in 528 subjects aged 9 to 13 years in Malaysia; 3) CD71: a phase 3b, randomized, open-label, multicentre study in 480 female subjects aged 9 to 14 years in Mexico. The package leaflet and the RMP (version 6.1) are updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet

#### **15.3.16. Erenumab - AIMOVIG (CAP) - EMEA/H/C/004447/II/0013/G**

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Applicant: Novartis Europharm Limited

PRAC Rapporteur: Kirsti Villikka

Scope: Grouped variations consisting of: 1) update of section 4.8 of the SmPC to add alopecia, oral sores and rash in line with revised clinical safety data; 2) update of sections 4.8 and 5.1 of the SmPC based on the study report from 5-year open-label study

20120178: a phase 2, multicentre, randomized, double-blind, placebo-controlled, parallel-group study of subjects with episodic migraine; 3) update of section 5.1 of the SmPC to include of the anatomical therapeutic chemical (ATC) classification system code for erenumab. The package leaflet and the RMP (version 3.0) are updated accordingly

#### 15.3.17. Ertugliflozin - STEGLATRO (CAP) - EMEA/H/C/004315/WS1953/0013; ertugliflozin, metformin hydrochloride - SEGLUROMET (CAP) - EMEA/H/C/004314/WS1953/0012

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Update of sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC of Steglatro (ertugliflozin) and Segluromet (ertugliflozin/metformin) in order to modify the indication, update posology recommendations and include efficacy and safety information based on the final results from study 8835-004/B1521021 (listed as a category 3 study in the RMP): a multicentre, multinational, randomised, double-blind, placebo-controlled study to evaluate the effect of ertugliflozin on cardiovascular risk in adult patients with type 2 diabetes (T2DM) and established atherosclerotic cardiovascular disease (VERTIS CV study). The package leaflet and the RMP (version 2.0) are updated accordingly

#### 15.3.18. Ertugliflozin, sitagliptin - STEGLUJAN (CAP) - EMEA/H/C/004313/II/0015

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Update of sections 4.2, 4.4, 4.8 and 5.1 of the SmPC for Steglujan (ertugliflozin/sitagliptin) in order to update clinical information following the final results from study 8835-004/B1521021 (listed as a category 3 study in the RMP): a multicentre, multinational, randomised, double-blind, placebo-controlled study to evaluate the effect of ertugliflozin on cardiovascular risk in adult patients with type 2 diabetes (T2DM) and established atherosclerotic cardiovascular disease (VERTIS CV study). The package leaflet and the RMP (version 2.0) are updated accordingly. In addition, the MAH took the opportunity to include an editorial change in section 4.1 of the SmPC

#### 15.3.19. Glecaprevir, pibrentasvir - MAVIRET (CAP) - EMEA/H/C/004430/X/0033/G

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Grouped application consisting of: 1) extension application to introduce a new pharmaceutical form (50/20 mg coated granules in sachet); 2) extension of indication to include the treatment of children from 3 to 12 years of age for the approved Maviret (glecaprevir/pibrentasvir) 100 mg/40 mg film-coated tablets. As a consequence, sections 4.1, 4.2, 5.1 and 5.2 of the SmPC are updated. The package leaflet, labelling and the RMP (version 5.0) are updated accordingly. Furthermore, the product information is brought in line with the latest quality review of documents (QRD) template (version 10.1)



#### **15.3.20. Glecaprevir, pibrentasvir - MAVIRET (CAP) - EMEA/H/C/004430/II/0039**

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Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Update of section 5.1 of the SmPC based on results from study M13-576 (listed as a category 3 study in the RMP): a non-drug interventional follow-up study to assess resistance and durability of response to AbbVie direct-acting antiviral agent (DAA) therapy (glecaprevir (ABT-493) and/or pibrentasvir (ABT-530)) in subjects who participated in phase 2 or 3 clinical studies for the treatment of chronic hepatitis C virus (HCV) infection. The RMP (version 6.0) is updated accordingly

#### **15.3.21. Insulin aspart - INSULIN ASPART SANOFI (CAP) - EMEA/H/C/005033/X/0003**

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Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Annika Folin

Scope: Extension application to introduce a new route of administration (intravenous use) for the 10 mL vial presentations only. The RMP (version 1.1) is updated accordingly

#### **15.3.22. Isatuximab - SARCLISA (CAP) - EMEA/H/C/004977/II/0003, Orphan**

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Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Eva Segovia

Scope: Extension of indication to add combination with carfilzomib and dexamethasone for the treatment of patients with multiple myeloma who have received at least one prior therapy. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 1.0) are updated accordingly. The MAH took the opportunity to introduce minor changes in sections 4.9, 6.3 and 6.6 of the SmPC and to update details of the local representatives

#### **15.3.23. Ivacaftor, tezacaftor, elexacaftor - KAFTRIO (CAP) - EMEA/H/C/005269/II/0003, Orphan**

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Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Martin Huber

Scope: Submission of the final clinical study report for study VX18-445-007 (study 007) (listed as a category 3 study in the RMP) with the aim to evaluate the pharmacokinetics (PK) of Kaftrio (ivacaftor/tezacaftor/elexacaftor) in subjects with moderate hepatic impairment. The RMP (version 1.2) is updated accordingly

#### **15.3.24. Lenvatinib - KISPLYX (CAP) - EMEA/H/C/004224/II/0041**

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Applicant: Eisai GmbH

PRAC Rapporteur: David Olsen

Scope: Update of sections 4.5 and 5.1 of the SmPC in order to update the drug-drug interaction with everolimus and to update the efficacy information based on the results from

study E7080-M001-221: a single-arm, multicentre, phase 2 trial to evaluate the safety and efficacy of lenvatinib in combination with everolimus in subjects with unresectable advanced or metastatic non clear cell renal cell carcinoma (nccRCC) who have not received any chemotherapy for advanced disease (in fulfilment of MEA 008.1). The RMP (version 12.1) is updated accordingly

#### **15.3.25. Lenvatinib - KISPLYX (CAP) - EMEA/H/C/004224/II/0042**

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Applicant: Eisai GmbH

PRAC Rapporteur: David Olsen

Scope: Submission of the final clinical study report (CSR) for study E7080-G000-218: a randomised, open-label (formerly double-blind), phase 2 trial to assess safety and efficacy of lenvatinib at two different starting doses (18 mg vs 14 mg once a day (QD)) in combination with everolimus (5 mg QD) in renal cell carcinoma following one prior Vascular endothelial growth factor (VEGF)-targeted treatment (in fulfilment of MEA 007.3). The RMP (version 12.2) is updated accordingly

#### **15.3.26. Lorlatinib - LORVIQUA (CAP) - EMEA/H/C/004646/II/0013**

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Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Update of sections 4.2, 4.4 and 4.8 of the SmPC in order to include hypertension and hyperglycaemia as new adverse drug reactions (ADRs) with frequency common and very common respectively together with recommended dose modifications and warnings, based on data from study B7461006: a phase 3, randomized, open-label study of lorlatinib monotherapy versus crizotinib monotherapy in the first-line treatment of patients with advanced anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC). In addition, the pooled safety dataset has been updated to include data from study B7461001: a phase 1/2 open-label, multiple-dose, dose-escalation, safety, pharmacokinetic, pharmacodynamic and anti-tumour efficacy exploration study; and study B7461006. As a consequence, the frequencies of ADRs have been updated in section 4.8 of the SmPC and existing warnings on hyperlipidaemia and lipase and amylase increase have been amended. The package leaflet and the RMP (version 2.0) is updated accordingly

#### **15.3.27. Nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/II/0092**

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Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include Opdivo (nivolumab) in combination with cabozantinib for the first line treatment of advanced renal cell carcinoma. 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 19.0) are updated in accordance

#### **15.3.28. Ocrelizumab - OCREVUS (CAP) - EMEA/H/C/004043/II/0021**

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Applicant: Roche Registration GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of section 4.4 in order to include the term 'anaphylaxis' among the possible symptoms of infusion-related reactions (IRRs), following an analysis of cases retrieved by anaphylactic reaction MedDRA<sup>71</sup> narrow standardised MedDRA queries (SMQ). The MAH took the opportunity to update Annex II-C on 'Other conditions and requirements of the marketing authorisation' and Annex II-D on 'Conditions or restrictions with regard to the safe and effective use of the medicinal product' 'in line with the latest quality review of documents (QRD) template (version 10.1). The RMP (version 6.0) is updated accordingly

#### 15.3.29. Olaparib - LYNPARZA (CAP) - EMEA/H/C/003726/II/0042

Applicant: AstraZeneca AB

PRAC Rapporteur: Amelia Cupelli

Scope: Update of sections 4.4, 4.8 and 5.1 of the SmPC in order to add myelodysplastic syndrome (MDS)/acute myeloid leukaemia (AML) to the list of adverse drug reactions with the frequency uncommon, to modify the existing warning on MDS/AML and to update efficacy information based on final results from study SOLO-2 (listed as a post-authorisation efficacy study (PAES) in Annex II-D on 'conditions or restrictions with regard to the safe and effective use of the medicinal product'): a phase 3 randomised, double blind, placebo controlled, multicentre study of olaparib maintenance monotherapy in platinum sensitive relapsed BRCA<sup>72</sup> mutated ovarian cancer patients who are in complete or partial response following platinum based chemotherapy. The package leaflet, Annex II and the RMP (version 21.1) are updated accordingly

#### 15.3.30. Pegaspargase - ONCASPAR (CAP) - EMEA/H/C/003789/II/0036/G

Applicant: Les Laboratoires Servier

PRAC Rapporteur: Annika Folin

Scope: Grouped variations consisting of: 1) submission of the results for study 12-266 A(12): an open label single arm phase 2 trial evaluating the efficacy and toxicity of treatment regimens including Oncaspar (pegaspargase) in adults aged 18-60 with newly diagnosed Philadelphia chromosome-negative acute lymphoblastic leukaemia ; 2) submission of the results for study CAALL-F01: a prospective multicentre cohort study evaluating Oncaspar (pegaspargase) used in the first-line treatment of children and adolescents with acute lymphoblastic leukaemia (ALL) along with multi-agent chemotherapy. As a consequence, Annex II is updated to remove both studies (i.e. post-authorisation safety studies (PAES)). Additionally, the product information is updated to remove the need for additional monitoring and to implement editorial changes. The RMP (version 4.1) is updated accordingly

#### 15.3.31. Pembrolizumab - KEYTRUDA (CAP) - EMEA/H/C/003820/II/0097

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

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<sup>71</sup> Medical Dictionary for Regulatory Activities

<sup>72</sup> BReast CAncer gene

Scope: Extension of indication to include in combination with chemotherapy, first-line treatment of locally advanced unresectable or metastatic carcinoma of the oesophagus or human epidermal growth factor receptor 2 (HER2) negative gastroesophageal junction adenocarcinoma in adults based on the results from the pivotal KEYNOTE-590 (KN590) trial: a phase 3, randomized, double-blind, placebo-controlled, multisite study to evaluate the efficacy and safety of pembrolizumab in combination with chemotherapy (cisplatin and 5-fluorouracil (5-FU)) versus chemotherapy (cisplatin with 5-FU) as first line treatment in participants with locally advanced unresectable metastatic adenocarcinoma or squamous cell carcinoma of the oesophagus or advanced/metastatic Siewert type 1 adenocarcinoma of the gastroesophageal junction. As a consequence, sections 4.1, 4.8 and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 30.1) are updated in accordance

#### **15.3.32. Risankizumab - SKYRIZI (CAP) - EMEA/H/C/004759/X/0012**

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Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Extension application to add a new strength of 150 mg for solution for injection in a pre-filled syringe and pre-filled pen. The RMP (version 2.0) is updated accordingly

#### **15.3.33. Secukinumab - COSENTYX (CAP) - EMEA/H/C/003729/X/0067**

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Applicant: Novartis Europharm Limited

PRAC Rapporteur: Eva Segovia

Scope: Extension application to introduce a new strength of 75 mg solution for injection. The RMP (version 8.0) is updated accordingly

#### **15.3.34. Sofosbuvir, velpatasvir, voxilaprevir - VOSEVI (CAP) - EMEA/H/C/004350/X/0045/G**

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Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Grouped application consisting of: 1) extension application to introduce a new strength (200 mg /50 mg /50 mg film-coated tablets). The new presentation is indicated for the treatment of chronic hepatitis C virus (HCV) infection in patients aged 12 years and older or weighing at least 30 kg. In addition, the MAH took the opportunity to implement minor editorial updates in module 3.2.P; 2) Extension of indication to include paediatric use in patients aged 12 years and older or weighing at least 30 kg to the existing presentation. Sections 4.2, 4.8, 5.1 and 5.2 of the SmPC and the package leaflet are updated to support the extended indication. The RMP (version 3.2) is updated in accordance

#### **15.3.35. Teriflunomide - AUBAGIO (CAP) - EMEA/H/C/002514/X/0031/G**

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Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Martin Huber

Scope: Grouped application consisting of: 1) extension application to add a new strength of 7 mg film-coated tablet for use in paediatric patients from 10 years of age and older with relapsing remitting multiple sclerosis (MS); 2) extension of indication to include treatment

of paediatric patients aged 10 years and older with relapsing remitting MS for Aubagio (teriflunomide) 14 mg tablet. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The package leaflet, labelling and the RMP (version 6.0) are updated in accordance. The MAH also applied for an extension of the market protection of one additional year in line with the guidance on elements required to support significant clinical benefit in comparison with existing therapies of a new therapeutic indication

#### **15.3.36. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/X/0030/G**

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Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Grouped application consisting of: 1) extension application to add a new strength (22 mg prolonged-release tablet); 2) update of sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of Xeljanz 11 mg prolonged-release tablets SmPC in order to include the treatment of adult patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic agent, as an alternative to the immediate release film-coated tablets. Section 4.2 of the SmPC of Xeljanz film-coated tablets is also updated to include switching with the prolonged-release tablet in the treatment of UC. The package leaflet and the RMP (version 15.1) are updated accordingly

#### **15.3.37. Trastuzumab - HERCEPTIN (CAP) - EMEA/H/C/000278/II/0168**

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Applicant: Roche Registration GmbH

PRAC Rapporteur: Brigitte Keller-Stanislowski

Scope: Update of sections 4.2 and 4.4 of the SmPC in order to modify the administration instructions by removing the observation time currently stipulated after administration and to amend the existing warning respectively based on final results from study MO28048 (SafeHER) (listed as a category 3 study in the RMP): a phase 3 prospective, two cohort non-randomized, multicentre, multinational, open label study to assess the safety of assisted- and self-administered subcutaneous Herceptin as adjuvant therapy in patients with operable human epidermal growth factor receptor 2 (HER2)-positive early breast cancer. The package leaflet and the RMP (version 22) are updated accordingly

#### **15.3.38. Trastuzumab - ZERCEPAC (CAP) - EMEA/H/C/005209/II/0003**

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Applicant: Accord Healthcare S.L.U.

PRAC Rapporteur: Brigitte Keller-Stanislowski

Scope: Addition of a new fill weight for Zercepac (trastuzumab) powder for concentrate for solution for infusion, 60mg/vial. The strength (concentration after reconstitution) is identical to the previously authorised finished product 150mg/vial presentation. The RMP (version 1.1) is updated accordingly

#### **15.3.39. Upadacitinib - RINVOQ (CAP) - EMEA/H/C/004760/X/0006/G**

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Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Grouped variations consisting of: 1) extension application to introduce a new strength (30 mg prolonged-release tablet); 2) extension of indication to add treatment of moderate to severe atopic dermatitis in adults and adolescents 12 years and older who are candidates for systemic therapy. As a consequence, sections 4.1, 4.2, 4.5, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The package leaflet and the RMP (version 4.0) are updated in accordance. In addition, the MAH took the opportunity to include a minor update in Annex II

## **16. Annex I - Periodic safety update reports (PSURs)**

Based on the assessment of the following PSURs, the 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. [Aclidinium bromide - BRETARIS GENUAIR \(CAP\); EKLIRA GENUAIR \(CAP\) - PSUSA/00009005/202007](#)**

Applicant(s): AstraZeneca AB

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

#### **16.1.2. [Alectinib - ALECENSA \(CAP\) - PSUSA/00010581/202007](#)**

Applicant: Roche Registration GmbH

PRAC Rapporteur: Jana Lukacisinova

Scope: Evaluation of a PSUSA procedure

#### **16.1.3. [Alirocumab - PRALUENT \(CAP\) - PSUSA/00010423/202007](#)**

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

#### 16.1.4. Ambrisentan - VOLIBRIS (CAP) - PSUSA/00000129/202006

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Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

#### 16.1.5. Asfotase alfa - STRENSIQ (CAP) - PSUSA/00010421/202007

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Applicant: Alexion Europe SAS

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

#### 16.1.6. Avanafil - SPEDRA (CAP) - PSUSA/00010066/202006

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Applicant: Menarini International Operations Luxembourg S.A.

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

#### 16.1.7. Beclometasone, formoterol, glycopyrronium bromide - RIARIFY (CAP); TRIMBOW (CAP); TRYDONIS (CAP) - PSUSA/00010617/202007

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Applicant(s): Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

#### 16.1.8. Birch bark extract<sup>73</sup> - EPISALVAN (CAP) - PSUSA/00010446/202007

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Applicant: Amryt GmbH

PRAC Rapporteur: Zane Neikena

Scope: Evaluation of a PSUSA procedure

#### 16.1.9. Botulinum toxin type B - NEUROBLOC (CAP) - PSUSA/00000428/202006

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Applicant: Sloan Pharma S.a.r.l

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

#### 16.1.10. Brexpiprazole - RXULTI (CAP) - PSUSA/00010698/202007

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Applicant: Otsuka Pharmaceutical Netherlands B.V.

PRAC Rapporteur: Michal Radik

Scope: Evaluation of a PSUSA procedure

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<sup>73</sup> Centrally authorised product(s) only

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**16.1.11. Brinzolamide, brimonidine tartrate - SIMBRINZA (CAP) - PSUSA/00010273/202006**

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Applicant: Novartis Europharm Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

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**16.1.12. Brodalumab - KYNTHEUM (CAP) - PSUSA/00010616/202007**

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Applicant: LEO Pharma A/S

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

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**16.1.13. Budesonide<sup>74</sup> - JORVEZA (CAP) - PSUSA/00010664/202007**

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Applicant: Dr. Falk Pharma GmbH

PRAC Rapporteur: Zane Neikena

Scope: Evaluation of a PSUSA procedure

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**16.1.14. Cenegermin - OXERVATE (CAP) - PSUSA/00010624/202007**

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Applicant: Dompe farmaceutici S.p.A.

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

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**16.1.15. Cladribine<sup>75</sup> - MAVENCLAD (CAP) - PSUSA/00010634/202007**

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Applicant: Merck Europe B.V.

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Evaluation of a PSUSA procedure

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**16.1.16. Darolutamide - NUBEQA (CAP) - PSUSA/00010843/202007**

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Applicant: Bayer AG

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

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**16.1.17. Glecaprevir, pibrentasvir - MAVIRET (CAP) - PSUSA/00010620/202007**

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Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

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<sup>74</sup> Centrally authorised product(s) only

<sup>75</sup> Indicated for the treatment of multiple sclerosis only



**16.1.18. Glucagon<sup>76</sup> - BAQSIMI (CAP) - PSUSA/00010826/202007**

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Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

**16.1.19. Guselkumab - TREMFYA (CAP) - PSUSA/00010652/202007**

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Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

**16.1.20. Idursulfase - ELAPRASE (CAP) - PSUSA/00001722/202007**

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Applicant: Shire Human Genetic Therapies AB

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

**16.1.21. Imipenem, cilastatin, relebactam - RECARBRIO (CAP) - PSUSA/00010830/202007**

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Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

**16.1.22. L-lysine hydrochloride, l-arginine hydrochloride - LYSAKARE (CAP) - PSUSA/00010786/202007**

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Applicant: Advanced Accelerator Applications

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

**16.1.23. Lonococog alfa - AFSTYLA (CAP) - PSUSA/00010559/202007**

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Applicant: CSL Behring GmbH

PRAC Rapporteur: Sonja Hrabcik

Scope: Evaluation of a PSUSA procedure

**16.1.24. Macimorelin - MACIMORELIN AETERNA ZENTARIS (CAP) - PSUSA/00010746/202007**

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Applicant: Aeterna Zentaris GmbH

PRAC Rapporteur: Liana Gross-Martirosyan

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<sup>76</sup> Centrally authorised product(s) only

Scope: Evaluation of a PSUSA procedure

**16.1.25. Metreleptin - MYALEPTA (CAP) - PSUSA/00010700/202007**

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Applicant: Amryt Pharmaceuticals DAC

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

**16.1.26. Nateglinide - STARLIX (CAP) - PSUSA/00002128/202006**

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Applicant: Novartis Europharm Limited

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

**16.1.27. Neratinib - NERLYNX (CAP) - PSUSA/00010712/202007**

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Applicant: Pierre Fabre Medicament

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

**16.1.28. Osilodrostat - ISTURISA (CAP) - PSUSA/00010820/202007**

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Applicant: Recordati Rare Diseases

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

**16.1.29. Palivizumab - SYNAGIS (CAP) - PSUSA/00002267/202006**

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Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

**16.1.30. Peginterferon alfa-2a - PEGASYS (CAP) - PSUSA/00009254/202007**

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Applicant: Roche Registration GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

**16.1.31. Peginterferon beta-1a - PLEGRIDY (CAP) - PSUSA/00010275/202007**

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Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

**16.1.32. Romosozumab - EVENITY (CAP) - PSUSA/00010824/202007**

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Applicant: UCB Pharma S.A.

PRAC Rapporteur: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

**16.1.33. Saxagliptin, dapagliflozin - QTERN (CAP) - PSUSA/00010520/202007**

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Applicant: AstraZeneca AB

PRAC Rapporteur: Ilaria Baldelli

Scope: Evaluation of a PSUSA procedure

**16.1.34. Sofosbuvir, velpatasvir, voxilaprevir - VOSEVI (CAP) - PSUSA/00010619/202007**

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Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

**16.1.35. Spheroids of human autologous matrix-associated chondrocytes - SPHEROX (CAP) - PSUSA/00010630/202007**

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Applicant: CO.DON AG, ATMP<sup>77</sup>

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

**16.1.36. Tasimelteon - HETLIOZ (CAP) - PSUSA/00010394/202007**

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Applicant: Vanda Pharmaceuticals Netherlands B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

**16.1.37. Tigecycline - TYGACIL (CAP) - PSUSA/00002954/202006**

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Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

**16.1.38. Voretigene neparvovec - LUXTURN A (CAP) - PSUSA/00010742/202007**

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Applicant: Novartis Europharm Limited, ATMP<sup>78</sup>

PRAC Rapporteur: Brigitte Keller-Stanislawski

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

<sup>78</sup> Advanced therapy medicinal product

Scope: Evaluation of a PSUSA procedure

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

### **16.2.1. Aripiprazole - ABILIFY (CAP); ABILIFY MAINTENA (CAP); ARIPIPRAZOLE SANDOZ (CAP); NAP - PSUSA/00000234/202007**

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Applicant(s): Otsuka Pharmaceutical Netherlands B.V. (Abilify, Abilify Maintena), Sandoz GmbH (Aripiprazole Sandoz), various

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

### **16.2.2. Caffeine<sup>79</sup> - PEYONA (CAP); NAP - PSUSA/00000482/202007**

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Applicant(s): Chiesi Farmaceutici S.p.A. (Peyona), various

PRAC Rapporteur: Sonja Hrabcik

Scope: Evaluation of a PSUSA procedure

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

### **16.3.1. Albendazole (NAP) - PSUSA/00000073/202007**

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Applicant(s): various

PRAC Lead: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

### **16.3.2. Alfalcidol (NAP) - PSUSA/00000080/202006**

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Applicant(s): various

PRAC Lead: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

### **16.3.3. Almotriptan (NAP) - PSUSA/00000101/202006**

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Applicant(s): various

PRAC Lead: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

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<sup>79</sup> Indicated in primary apnoea of premature newborns

16.3.4. Ascorbic acid, paracetamol, phenylephrine hydrochloride (NAP) - PSUSA/00000255/202006

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Applicant(s): various

PRAC Lead: Rugilė Pilvinienė

Scope: Evaluation of a PSUSA procedure

16.3.5. Benzylpenicillin (NAP) - PSUSA/00000383/202006

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Applicant(s): various

PRAC Lead: Maia Uusküla

Scope: Evaluation of a PSUSA procedure

16.3.6. Bethanechol (NAP) - PSUSA/00000402/202006

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Applicant(s): various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.3.7. Betula verrucosa<sup>80 81 82</sup> (NAP) - PSUSA/00010815/202007

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Applicant(s): various

PRAC Lead: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

16.3.8. Carrageenin, titanium dioxide, zinc oxide (NAP); carrageenin, lidocaine, titanium dioxide, zinc oxide (NAP); titanium dioxide, zinc oxide, tetracaine hydrochloride (NAP) - PSUSA/00001869/202006

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Applicant(s): various

PRAC Lead: Melinda Palfi

Scope: Evaluation of a PSUSA procedure

16.3.9. Diphtheria, tetanus, pertussis (acellular, component), poliomyelitis (inactivated) vaccine (adsorbed) (NAP); diphtheria, tetanus, pertussis (acellular, component), poliomyelitis (inactivated) vaccine (adsorbed, reduced antigen(s) content) (NAP) - PSUSA/00001126/202007

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Applicant(s): various

PRAC Lead: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

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<sup>80</sup> Allergen for therapy

<sup>81</sup> Sublingual tablet(s) only

<sup>82</sup> Decentralised authorised product(s) only

#### 16.3.10. Epirubicin (NAP) - PSUSA/00001234/202006

Applicant(s): various

PRAC Lead: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

#### 16.3.11. Hepatitis A (inactivated), typhoid polysaccharide vaccine (adsorbed) (NAP) - PSUSA/00001594/202006

Applicant(s): various

PRAC Lead: Brigitte Keller-Stanislowski

Scope: Evaluation of a PSUSA procedure

#### 16.3.12. Ibuprofen, pseudoephedrine (NAP) - PSUSA/00001711/202007

Applicant(s): various

PRAC Lead: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

#### 16.3.13. Lidocaine, tetracaine (NAP) - PSUSA/00001868/202006

Applicant(s): various

PRAC Lead: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

#### 16.3.14. Magnesium sulfate (NAP) - PSUSA/00009225/202006

Applicant(s): various

PRAC Lead: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

#### 16.3.15. Nitrous oxide (NAP); nitrous oxide, oxygen (NAP) - PSUSA/00010572/202006

Applicant(s): various

PRAC Lead: John Joseph Borg

Scope: Evaluation of a PSUSA procedure

#### 16.3.16. Octenidine (NAP) - PSUSA/00010748/202007

Applicant(s): various

PRAC Lead: Nikica Mirošević Skvrce

Scope: Evaluation of a PSUSA procedure

#### 16.3.17. Oxytocin (NAP) - PSUSA/00002263/202006

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Applicant(s): various

PRAC Lead: Karen Pernille Harg

Scope: Evaluation of a PSUSA procedure

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

None

### 17. Annex I – Post-authorisation safety studies (PASS)

Based on the assessment of the following PASS protocol(s), result(s), interim result(s) or feasibility study(ies), and following endorsement of the comments received, the PRAC adopted the conclusion of the Rapporteurs on their assessment for the medicines listed below without further plenary discussion.

#### 17.1. Protocols of PASS imposed in the marketing authorisation(s)<sup>83</sup>

##### 17.1.1. Alemtuzumab - LEMTRADA (CAP) - EMEA/H/C/PSP/S/0087.1

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Applicant: Sanofi Belgium

PRAC Rapporteur: Anette Kirstine Stark

Scope: MAH's response to PSP/S/0087 [protocol for a non-interventional PASS to investigate the risk of mortality in patients prescribed Lemtrada (alemtuzumab) relative to comparable patients using other disease modifying therapies: a cohort study] as per the request for supplementary information (RSI) adopted in October 2020

##### 17.1.2. Alemtuzumab - LEMTRADA (CAP) - EMEA/H/C/PSP/S/0088.1

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Applicant: Sanofi Belgium

PRAC Rapporteur: Anette Kirstine Stark

Scope: MAH's response to PSP/S/0087 [protocol for a non-interventional PASS to investigate drug utilisation and safety monitoring patterns for Lemtrada (alemtuzumab)] as per the request for supplementary information (RSI) adopted in October 2020

##### 17.1.3. Asfotase alfa - STRENSIQ (CAP) - EMEA/H/C/PSA/S/0064

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Applicant: Alexion Europe SAS

PRAC Rapporteur: Rhea Fitzgerald

Scope: Substantial amendment to a protocol previously agreed in October 2020 (PSA/S/0050.1) for study ALX-HPP-501: an observational, longitudinal, prospective, long-term registry of patients with hypophosphatasia to collect information on the epidemiology of the disease, including clinical outcomes and quality of life, and to evaluate safety and

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

effectiveness data in patients treated with Strensiq (asfotase alfa)

#### **17.1.4. Blinatumomab – BLINCYTO (CAP) - EMEA/H/C/PSA/S/0065**

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Applicant: Amgen Europe B.V.

PRAC Rapporteur: Eva Jirsová

Scope: Substantial amendment to a protocol previously agreed in November 2017 (PSA/S/0024) for study 20150136 (EUPAS17848): an observational study of blinatumomab safety and effectiveness, utilisation and treatment practices in order to characterise the safety of blinatumomab in routine clinical practice, its effectiveness, medication errors and utilisation

#### **17.1.5. Valproate (NAP) - EMEA/H/N/PSA/J/0063**

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

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Substantial amendment to a joint protocol previously agreed in September 2020 (PSA/J/0059) for a joint survey among healthcare professionals (HCP) to assess the knowledge of HCP and behaviour with regard to the pregnancy prevention programme (PPP), the receipt/use of direct healthcare professional communication (DHPC) and educational materials as well as for a survey among patients to assess the knowledge of patients with regards to PPP and 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 (EMA/H/A-31/1454)

### **17.2. Protocols of PASS non-imposed in the marketing authorisation(s)<sup>84</sup>**

#### **17.2.1. Cannabidiol - EPIDYOLEX (CAP) - EMEA/H/C/004675/MEA 007.1**

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Applicant: GW Pharma (International) B.V.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: MAH's response to MEA 007 [protocol for study GWEP19022 (listed as a category 3 study in the RMP): a long-term safety study to assess the potential for chronic liver injury in patients treated with Epidyolex (cannabidiol oral solution)] as per the request for supplementary information (RSI) adopted in September 2020

#### **17.2.2. Dulaglutide - TRULICITY (CAP) - EMEA/H/C/002825/MEA 006.2**

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Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Ilaria Baldelli

Scope: MAH's response to MEA 006.1 [protocol for study H9X-MC-B013 (listed as a category 3 study in the RMP): a non-interventional retrospective study to estimate the incidence rates of events of interest among type 2 diabetes mellitus (T2DM) patients

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<sup>84</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



treated with dulaglutide compared to other glucagon-like peptide 1 (GLP-1) receptor agonists in order to better characterise the safety profile of dulaglutide in terms of acute pancreatitis, pancreatic and thyroid malignancies] as per the request for supplementary information (RSI) adopted in May 2020

#### **17.2.3. Inotersen - TEGSEDI (CAP) - EMEA/H/C/004782/MEA 007.1**

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Applicant: Akcea Therapeutics Ireland Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: MAH's response to MEA 007 [protocol for study TEG4005: a pregnancy surveillance programme of infants and women exposed to Tegsedi (inotersen) during pregnancy] as per the request for supplementary information (RSI) adopted in October 2020

#### **17.2.4. Linaclotide - CONSTELLA (CAP) - EMEA/H/C/002490/MEA 009.4**

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Applicant: Allergan Pharmaceuticals International Limited

PRAC Rapporteur: Martin Huber

Scope: Substantial amendment to a protocol previously agreed in September 2019 for a PASS: linaclotide safety study assessing the complications of diarrhoea and associated risk factors in selected European populations with irritable bowel syndrome with constipation (IBS-C) for Constella (linaclotide) 290µg capsule

#### **17.2.5. Micafungin - MYCAMINE (CAP) - EMEA/H/C/000734/MEA 015.13**

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Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Martin Huber

Scope: MAH's response to MEA 015.12 [protocol for study 9463-PV-0002 (listed as a category 3 study in the RMP): a non-interventional PASS/survey on the effectiveness of the updated prescriber checklist for Mycamine (micafungin)] as per the request for supplementary information (RSI) adopted in October 2020

#### **17.2.6. Pegvaliase - PALYNZIQ (CAP) - EMEA/H/C/004744/MEA 003.2**

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Applicant: BioMarin International Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: MAH's response to MEA 003.1 [protocol for study 165-501: a multicentre, prospective global observational study to evaluate the long term safety of subcutaneous injections of pegvaliase in patients with phenylketonuria [final clinical study report (CSR) expected in Q2 2030]] as per the request for supplementary information (RSI) adopted in September 2020

#### **17.2.7. Risankizumab - SKYRIZI (CAP) - EMEA/H/C/004759/MEA 002.3**

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Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: MAH's response to MEA 002.2 [protocol for study P16-751 on pregnancy exposures and outcomes in psoriasis patients treated with risankizumab: a cohort study utilising large healthcare databases with mother-baby linkage in the United States [final study report expected in Q3 2026]] as per the request for supplementary information (RSI) adopted in September 2020

#### **17.2.8. Tafamidis - VYNDAQEL (CAP) - EMEA/H/C/002294/MEA 016.2**

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Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Tiphaine Vaillant

Scope: MAH's response to MEA 016.1 [amendment to a protocol previously agreed by CHMP for study B3461001: a sub-analysis of 'transthyretin amyloidosis outcomes survey (THAOS)': a global, multicentre, longitudinal, observational survey of patients with documented transthyretin (TTR) gene mutations or wild-type ATTR amyloidosis, in order to evaluate the effects of tafamidis in non-V30M patients] as per the request for supplementary information (RSI) adopted in October 2020

#### **17.2.9. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/MEA 013.2**

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Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: MAH's response to MEA 013.1 [protocol for study A3921344 (listed as a category 3 study in the RMP): an active surveillance, post-authorisation study to characterise the safety of tofacitinib in patients with moderately to severely active ulcerative colitis (UC) in the real-world setting using data from the Swedish Quality Register for Inflammatory Bowel Disease (SWIBREG) registry as requested in the conclusions of procedure X/0005/G finalised in May 2018 and in the conclusions of the referral procedure under Article 20 of Regulation (EC) No 726/2004 (EMA/H/A-20/1485) finalised in November 2019] as per the request for supplementary information (RSI) adopted in October 2020

#### **17.2.10. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/MEA 014.2**

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Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: MAH's response to MEA 014.1 [protocol for study A3921321: a drug utilisation study (DUS) on the utilisation and prescribing patterns of Xeljanz (tofacitinib) in two European countries using administrative claims databases and national registries for assessment, as requested in the conclusions of the referral procedure under Article 20 of Regulation (EC) No 726/2004 (EMA/H/A-20/1485) finalised in November 2019] as per the request for supplementary information (RSI) adopted in December 2020

#### **17.2.11. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/MEA 047.1**

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Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Rhea Fitzgerald

Scope: MAH's response to MEA 047 [protocol for study SWIBREG-UST UC: an observational

PASS to describe the safety of ustekinumab and other ulcerative colitis treatments in a cohort of patients with ulcerative colitis using the Swedish Inflammatory Bowel Disease Register (SWIBREG) as requested in the conclusions of variation II/071 finalised in July 2019 [final clinical study report (CSR) expected in May 2027]] as per the request for supplementary information (RSI) adopted in September 2020

#### **17.2.12. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/MEA 048.1**

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Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Rhea Fitzgerald

Scope: MAH's response to MEA 048 [protocol for study SNDS-UST UC: an observational PASS to describe the safety of ustekinumab and other ulcerative colitis treatments in a cohort of patients with ulcerative colitis using the French administrative healthcare database (SNDS<sup>85</sup>) as requested in the conclusions of variation II/071 finalised in July 2019 [final clinical study report (CSR) expected in May 2027]] as per the request for supplementary information (RSI) adopted in September 2020

### **17.3. Results of PASS imposed in the marketing authorisation(s)<sup>86</sup>**

None

### **17.4. Results of PASS non-imposed in the marketing authorisation(s)<sup>87</sup>**

#### **17.4.1. Alectinib - ALECENSA (CAP) - EMEA/H/C/004164/II/0030**

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Applicant: Roche Registration GmbH

PRAC Rapporteur: Jana Lukacisinova

Scope: Submission of the final report from study BO40643 (listed as a category 3 study in the RMP): a non-interventional PASS aimed at evaluating the effectiveness of the risk minimisation measures (RMMs) for the important identified risks of interstitial lung disease (ILD)/pneumonitis, hepatotoxicity, bradycardia, photosensitivity, severe myalgia, and creatine phosphokinase (CPK) elevations for Alecensa (alectinib)

#### **17.4.2. Anakinra - KINERET (CAP) - EMEA/H/C/000363/II/0078**

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Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Anette Kirstine Stark

Scope: Submission of the final report from study Sobi-ANAKIN-201 (listed as a category 3 study in the RMP): a non-interventional PASS to evaluate the safety of Kineret (anakinra) in the treatment of cryopyrin associated periodic syndromes (CAPS) in routine clinical care with regard to serious infections, malignancies, injection site reactions, allergic reactions and medication errors, including reuse of syringe. The RMP (version 5.4) is updated accordingly. In addition, the RMP is updated to include information about a completed

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<sup>85</sup> Système National des Données de Santé

<sup>86</sup> In accordance with Article 107p-q of Directive 2001/83/EC

<sup>87</sup> In accordance with Article 61a (6) of Regulation (EC) No 726/2004, in line with the revised variations regulation for any submission as of 4 August 2013

paediatric study (Sobi.ANAKIN-301) assessed as per Article 46 of Regulation No 1901/2006 (P46/031): a randomised, double-blind, placebo-controlled, multicentre, phase 3 study which evaluated the efficacy, safety, pharmacokinetics and immunogenicity of anakinra as compared to placebo in newly diagnosed Still's disease patients (including systemic juvenile idiopathic arthritis [SJIA] and adult-onset Still's disease [AOSD])

#### **17.4.3. Bedaquiline - SIRTURO (CAP) - EMEA/H/C/002614/II/0042, Orphan**

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Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of the final report for study TMC207TBC4002 (listed as a category 3 study in the RMP): a non-interventional multi-country multidrug-resistant tuberculosis patient registry in South Africa and South Korea to monitor bedaquiline safety, utilisation and emergence of resistance (in fulfilment of MEA 010.6). The RMP (version 8.1) is updated accordingly

#### **17.4.4. Florbetaben (<sup>18</sup>F) - NEURACEQ (CAP) - EMEA/H/C/002553/II/0033**

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Applicant: Life Radiopharma Berlin GmbH

PRAC Rapporteur: Martin Huber

Scope: Submission of the final report from study FBB-01\_03\_13 (PASS-2) (listed as a category 3 study in the RMP): a non-interventional, cross-sectional, retrospective, multicentre, multi-country registry to observe usage pattern, safety and tolerability of the diagnostic agent NeuraCeq (florbetaben (<sup>18</sup>F)) in European clinical practice. The RMP (version 5.9) is updated accordingly

#### **17.4.5. Meningococcal group B vaccine (recombinant, component, adsorbed) - BEXSERO (CAP) - EMEA/H/C/002333/II/0098**

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Applicant: GSK Vaccines S.r.l

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of the final report from study V72\_360B (205512) (listed as a category 3 study in the RMP): an observational PASS after Bexsero (meningococcal group B vaccine) vaccination within the UK National Immunisation Programme (NIP) by further characterising the important potential risks of seizures, vasculitis/Kawasaki syndrome (KD), anaphylaxis, acute disseminated encephalomyelitis (ADEM) and Guillain-Barré syndrome (GBS) in routine UK care. The RMP (version 9.0) is updated accordingly

#### **17.4.6. Nitisinone - ORFADIN (CAP) - EMEA/H/C/000555/II/0074**

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Applicant: Swedish Orphan Biovitrum International AB

PRAC Rapporteur: Amelia Cupelli

Scope: Submission of the final report from study Sobi.NTBC-005 (listed as a category 3 study in the RMP): a non-interventional PASS to evaluate the long-term safety of Orfadin (nitisinone) treatment in hereditary tyrosinaemia type 1 (HT-1) patients in standard clinical care. The RMP (version 5.3) is updated accordingly

#### **17.4.7. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/II/0082**

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Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Rhea Fitzgerald

Scope: Submission of the final safety registry report of study CNTO1275PSO4005 (listed as a category 3 study in the RMP): a Nordic database initiative for exposure to ustekinumab - a review and analysis of adverse events from the Swedish and Danish national registry systems. The RMP (version 18.2) 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. Cabozantinib - CABOMETYX (CAP) - EMEA/H/C/004163/MEA 001.4**

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Applicant: Ipsen Pharma

PRAC Rapporteur: Menno van der Elst

Scope: Interim report for study F-FR-60000-001 (CASSIOPE): a prospective non-interventional study of the utilisation of cabozantinib tablets in adults with advanced renal cell carcinoma (RCC) following prior vascular endothelial growth factor (VEGF)-targeted therapy in real life settings in terms of dose modifications due to adverse events (AEs) when used as a second line therapy or third and later line therapy

#### **17.5.2. Delamanid - DELTYBA (CAP) - EMEA/H/C/002552/MEA 002.3**

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Applicant: Otsuka Novel Products GmbH

PRAC Rapporteur: Laurence de Fays

Scope: Fourth annual progress report for study 242-12-402 (listed as a category 3 study in the RMP): a multicentre EU-wide observational non-interventional post-authorisation study to assess the safety and drug usage of delamanid (OPC-67683) in routine medical practice in multidrug-resistant tuberculosis patients (Delamanid registry)

#### **17.5.3. Filgrastim - NIVESTIM (CAP) - EMEA/H/C/001142/MEA 015.5**

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Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Kirsti Villikka

Scope: Fourth annual report for study ZOB-NIV-1513 (C1121008): a multinational, multicentre, prospective, non-interventional PASS in healthy donors (HDs) exposed to Nivestim (biosimilar filgrastim) for haematopoietic stem cell (HSC) mobilisation (NEST) [final clinical study report (CSR) expected in March 2023]

#### **17.5.4. Insulin glargine, lixisenatide - SULIQUA (CAP) - EMEA/H/C/004243/MEA 002.6**

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Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Menno van der Elst

Scope: Interim results for study INSLIC08571 (listed as a category 3 study in the RMP): a

cross-sectional multinational, multichannel survey conducted among healthcare professionals and patients to measure the effectiveness of Suliqua (insulin glargine/lixisenatide) educational materials set up to evaluate the knowledge and understanding of the key safety messages in the healthcare professional guide and the patient guide

#### **17.5.5. Lumacaftor, ivacaftor - ORKAMBI (CAP) - EMEA/H/C/003954/ANX 003.5**

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Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Fourth annual report for study VX14 809 108: an observational study to evaluate the utilisation patterns and long-term effects of lumacaftor/ivacaftor therapy in patients with cystic fibrosis (CF) [final report expected in December 2021] together with MAH's response to ANX 003.4 [third annual report for study VX14 809 108] as per the request for supplementary information (RSI) adopted in February 2020

#### **17.5.6. Pitolisant - WAKIX (CAP) - EMEA/H/C/002616/ANX 001.3**

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Applicant: Bioprojet Pharma

PRAC Rapporteur: Kirsti Villikka

Scope: Third annual interim study report for study P15-11: a multicentre, observational PASS to document the drug utilisation of Wakix (pitolisant) and to collect information on the safety of Wakix (pitolisant) when used in routine medical practice [final results expected in 2023]

#### **17.5.7. Tisagenlecleucel - KYMRIA (CAP) - EMEA/H/C/004090/ANX 003.4**

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Applicant: Novartis Europharm Limited, ATMP<sup>88</sup>

PRAC Rapporteur: Brigitte Keller-Stanislowski

Scope: First five-yearly interim report for a study based on disease registry CCTL019B2401 (listed as a category 1 study in Annex II and the RMP): a non-interventional PASS in acute lymphoblastic leukaemia (ALL) and diffuse large B-cell lymphoma (DLBCL) patients in order to further characterise the safety, including long-term safety, of Kymriah (tisagenlecleucel) [final study report expected in December 2038]

#### **17.5.8. Tisagenlecleucel - KYMRIA (CAP) - EMEA/H/C/004090/MEA 005**

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Applicant: Novartis Europharm Limited, ATMP<sup>89</sup>

PRAC Rapporteur: Brigitte Keller-Stanislowski

Scope: First five-yearly interim report for study CCTL019A2205B (listed as a category 3 study in the RMP): a long-term follow-up of patients exposed to lentiviral-based CD<sup>90</sup>19 directed chimeric antigen receptor T (CAR-T)-cell therapy in order to describe selected, delayed adverse events (AEs) suspected to be related to previous CD19 CAR-T-cell therapy

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<sup>88</sup> Advanced therapy medicinal product

<sup>89</sup> Advanced therapy medicinal product

<sup>90</sup> Cluster of differentiation

as outlined in current Health Authority guidelines [final study report expected in December 2037] (from opinion/marketing authorisation)

#### **17.5.9. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/MEA 022.21**

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Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Rhea Fitzgerald

Scope: MAH's response to MEA 022.20 [ninth annual report for study C0168Z03 (PSOLAR: PSOriasis Longitudinal Assessment and Registry): an international prospective cohort study/registry programme designed to collect data on psoriasis (PSO) patients that are eligible to receive systemic therapies, including generalised phototherapy and biologics] as per the request for supplementary information (RSI) adopted in September 2020

#### **17.5.10. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/MEA 024.15**

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Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Rhea Fitzgerald

Scope: MAH's response to MEA 024.14 [tenth annual interim report for study CNT01275PSO4007 (Nordic pregnancy research initiative) (C0743T): exposure to ustekinumab during pregnancy in patients with psoriasis: a review and analysis of birth outcomes from the Swedish, Danish, and Finnish medical birth registers] as per the request for supplementary information (RSI) adopted in September 2020

#### **17.5.11. Voriconazole - VFEND (CAP) - EMEA/H/C/000387/MEA 091.4**

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Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Third interim report for non-interventional study A1501103: an active safety surveillance programme to monitor selected events in patients with long-term voriconazole use

### **17.6. Others**

#### **17.6.1. Damoctocog alfa pegol - JIVI (CAP) - EMEA/H/C/004054/MEA 002**

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Applicant: Bayer AG

PRAC Rapporteur: Menno van der Elst

Scope: Interim progress report for study 19764: an interventional post-marketing investigation (PMI) to assess safety and efficacy of Jivi (damoctocog alfa pegol (BAY 94-9027) treatment in participants with haemophilia A to fulfil EMA guidelines regarding the requirements for applications of marketing authorisation for recombinant or plasma derived factor VIII products [final study report expected by 2023]

## **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, the 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. Cholic acid - ORPHACOL (CAP) - EMEA/H/C/001250/S/0038 (without RMP)**

Applicant: Laboratoires CTRS

PRAC Rapporteur: Sofia Trantz

Scope: Annual reassessment of the marketing authorisation

### **18.1.2. Defibrotide - DEFITELIO (CAP) - EMEA/H/C/002393/S/0051 (without RMP)**

Applicant: Gentium S.r.l.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Annual reassessment of the marketing authorisation

### **18.1.3. Mecasermin - INCRELEX (CAP) - EMEA/H/C/000704/S/0064 (with RMP)**

Applicant: Ipsen Pharma

PRAC Rapporteur: Kirsti Villikka

Scope: Annual reassessment of the marketing authorisation



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

### **18.2.1. Betibeglogene autotemcel - ZYNTEGLO (CAP) - EMEA/H/C/003691/R/0018 (without RMP)**

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Applicant: bluebird bio (Netherlands) B.V, ATMP<sup>91</sup>

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Conditional renewal of the marketing authorisation

### **18.2.2. Parathyroid hormone - NATPAR (CAP) - EMEA/H/C/003861/R/0027 (without RMP)**

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Applicant: Shire Pharmaceuticals Ireland Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Conditional renewal of the marketing authorisation

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

### **18.3.1. Atazanavir - ATAZANAVIR MYLAN (CAP) - EMEA/H/C/004048/R/0016 (without RMP)**

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Applicant: Mylan S.A.S

PRAC Rapporteur: Adrien Inoubli

Scope: 5-year renewal of the marketing authorisation

### **18.3.2. Bortezomib - BORTEZOMIB HOSPIRA (CAP) - EMEA/H/C/004207/R/0020 (without RMP)**

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Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Amelia Cupelli

Scope: 5-year renewal of the marketing authorisation

### **18.3.3. Bortezomib - BORTEZOMIB SUN (CAP) - EMEA/H/C/004076/R/0015 (without RMP)**

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Applicant: Sun Pharmaceutical Industries Europe B.V.

PRAC Rapporteur: Amelia Cupelli

Scope: 5-year renewal of the marketing authorisation

### **18.3.4. Cabozantinib - CABOMETYX (CAP) - EMEA/H/C/004163/R/0018 (with RMP)**

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Applicant: Ipsen Pharma

PRAC Rapporteur: Menno van der Elst

Scope: 5-year renewal of the marketing authorisation

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<sup>91</sup> Advanced therapy medicinal product

#### 18.3.5. Elbasvir, grazoprevir - ZEPATIER (CAP) - EMEA/H/C/004126/R/0026 (with RMP)

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: 5-year renewal of the marketing authorisation

#### 18.3.6. Methotrexate - NORDIMET (CAP) - EMEA/H/C/003983/R/0018 (without RMP)

Applicant: Nordic Group B.V.

PRAC Rapporteur: Martin Huber

Scope: 5-year renewal of the marketing authorisation

#### 18.3.7. Pemetrexed - PEMETREXED FRESENIUS KABI (CAP) - EMEA/H/C/003895/R/0023 (with RMP)

Applicant: Fresenius Kabi Deutschland GmbH

PRAC Rapporteur: Tiphaine Vaillant

Scope: 5-year renewal of the marketing authorisation

#### 18.3.8. Reslizumab - CINQAERO (CAP) - EMEA/H/C/003912/R/0038 (with RMP)

Applicant: Teva B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: 5-year renewal of the marketing authorisation

## 19. Annex II – List of participants

including any restrictions with respect to involvement of members / alternates / experts following evaluation of declared interests for the 08-11 February 2021 meeting (marked as 'a'), and for the 25 February 2021 ORGAM teleconference (marked as 'b').

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</sup>	Chair	The Netherlands	No interests declared	Full involvement
Jan Neuhauser <sup>a, b</sup>	Member	Austria	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
Sonja Hrabcik <sup>a</sup>	Alternate	Austria	No interests declared	Full involvement
Jean-Michel Dogné <sup>a, b</sup>	Member	Belgium	No interests declared	Full involvement
Laurence de Fays <sup>a, b</sup>	Alternate	Belgium	No interests declared	Full involvement
Maria Popova-Kiradjieva <sup>a, b</sup>	Member	Bulgaria	No interests declared	Full involvement
Nikica Mirošević Skvrce <sup>a, b</sup>	Member	Croatia	No interests declared	Full involvement
Panagiotis Psaras <sup>a, b</sup>	Member	Cyprus	No interests declared	Full involvement
Christina Sylvia Chrysostomou <sup>a, b</sup>	Alternate	Cyprus	No interests declared	Full involvement
Eva Jirsová <sup>a, b</sup>	Member	Czechia	No interests declared	Full involvement
Jana Lukacisinova <sup>a, b</sup>	Alternate	Czechia	No interests declared	Full involvement
Anette Stark <sup>a, b</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</sup>	Member	Estonia	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
Kirsti Villikka <sup>a, b</sup>	Member	Finland	No interests declared	Full involvement
Kimmo Jaakkola <sup>a, b</sup>	Alternate	Finland	No interests declared	Full involvement
Adrien Inoubli <sup>a, b</sup>	Member	France	No interests declared	Full involvement
Tiphaine Vaillant <sup>a, b</sup>	Alternate	France	No interests declared	Full involvement
Martin Huber <sup>a, b</sup>	Member (Vice-Chair)	Germany	No interests declared	Full involvement
Brigitte Keller-Stanislawski <sup>a</sup>	Alternate	Germany	No interests declared	Full involvement
Agni Kapou <sup>a</sup>	Member	Greece	No interests declared	Full involvement
Julia Pallos <sup>a, b</sup>	Member	Hungary	No restrictions applicable to this meeting	Full involvement
Melinda Palfi <sup>a</sup>	Alternate	Hungary	No interests declared	Full involvement
Guðrún Stefánsdóttir <sup>a, b</sup>	Member	Iceland	No participation in discussion, final deliberations and voting on:	4.3.2. Filgrastim – ACCOFIL (CAP), FILGRASTIM HEXAL (CAP), GRASTOFIL (CAP), NIVESTIM (CAP), RATIOGRASTIM (CAP), TEVAGRASTIM (CAP), ZARZIO (CAP); NAP  5.1.6. Roxadustat - EMEA/H/C/004871

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				5.2.2. Tacrolimus - ADVAGRAF (CAP) - EMEA/H/C/000712/WS18 05/0057; MODIGRAF (CAP) - EMEA/H/C/000954/WS18 05/0035; NAP  17.2.5. Micafungin - MYCAMINE (CAP) - EMEA/H/C/000734/MEA 015.13
Rhea Fitzgerald <sup>a, b</sup>	Member	Ireland	No interests declared	Full involvement
Ronan Grimes <sup>a, b</sup>	Alternate	Ireland	No interests declared	Full involvement
Amelia Cupelli <sup>a, b</sup>	Member	Italy	No interests declared	Full involvement
Ilaria Baldelli <sup>a, b</sup>	Alternate	Italy	No interests declared	Full involvement
Zane Neikena <sup>a, b</sup>	Member	Latvia	No interests declared	Full involvement
Rugile Pilviniene <sup>a, b</sup>	Member	Lithuania	No interests declared	Full involvement
Nadine Petitpain <sup>a</sup>	Member	Luxembourg	No restrictions applicable to this meeting	Full involvement
Anne-Cécile Vuillemin <sup>a, b</sup>	Alternate	Luxembourg	No interests declared	Full involvement
John Joseph Borg <sup>a</sup>	Member (CHMP member)	Malta	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
Menno van der Elst <sup>a, b</sup>	Member	Netherlands	No interests declared	Full involvement
Liana Gross-Martirosyan <sup>a, b</sup>	Alternate	Netherlands	No interests declared	Full involvement
David Olsen <sup>a, b</sup>	Member	Norway	No participation in final deliberations and voting on:	6.1.16. Darolutamide - NUBEQA (CAP) - PSUSA/00010843/202007 6.3.4. Iopromide (NAP) - PSUSA/00001773/202006 15.3.2. Aflibercept - EYLEA (CAP) - EMEA/H/C/002392/II/0069 17.6.1. Damoctocog alfa pegol - JIVI (CAP) - EMEA/H/C/004054/MEA002
Karen Pernille Harg <sup>a, b</sup>	Alternate	Norway	No interests declared	Full involvement
Adam Przybylkowski <sup>a, b</sup>	Member	Poland	No interests declared	Full involvement
Katarzyna Ziolkowska <sup>b</sup>	Alternate	Poland	No interests declared	Full involvement
Ana Diniz Martins <sup>a, b</sup>	Member	Portugal	No interests declared	Full involvement
Marcia Silva <sup>a, b</sup>	Alternate	Portugal	No interests declared	Full involvement
Roxana Dondera <sup>a, b</sup>	Member	Romania	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
Alexandra - Maria Spurni <sup>a, b</sup>	Alternate	Romania	No interests declared	Full involvement
Michal Radik <sup>a, b</sup>	Member	Slovakia	No interests declared	Full involvement
Marek Juracka <sup>a, b</sup>	Alternate	Slovakia	No interests declared	Full involvement
Gabriela Jazbec <sup>a</sup>	Member	Slovenia	No interests declared	Full involvement
Jasmina Klopčič <sup>b</sup>	Alternate	Slovenia	No interests declared	Full involvement
Eva Segovia <sup>a, b</sup>	Member	Spain	No interests declared	Full involvement
Maria del Pilar Rayon <sup>a, b</sup>	Alternate	Spain	No interests declared	Full involvement
Ulla Wändel Liminga <sup>a, b</sup>	Member	Sweden	No interests declared	Full involvement
Annika Folin <sup>a</sup>	Alternate	Sweden	No interests declared	Full involvement
Birgitta Grundmark <sup>a, b</sup>	Member	Independent scientific expert	No interests declared	Full involvement
Daniel Morales <sup>a</sup>	Member	Independent scientific expert	No interests declared	Full involvement
Hedvig Nordeng <sup>a</sup>	Member	Independent scientific expert	No interests declared	Full involvement
Milou Daniel Drici <sup>a</sup>	Member	Independent scientific expert	No restrictions applicable	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			to this meeting	
Stefan Weiler <sup>a</sup>	Member	Independent scientific expert	No restrictions applicable to this meeting	Full involvement
Raymond Anderson <sup>a</sup>	Member	Healthcare Professionals' Representative	No interests declared	Full involvement
Roberto Frontini <sup>a, b</sup>	Alternate	Healthcare Professionals' Representative	No restrictions applicable to this meeting	Full involvement
Cathalijne van Doorne <sup>a, b</sup>	Member	Patients' Organisation Representative	No interests declared	Full involvement
Virginie Hivert <sup>a, b</sup>	Alternate	Patients' Organisation Representative	No restrictions applicable to this meeting	Full involvement
Christelle Bizimungu <sup>a, b</sup>	Expert - via telephone *	Belgium	No restrictions applicable to this meeting	Full involvement
Sophie Colyn <sup>a</sup>	Expert - via telephone *	Belgium	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
Nele Matthijs <sup>a</sup>	Expert - via telephone *	Belgium	No interests declared	Full involvement
Nicolas Nyssen <sup>a</sup>	Expert - via telephone *	Belgium	No interests declared	Full involvement
Martine Sabbe <sup>a, b</sup>	Expert - via telephone *	Belgium	No interests declared	Full involvement
Françoise Wuillaume <sup>b</sup>	Expert - via telephone *	Belgium	No interests declared	Full involvement
Magdalena Fabiánová <sup>a</sup>	Expert - via telephone *	Czechia	No interests declared	Full involvement
Petra Kaftanová <sup>b</sup>	Expert - via telephone *	Czechia	No interests declared	Full involvement
Kristýna Schneiderová <sup>a</sup>	Expert - via telephone *	Czechia	No interests declared	Full involvement
Petra Vacková <sup>a</sup>	Expert - via telephone *	Czechia	No interests declared	Full involvement
Jan Vosátka <sup>a</sup>	Expert - via telephone *	Czechia	No interests declared	Full involvement
Barbara Kovačić <sup>a</sup>	Expert - via telephone *	Croatia	No interests declared	Full involvement
Ivana Ljubičić <sup>a, b</sup>	Expert - via	Croatia	No restriction	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
	telephone *		s applicable to this meeting	
Krõõt Aab <sup>a</sup>	Expert - via telephone *	Estonia	No interests declared	Full involvement
Karin Erneholm <sup>a, b</sup>	Expert - via telephone *	Denmark	No restrictions applicable to this meeting	Full involvement
Astrid Munch Hestbæk <sup>a</sup>	Expert - via telephone *	Denmark	No restrictions applicable to this meeting	Full involvement
Jens Lichtenberg <sup>a</sup>	Expert - via telephone *	Denmark	No restrictions applicable to this meeting	Full involvement
Anita Vibsig Neutzsky-Wulff <sup>b</sup>	Expert - via telephone *	Denmark	No interests declared	Full involvement
Peter Horskjær Rose <sup>a</sup>	Expert - via telephone *	Denmark	No interests declared	Full involvement
Emma Louise Nautrup Ravn Stadsbjerg <sup>a, b</sup>	Expert - via telephone *	Denmark	No interests declared	Full involvement
Josiane Uwera <sup>a</sup>	Expert - via	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
	telephone *		applicable to this meeting	
Päivi Susanna Worsøe <sup>b</sup>	Expert - via telephone *	Denmark	No interests declared	Full involvement
Camille De Kervasdoue <sup>a</sup>	Expert - via telephone *	France	No interests declared	Full involvement
Laure Tiquet <sup>a</sup>	Expert - via telephone *	France	No interests declared	Full involvement
Marion Haberkamp <sup>a</sup>	Expert - via telephone *	Germany	No interests declared	Full involvement
Jelena Katic <sup>a</sup>	Expert - via telephone *	Germany	No interests declared	Full involvement
Dennis Lex <sup>a, b</sup>	Expert - via telephone *	Germany	No restrictions applicable to this meeting	Full involvement
Aine McKenna <sup>a</sup>	Expert - via telephone *	Ireland	No interests declared	Full involvement
Carla Herberts <sup>a</sup>	Expert - via telephone *	Netherlands	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
Marianne Klanker <sup>a</sup>	Expert - via telephone *	Netherlands	No interests declared	Full involvement
Lieke Sandberg-Smits <sup>a</sup>	Expert - via telephone *	Netherlands	No restrictions applicable to this meeting	Full involvement
Paul ten Berg <sup>a</sup>	Expert - via telephone *	Netherlands	No interests declared	Full involvement
Janneke van Leeuwen <sup>a</sup>	Expert - via telephone *	Netherlands	No interests declared	Full involvement
María Martínez Gonzalez <sup>a</sup>	Expert - via telephone *	Spain	No restrictions applicable to this meeting	Full involvement
Consuelo Mejías Pavón <sup>a</sup>	Expert - via telephone *	Spain	No interests declared	Full involvement
Helena Back <sup>b</sup>	Expert - via telephone *	Sweden	No interests declared	Full involvement
Charlotte Backman <sup>a, b</sup>	Expert - via telephone *	Sweden	No interests declared	Full involvement
Jessica Mwinyi <sup>b</sup>	Expert - via telephone *	Sweden	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
Karin Nylen <sup>a</sup>	Expert - via telephone *	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 only 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, the EMA is requested to conduct a scientific assessment of a particular medicine or class of medicines on behalf of the European Union (EU). For further detailed information on safety related referrals please see:

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

### Signals assessment and prioritisation

(Item 4 of the PRAC minutes)

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

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

The evaluation of safety signals may not necessarily conclude that the medicine caused the adverse event in question. In cases where a causal relationship is confirmed or considered likely, regulatory action

may be necessary and this usually takes the form of an update of the summary of product characteristics and the package leaflet.

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

(Item 5 of the PRAC minutes)

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

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

(Item 6 of the PRAC minutes)

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

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

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

(Item 7 of the PRAC minutes)

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

### **Product related pharmacovigilance inspections**

(Item 9 of the PRAC minutes)

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

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

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